Sedation in Paediatric Intensive Care

Karen Margaret Whitfield

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Aston University

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ABSTRACT

Paediatric intensive care is an expanding specialty that has been shown to improve the quality of care provided to critically ill children. An important aspect of the management of critically ill children includes the provision of effective sedation to reduce stress and anxiety during their stay in intensive care. However, to achieve effective and safe sedation in these children, is recognised as a challenge that is not without risk. Often children receive too much or too little sedation resulting in over sedation or under sedation respectively. These problems have arisen owing to a lack of information regarding altered pharmacokinetics and pharmacodynamics of medicines administered to critically ill children. In addition there are few validated sedation scoring systems in practice with which to monitor level of sedation and titrate medication appropriately. This study consisted of two stages. Stage 1 investigated the reproducibility and practicality of two observational sedation assessment scales for use in critically ill children. The two scales were different in design, the first being simple in design requiring a single assessment of the patient. The second was more complex in design requiring assessment of five patient parameters to obtain an overall sedation score. Both scales were found to achieve good reproducibility (kappa values 0.50 and 0.62 respectively). Practicality of each sedation scale was undertaken by obtaining nursing staff opinion about both scales using questionnaire and interview technique. It was established that nursing staff preferred the second, more complex sedation scale mainly because it was perceived to give a more accurate assessment of level of sedation and anxiety rather than merely level of sedation. Stage 2 investigated the pharmacokinetics and pharmacodynamics of midazolam in critically ill children. 52 children, aged between 0 and 18 years were recruited to the study and 303 blood samples taken to analyse midazolam and its metabolites, 1-hydroxymidazolam (1-OH) and 4-hydroxymidazolam (4-OH). Analysis of plasma was undertaken using high performance liquid chromatography. A significant correlation was found between midazolam plasma concentration and sedative effect ($r=0.598$, $p=0.01$). It was found that a midazolam plasma concentration of 223ng/ml (±31.9) achieved a satisfactory level of sedation. Only a poor correlation was found between dose of midazolam and plasma concentration of midazolam. Similarly only a poor correlation was found between sedative effect and dose of midazolam. Clearance of midazolam was found to be 6.3ml/kg/min (±0.36), which is lower than that reported in healthy children (9.11-13.3ml/kg/min). Age related differences in midazolam clearance were observed in the study. Neonates produced the lowest clearance values (1.63ml/kg/min), compared to children aged 1 to 12 months (8.52ml/kg/min) who achieved the highest clearance values. Clearance was found to decrease after the age of 12 months to values of 5.34ml/kg/min in children aged 7 years and above. Patients with renal ($n=5$) and liver impairment ($n=4$) were found to have reduced midazolam clearance (1.37 and 0.74ml/kg/min respectively). Plasma concentrations of 1-OH and 4-OH ranged from 0-5189ng/ml and 0-271ng/ml respectively. All children were found to be capable of producing both metabolites irrespective of age, although no trend was established between age and extent of production of either metabolite. Disease state was found to affect production of 1-OH. Patients with renal impairment ($n=5$) produced the lowest 1-OH midazolam plasma ratio (0.059) compared to patients with head injury (0.858). Patients with severe liver impairment were found to be capable of manufacturing both metabolites despite having a severely damaged liver.

Key words
Critically ill children, sedation assessment, midazolam pharmacokinetics and pharmacodynamics

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1.1 General introduction

1.1.1 The philosophy of paediatric intensive care

There are in total eighteen Paediatric Intensive Care Units (PICUs) throughout the United Kingdom, which are responsible for caring for critically ill children from the ages of 0 to 18 years. It has been demonstrated that the outcome for children receiving intensive care in PICUs is better than those cared for in adult intensive care units (Pollack, Alexander et al. 1991; Pearson and Shann 1998). In 1993 a report of the multidisciplinary working party on paediatric intensive care recommended that a properly staffed and equipped paediatric intensive care unit was the best environment in which to care for critically ill children and that in the long term virtually all children should be cared for in such units (British Paediatric Association 1993). However, a report undertaken in 1998 by the Department of Health revealed that 22% of children requiring intensive care in the North West had their care provided on general children's wards or adult intensive care units (Department of Health 1998). The numbers of children requiring intensive care averages 1.2 admissions per 1000 children per year and, although no data has yet been collated to show an increase in the demand for PICU beds, such an increase can be expected as a consequence of the advances in technology and therapeutic intervention for critically ill children (Department of Health 1998). Clearly paediatric intensive care is a growing field that requires specialists equipped with the knowledge and expertise to care for critically ill children. It is also evident, however, that a substantial number of critically ill children are cared for outside these specialist areas but who require the same quality and standard of care provided in PICUs.

1.1.2 Sedation in paediatric intensive care

Intensive Care Units can be very stressful and frightening places for any child and consequently it is imperative that the appropriate treatment is given to reduce any anxiety and distress. Factors that have been identified to cause distress in critically ill adults include the following (Bion 1988; Johnson and Sexton 1990):

- Pain
- Anxiety
- Inability to speak
- Being uncomfortable
- Body position
- Tugging of ventilator tube
- Suction of the endotracheal tube
- Bright lights
- Alarm noises
- Hectic pace of the unit
- Inability to distinguish between day and night
- Times when recovery seemed doubtful
- Fears of dying
- Therapeutic paralysis
- Lack of rest
- Thirst
- Face mask
- Nasogastric tube
- Physiotherapy
- Urinary catheter

It can be seen that there are a considerable number of factors that may contribute to the distress of critically ill patients. However, not all of these factors will necessarily need pharmacological intervention to alleviate distress. Distraction, relaxation techniques and positive imagery have all been suggested to reduce anxiety in children (Bhatt-Mehta and Rosen 1998). Sleep deprivation has been shown to be common and it has been suggested that efforts should be made to promote natural sleep patterns particularly in children (Cureton-Lane and Fontaine 1997). It is therefore imperative to establish the cause of distress and to treat it appropriately.

Sedation remains an important aspect of treatment for children in intensive care, particularly for those who are receiving mechanical ventilation (Halloran 1991). Administering sedation not only reduces some of the anxiety associated with this procedure but also aids compliance with the ventilator allowing greater synchrony and thus reducing the potential for adverse effects. Sedation also induces amnesia, and has been reported to reduce recall of unpleasant or frightening memories that can contribute to post traumatic stress disorder symptoms (Cheng 1996; Schelling, Stoll et al. 1998). Studies investigating children's recollection of PICU have found that children sedated with

midazolam remember very little of mechanical ventilation (Playfor, Thomas et al. 2000). Commonly identified goals of sedation are to reduce patient discomfort or distress to enable delivery of effective patient care (Hooper and George-Gay 1997). Optimal levels of sedation have not been universally agreed but many intensive care units aim to keep patients lightly asleep and easily rousable or awake but not distressed (Burns, Shelly et al; Murdoch and Cohen 2000).

Achieving effective sedation in critically ill children has been recognised as a challenge that is not without risk (Bhatt-Mehta and Rosen 1998). The administration of sedation has been reported to be poorly undertaken in critically ill children often resulting in either too much or too little sedation being prescribed (Milner and Gunning 2000). Over sedation can cause patients to be deeply asleep and difficult to rouse. It has been reported to result in increased time on mechanical ventilation and consequently increased length of stay in intensive care (Shafer 1998). In addition there have been many reports of children suffering toxicity from the commonly prescribed sedative, midazolam, including tolerance, withdrawal symptoms and physical dependency (Yaster, Kost-Byerley et al; van Engelen, Gimbrere et al; Tobias 2000). Under sedation can lead to a child becoming distressed and anxious and has resulted in children pulling out indwelling catheters and displacing the endotracheal tube (ET) leading to inadvertent extubation (Little, Koenig et al. 1990).

1.1.3 Factors affecting the safe administration of sedation

There appears to be no one clear reason why the administration of effective sedation to critically ill children is undertaken poorly, but a combination of factors that can be separated into drug related and patient related factors.

Drug related factors

It has been shown that many drugs remain unlicensed for use in children and are prescribed outside of their license in paediatric care (Conroy, Choonara et al. 2000). This creates problems for the prescriber and has led to a wide variation in the dose of many medications used in paediatric therapy across the United Kingdom as well as internationally. There is a general lack of accurate and reliable information about the altered pharmacokinetics and pharmacodynamics of sedative drugs in children. This is as a result of a lack of quality research undertaken in the paediatric field (Nahata 1992; Wilson, Kearns et al. 1994). This

is not unique to sedative drugs but is a widespread problem with regard to paediatric pharmacology. Improving knowledge of the pharmacological action and effect of drugs in children will help prevent adverse drug reactions and alert medical staff to possible or likely dose-related adverse effects (Rylance and Armstrong 1997).

Patient related factors

Differing levels of sedation will be required according to the individual child and will be dependant on the condition of the child and severity of illness. The key to successful management of sedation in critically ill children is to understand more fully the pharmacokinetics and pharmacodynamics of these drugs in this patient group. However, in order to do this effectively, a reliable method of sedation assessment is necessary to correlate level of sedation with pharmacological effect (Murray 1997). Sedation assessment is difficult in critically ill patients and the situation is exacerbated by the lack of a robust and reliable sedation assessment scale that can be used in critically ill children (Bhatt-Mehta and Rosen 1998).

It is clear that the administration of sedation in critically ill children is far from ideal and there are a number of issues that need to be addressed to improve upon safe and effective prescribing of sedatives in paediatric care. The purpose of the present work is separated into two stages. Stage 1 is to develop and validate a sedation assessment scoring system that can be used in critically ill children. Stage 2 is to investigate the pharmacokinetics and pharmacodynamics of midazolam in critically ill children of different ages and different medical conditions.

1.2 Sedation

1.2.1 Sedative agents used in paediatric intensive care

There are a number of agents that have been used for sedation in critically ill children including, benzodiazepines, clonidine, anaesthetic agents, ketamine, propofol and chloral hydrate.

Benzodiazepines

Benzodiazepines possess amnesic, anxiolytic and hypnotic properties as well as anticonvulsant and muscle relaxant properties. The most commonly used benzodiazepines in critical care are lorazepam and midazolam (Hansen-Flaschen, Brazinsky et al. 1991). The most widely used sedative in critically ill children in the UK is midazolam, which is administered intravenously either as a continuous infusion or as bolus doses (Rosen and Rosen 1991; Tobias and Rasmussen 1994). Midazolam has a rapid onset of action and a short duration of action and is thought not to accumulate. Lorazpam is a benzodiazepine that is used as a sedative more frequently in the United States than in the UK, principally because of cost (McCollam, O'Neil et al. 1999). Lorazepam has a longer half-life than midazolam and as such its effects may be prolonged and cause delayed patient wakening (Barr, Zomorodi et al. 2001). Consequently it is usually prescribed as regular bolus doses rather than as a continuous infusion.

Benzodiazepines have minimal effects on the cardiovascular system but can cause hypotension when used in the hypovolaemic patient or when used concomitantly with opioid analgesics such as morphine (Shafer 1998). Physiological dependence can develop in patients receiving benzodiazepines for prolonged periods. Therefore it is recommended that doses should be weaned gradually in patients who have received treatment with continuous benzodiazepines (Yaster, Kost-Byerly et al. 1996). Although extensively used in PICU, midazolam has been highlighted as an agent responsible for causing a significant number of adverse drug reactions in critically ill children (Gill, Leach et al. 1995).

Clonidine

Clonidine is an alpha 2-adrenoceptor agonist that has both sedative and analgesic properties and has been investigated as a suitable sedative agent (Hall, Uhrich et al. 2001). Clonidine has been prescribed at doses of 0.1-2mcg/kg/hr in children as an adjunctive sedative agent in combination with midazolam (Ambrose, Sale et al. 2000). Dexmedetomidine is a potent alpha 2-adrenocptor agonist with eight times higher affinity for the alpha 2-adrenocptor than clonidine. It has sedative, analgesic and anxiolytic properties and is being investigated as an alternative sedative agent in critically ill patients (Bhana, Goa et al. 2000; Tobias and Berkenbosch 2002).

Ketamine

Ketamine is an anaesthetic agent that has been shown to provide effective sedation and analgesia in critically ill children (Tobias, Martin et al. 1990). Ketamine has a short duration of action and is used as a continuous infusion for sedation during mechanical ventilation. Ketamine is a potent cerebral vasodilator and therefore is inappropriate to be used for patients with a closed head injury or increased intra cranial pressure. Ketamine relaxes airway smooth muscle and decreases airway resistance making it particularly useful in the asthmatic patient (Youssef-Ahmed, Silver et al. 1996). A problem that has been associated with ketamine is the dose-related phenomenon of unpleasant hallucinations whilst emerging from therapy. These can include auditory and visual hallucinations and agitation. These reactions can be reduced with concomitant use of benzodiazepines (Bhatta-Mehta and Rosen 1998).

Propofol

Propofol is an anaesthetic agent that is used regularly in critically ill adults for sedation. It has a rapid onset of action followed by redistribution from the central nervous system to peripheral compartments resulting in a short duration of action (Bryson, Fulton et al. 1995). These properties are advantageous and allow easy, sensitive and rapid adjustments to be made to the level of sedation. Propofol has been studied as an alternative sedative agent in children and was thought to compare favourably with other sedative agents (Reed, Yamashita et al. 1996; Pepperman and Macrae 1997). However, it has been associated with

severe adverse effects in children including metabolic acidosis with cardiac failure and has resulted in a number of fatalities (Parke, Stevens et al. 1992; Strickland and Murray 1995; Martin, Murthy et al. 1997). It is no longer recommended for sedation in mechanically ventilated patients aged 16 years and younger (Committee Safety Medicines 2001).

Chloral Hydrate

Chloral hydrate is a nonbarbiturate hypnotic agent that has been used extensively in children to provide sedation for painless procedures and sedation in PICU (Marx, Rosenberg et al. 1993). It has an onset of action within 20-40 minutes and its effects can last up to 4-8 hours. It is metabolised to trichloroethanol, which is its active metabolite. Chloral hydrate and trichloroethanol have been shown to accumulate in neonates and therefore repeated administration is not recommended in this age group (Jacqz-Aigrain and Burtin 1996). Chloral hydrate is only available for oral and rectal administration and is useful when weaning patients from intravenous sedation.

1.2.2 The ideal sedative agent

Tobias and Rasmussen (1994) have suggested that the characteristics of the ideal sedative agent for use in the intensive care setting should include the following:

- Rapid onset
- Predictable duration of activity
- No active metabolites
- Effects dissipate rapidly when agent discontinued
- Multiple options for route of delivery
- Easy to titrate by continuous infusion
- Limited effects on cardiorespiratory function
- Effects and duration not altered by renal and hepatic disease
- No interference with effect or metabolism by other drugs
- Wide therapeutic index.

No one agent fulfils all the requirements of the ideal sedative agent. Midazolam is the most commonly prescribed sedative drug in PICU and, although it does have a number of disadvantages it has been shown to fulfill a number of criteria for the ideal sedative agent.

It has a very rapid onset of action and in healthy adults and children has a short half-life (Greenblatt, Abernathy et al. 1984; Payne and Mattheyse 1989). In the short term the effects of the drug have been shown to wear off very quickly once the agent has been discontinued.

Some of the drawbacks of midazolam include active metabolites that are thought to enhance its pharmacodynamic effect. Midazolam is also metabolized by the P450 enzyme system and as such, enzyme inducers and enzyme inhibitors affect its metabolism. Examples of such drugs that interact with midazolam include ciprofloxacin, erythromycin, carbamazepine and ketoconazole, all of which are commonly prescribed in critically ill patients (Yeates, Laufen et al. 1997; Pea and Furlanut 2001). In critically ill children midazolam has been associated with physical dependency and withdrawal problems characterized by visual and auditory hallucinations, and abnormal behaviour (Hughes, Gill et al 1994). In addition some of the ideal characteristics of midazolam no longer apply when prescribed in the critically ill patient. In critically ill adults the half-life of midazolam has been shown to be prolonged and its clearance reduced (Byatt and Lewis 1984; Shafer 1998). There is also some evidence that the metabolites of midazolam can accumulate in renal impairment and lead to prolonged sedation in critically ill patients (Bauer, Ritz et al 1995).

1.3 Midazolam

1.3.1 Pharmacology of midazolam

Midazolam hydrochloride is an imidazobenzodiazepine, 8-chloro-6-(2-flurophenyl)-1methyl-4H-imidazo[1,5-a][1,4] benzodiazepine hydrochloride (C18H14Cl2FN3-HCL, molecular weight of 362.25). It is available as a parenteral preparation as a water-soluble salt at acidic pH. Its solubility in water is 2.9mg/ml and at a pH of 5 or less, the benzodiazepine ring is open. At physiological pH the ring closes and it becomes fat-soluble and is taken up into the tissues very quickly.

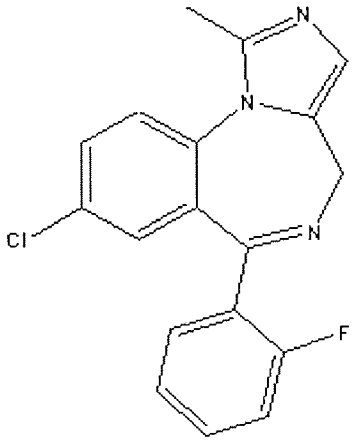


Figure I
Chemical structure of midazolam

All benzodiazepines exert similar pharmacodynamic effects, which include hypnotic, sedative, anxiolytic, anterograde amnesic, anticonvulsant and muscle relaxant properties. Benzodiazepines exert their effects by interaction with the gamma-aminobutyric acid receptor (GABA). Two receptors for GABA have been identified in the central nervous system - $GABA_A$ and $GABA_B$. $GABA_A$ receptors are more common and exhibit binding sites for two classes of modulators, namely benzodiazepines and barbiturates (Nicholls and Martin 1992). Benzodiazepines bind to the γ subunit of the $GABA_A$ receptor and increase GABA-induced chloride current by increasing the frequency of the channel opening. The highest receptor densities are to be found in the cortex, cerebellum and hippocampus (Doble and Martin 1996). $GABA_A$ receptors can be found in adults and children but the

binding capacity of the benzodiazepine receptors are thought to alter with age. Binding capacity in a full term neonate within the cerebellum was found to be similar to adults but lower within the cortex.

1.3.2 Physiological differences between children and adults

Children are both physically, physiologically and psychologically immature compared to adults. Children are physically smaller than adults with immature respiratory and cardiovascular systems. Younger children will also have immature kidney and liver functions that will affect the metabolism and elimination of drugs. Children have physiological differences compared to adults. A child's metabolic rate is more rapid than in adults and thus requires a higher cardiac output and higher fluid and caloric intake per kilogram of body weight compared to adults. Children are emotionally immature and their communication skills are not refined and therefore approach to care must be appropriate to the development of a particular child (Hazinski 1992).

Cardiovascular differences

The circulating blood volume in children is higher per kilogram body weight (Table I) than that in adults. However, a child's blood volume is still relatively small in comparison to adults and therefore even small blood losses may result in volume depletion. This is also relevant when considering the implications of blood used for laboratory analysis (Levin and Morriss 1997).

Table I Circulating blood volume in children and adults (Hazinski 1992)

Age of child	Blood volume (ml/kg)
Neonates (<1month)	85-90
Infants (1month – 12 months)	75-80
Children	70-75
Adults	65-70

At birth, the cardiac output is higher per kilogram body weight averaging 400ml/kg/min, which is reduced during adolescence to 100ml/kg/min, falling eventuality to 70 to

80ml/kg/min during adulthood (Levin and Morriss 1997). Cardiac output is directly proportional to heart rate, which is much higher in the neonate compared to older children and adults (Table II).

Table II Normal heart rates in children (Hazinski 1992; Levin and Morriss 1997)

Age	Awake heart rate (per min)	Sleeping heart rate (per min)
Neonate	100-180	80-160
Infants (< 1year)	100-160	75-160
Toddler (1-3years)	80-110	60-90
Preschooler (4-5years	70-110	60-90
School age (5-13years)	65-110	60-90
Adolescent	60-90	50-90

Heart rate will increase with anxiety, activity, pain and fever and in the presence of cardiovascular disease. Heart rate will be slowed during sleep and when a child is sedated.

Fluid and electrolyte balance

A major proportion of body weight is made up of water. In the adult, water comprises approximately 65-70% of a persons total body weight. In young children the proportion is higher; in the full term baby it is 75%. During the first year of life most body water is located in the extracellular compartment and much of the water is exchanged daily. This proportionately large amount of extracellular fluid increases the effective volume of drug distribution in the first year of life. Neonates and young children have a large surface area to weight ratio and therefore loose a larger amount of water via evaporation compared to the adult (Levin and Morriss 1997).

Renal Function

At birth a child's kidneys are not fully developed and the glomerular filtration rate as well as tubular secretion are reduced. The glomerular filtration rate (GFR) increases significantly at 34 weeks and continues to mature over the first year of life, but is still comparatively lower than that found in older children (Table III).

Table III Glomerular filtration rates in children and adults (Hazinski 1992)

Age	GFR (ml/min)
Full term neonate	30-40
2 months	70-80
6 months	100-110
3 years	100-150
adult	120-150

At birth renal blood flow accounts for only 5-10% of total cardiac output and only approximately 50% of renal blood flow passes though the cortex. This is because the cortical glomeruli are immature and the renal vascular resistance is high. In children aged above 3 years 25% of the total cardiac output passes through the kidneys. There is therefore the potential for drugs that are renally eliminated to accumulate in the neonate and younger child. The elimination of water-soluble metabolites may also be impaired.

Liver Function

Plasma protein binding is decreased in the neonatal period, as a result of reduced circulating levels of alpha-1-acid glycoprotein and beta globulins. In addition, neonates have lower serum albumin concentrations compared to adults and the binding capacity of albumin is less. Plasma concentrations of bilirubin are higher in neonates and these will compete with drugs for protein binding sites (Edwards 1986). At birth the liver is still immature and enzyme systems responsible for the metabolism of many drugs may not be fully developed. Phase 1 reactions, which include oxidation, reduction, hydroxylation and hydrolysis, demonstrate considerable variation during child development. Phase II reactions, such as conjugation reactions that create more water-soluble compounds for elimination, are also immature at birth. It is unknown the time after birth at which both the liver and kidney are fully developed but it is thought that it could take as long as 1 year (Nahata 1992).

1.3.3 Midazolam pharmacokinetics in healthy adults and children

The pharmacokinetics of midazolam are said to be linear; that is the amount of drug transferred per unit time to and from the peripheral compartments and the amount of drug eliminated per unit of time by the metabolic processes are proportional to the drug concentrations in the respective compartments (Allonen, Ziegler et al. 1981). Therefore, the total amount of midazolam distributed and eliminated per unit time is not constant and greater amounts are transferred when drug concentrations are higher (e.g. after a bolus dose) than in the case of low concentrations.

Midazolam has been shown to be short acting agent with a half-life of approximately 1.3 to 3 hours, and a volume of distribution of 1.6L/kg in healthy adults (Allonen, Ziegler et al. 1981; Greenblatt, Abernethy et al. 1984). The short duration of action after a single bolus dose has been attributed to its rapid redistribution into peripheral tissues (Barr and Donner 1995). As a consequence of its short duration of action and half-life, midazolam is thought not to accumulate in the body. Clearance, which is defined as the volume of plasma cleared of a drug per unit of time, has been reported to range between 6 and 8ml/kg/min in adults (Greenblatt, Abernethy et al. 1984).

The pharmacokinetics of midazolam have been studied in healthy children aged between 3 and 10 years (Payne, Mattheyse et al. 1989; Jones, Chan et al. 1993). The half-life was found to range between 1 and 2 hours and volume of distribution to be 1.29L/kg. Clearance of midazolam was reported to range between 9.11ml/kg/min and 15ml/kg/min. The results of these studies demonstrate that the metabolic turnover of midazolam is more rapid in children than adults.

1.3.4 Age related differences in midazolam metabolism

It has been widely established that children metabolise and handle drugs differently to adults (Nahata 1992). This phenomenon has been described with a wide range of agents including neuromuscular blocking agents, cardiovascular agents, opioid analgesics and benzodiazepines (Olkkola, Maunuksela et al. 1988; Notterman, Greenwald et al. 1990; Jacqu-Aigrain, Burtin et al. 1992; Vuksanaj and Fisher 1995). The rapidly changing

physiological status of a neonate can have considerable implications when prescribing and administering drugs to this age group (Edwards 1986; Nahata 1992).

The mean clearance of midazolam in 10 critically ill neonates after an intravenous bolus of midazolam was found to be 2ml/kg/min and the half-life to be 6.5 hours (Jacqz-Aigrain, Wood et al. 1990). These results can be compared to values found in healthy adults where the clearance of midazolam has been found to be between 6-8ml/kg/min and the half-life between 1.3 to 3 hours (Greenblatt and Abernethy et al. 1984). In healthy children clearance values have been found to be approximately 9.11-15ml/kg/min and half-life in the region of 1 to 2 hours (Payne, Mattheyse et al. 1989; Jones, Chan et al. 1993).

Mean midazolam plasma concentrations of 634ng/ml and 628ng/ml have been achieved at 24 and 48 hours treatment respectively in critically ill neonates, using a dosage regimen of 1mcg/kg/min in neonates above 33 weeks gestation and reducing the dose to 0.5mcg/kg/min after 24 hours therapy in those below 33 weeks of gestation (Jacqz-Aigrain, Daoud et al. 1994). Plasma levels of midazolam ranged from 200-1000ng/ml in the majority of patients and drug accumulation was not evident over the treatment period of 5 days. However, a study undertaken in 187 neonates from 6 Neonatal Intensive Care Units found a high proportion of midazolam plasma levels above 1000ng/ml (0-7100ng/ml), 19.8% above 1000ng/ml and of these 4.7% above 2000ng/ml (Burtin, Jacqu-Aigrain et al. 1994). Clearance was found to be 1.17ml/kg/min in patients younger than 39 weeks of gestation and 1.84ml/kg/min in patients older than 39 weeks of gestation. The conclusions from this study suggested the need for substantially lower dosage regimens in critically ill neonates. However, dose prediction and a therapeutic interval was deemed inappropriate owing to inter-individual variability and required further pharmacokinetic and pharmacodynamic work to be defined. Premature neonates weighing less than 1000g at birth are particularly at risk of the adverse effects of midazolam and have also been shown to have significantly lower midazolam clearance values than neonates weighing more than 1000g at birth in a study undertaken by Lee, Charles et al. (1999).

1.3.5 Disease related factors affecting pharmacokinetics of midazolam

1.3.5.1 Respiratory impairment and mechanical ventilation

The effect of mechanical ventilation on the pharmacokinetics of drugs has not been extensively studied but it has been suggested that it could be an additional factor to disease-induced changes in drug elimination in critically ill patients (Perkins, Dasta et al. 1989). Although the underlying mechanism for this has not been fully established it is thought that intermittent positive pressure ventilation induces an increase in intrathoracic pressure associated with a reduction in central blood volume leading to a decrease in cardiac index (Taubert, Tollier et al. 1990). A decrease in cardiac output can produce a reduction in hepatic and renal blood flow and consequently alter drug metabolism and elimination.

1.3.5.2 Cardiac impairment

Adults with congestive cardiac failure have been shown to have a 30% reduction in the clearance of midazolam (376 versus 551ml/min) and a prolonged half-life, up to 4 hours, compared to healthy adults (Patel, Soni et al. 1990). Adults recovering from cardiac surgery have also been found to have an increased midazolam elimination half-life (10.3hours) compared to that found in other surgical patients (2-5hours) (Maitre, Funk et al. 1989). Midazolam clearance was also reduced in these patients, reaching values of 250ml/min compared to other healthy surgical patients (350-500ml/min).

There have been few studies looking at the effects of cardiac disease on the pharmacokinetics of drugs in children. It has been suggested that in children who have undergone cardiac surgery, a dose reduction of morphine of up to 50%, may be required, particularly in those requiring ionotropic support (Dagan, Klein et al. 1993). However, the effects of cardiac disease on the metabolism of midazolam in critically ill children have not been extensively studied. In children over 3 months of age following cardiopulmonary bypass (CPB) clearance of midazolam has been found to be 8.5ml/kg/min and half-life 3.3 hours (Mathews, Carson et al. 1988). Mean midazolam concentrations achieved in these patients were reported to be between 80-100ng/ml using a dose of 0.8mcg/kg/min. However, mean midazolam concentrations of 421ng/ml have been reported in cardiac children receiving a dose of midazolam of between 2-6mcg/kg/min (Booker, Beechey et al.

1986). Two of the children in the study developed very high plasma levels of midazolam (1200ng/ml-3315ng/ml). One child had normal renal and liver function, whereas the other developed both renal and liver impairment following surgery.

1.3.5.3 Renal impairment

Reports of the effect of renal impairment on the pharmacokinetics of midazolam are conflicting. Some work has reported that the pharmacokinetics of midazolam are unchanged by renal impairment and in addition, that there are no alterations in the pharmacokinetics during haemofiltration (Bodenham, Shelly et al. 1988). Other studies have demonstrated an increase in the half-life of midazolam in patients with renal impairment, which has led to an enhanced pharmacodynamic response (Driessen, Vree et al. 1991). A more recent study undertaken in four intensive care adults undergoing continuous venovenous haemodialysis has demonstrated that midazolam is not removed efficiently using this method and that only approximately half of the 1-hydroxymetabolite is removed by dialysis (Bolon, Bastien et al. 2001). The half-life of midazolam was found to be prolonged (7.6-22.8 hours) and clearance was found to be between 0.57-4.7ml/kg/min. Adult patients suffering acute renal impairment have also been shown to have a reduced clearance of midazolam's major metabolite 1-hydroxymidazolam (Bauer, Ritz et al. 1995).

1.3.5.4 Liver impairment

Blood flow to the liver, clearance by the liver and the fraction of the drug bound to protein all affect the ability of the liver to extract a drug from the blood. Changes in blood flow will affect hepatic clearance of drugs. Examples of conditions, which alter hepatic blood flow, include, hypotensive shock, cardiac impairment and burns injury (Bodenham Shelly et al. 1988). Factors that affect the intrinsic ability of the liver to clear a drug from the body include, age, pathological factors and the presence of hepatic enzyme inducers and inhibitors. Studies in adults with cirrhotic liver disease have shown a prolonged half-life of midazolam and a reduced clearance (Trouvin, Farinotti et al. 1988). Interestingly data from four adult patients given a 10mg bolus of midazolam, following liver transplant due to chronic liver disease, showed that these patients had considerable midazolam metabolising capacity either by the liver or extra hepatic sites (Shelly, Dixon et al. 1989). Moreover, plasma concentrations of 1-hydroxymidazolam were found to be higher in these patients

than in healthy subjects. There are no studies investigating changes in pharmacokinetic and pharmacodynamic variables in children with liver disease.

1.3.6 Midazolam pharmacodynamics in critically ill adults and children

Although midazolam has been used extensively in mechanically ventilated children to provide sedation and reduce anxiety, prescribing still remains empiric (Silvasi, Rosen et al. 1988; Rosen and Rosen 1991). A number of studies have been undertaken to try to establish the dose of midazolam required to achieve adequate sedation and the plasma concentration at which this occurs. However, this has proved difficult and many studies have been unable to correlate midazolam plasma concentrations with effect owing to large inter-individual differences (Hughes, Gill et al. 1996; Nahara, McMorrow et al. 2000). Studies undertaken in critically ill adults following cardiac surgery found that an adequate concentration of sedation occurred at midazolam plasma concentrations of 200ng/ml (Somma, Donner et al. 1998). Optimal levels of sedation in critically ill children, between the ages of 26 days and 5 years, have been achieved at midazolam plasma concentrations between 100-500ng/ml (Hartwig, Roth et al. 1991). The correlation between midazolam plasma concentration and level of sedation was only evident for the first 24-72 hours. Subsequently, no correlation between level of sedation and midazolam plasma concentration could be established. Only a weak correlation was found between the dose of midazolam administered and plasma concentration of midazolam. Other studies have stated that a midazolam plasma concentration above 250ng/ml is required to achieve adequate sedation in children (Lloyd-Thomas and Booker 1986).

1.3.7 Midazolam pharmacokinetics in critically ill adults and children

Midazolam appears to possess a number of qualities required of an ideal sedative agent. However, a number of studies have now shown that in the critically ill, some of these properties are not evident and midazolam has been shown to accumulate markedly to cause a variety of problems and adverse effects.

Pharmacokinetics in critically ill adults have been reported to be significantly altered as a result of organ dysfunction, including changes in hepatic, renal and cardiac function (Power, Forbes et al. 1998). The pharmacokinetics of midazolam have been shown to be altered in critically ill adults, including a prolonged half-life, up to 10 hours compared to 2.3 hours in healthy individuals (Boulieu, Lehmann et al. 1998). The volume of distribution has been reported to be larger in critically ill adults (3.1L/kg) compared to that observed in healthy adults (0.9L/kg). Clearance was not found to be significantly different, 6.3ml/kg/min compared to 4.9ml/kg/min in healthy adults (Malacrida, Fritz et al. 1992).

An optimal dose regimen for midazolam to sedate critically ill children has not been established. There is considerable variation within paediatric formularies regarding a suitable starting dose of midazolam and this is reflected in the variations in midazolam doses prescribed in different PICUs. Marked differences in the steady state plasma concentrations of midazolam achieved in critically ill children have been reported. A study undertaken by Nahara, McMorrow et al. in 2000 in 22 patients aged between 8 days and 16 years showed plasma levels of midazolam in the range of 49-385ng/ml. The half-life ranged from 0.3-10.9 hours and clearance values were found in the range of 0.1-3.1L/kg/hr. The variation in the pharmacokinetic parameters seen in these studies may result from many conflicting factors such as age and disease state, which will need further investigation.

There is some evidence to indicate that midazolam clearance increases with continued use. This maybe caused by auto induction and as a result tolerance can develop with continuous use of intravenous midazolam (Hartwig, Roth et al. 1991). The lack of pharmacokinetic and pharmacodynamic work undertaken in children encourages the practice of extrapolation from adult data. It cannot be assumed that adults and children will respond equally to similar drug concentrations. Receptor drug concentrations and/or sensitivity in

children can differ from those in adults (Gilman 1992). Developing pharmacological knowledge in critically ill children will provide a more rational basis for dosage determination and thus optimise therapy.

1.3.8 Midazolam metabolites

Midazolam is metabolised by the liver to 1-hydroxymidazolam (1-OH) and 4-hydroxymidazolam (4-OH), which are both water-soluble. There has been much controversy over the potency of 1-OH and its contribution to the sedative effects of midazolam. Some workers consider the metabolite insignificant whilst others consider it equipotent to midazolam and therefore that it can contribute significantly to the pharmacodynamic effect of midazolam if present in sufficiently high concentrations (Mandema, Tuk et al. 1992; Boulieu, Lehmann et al. 1998). 1-OH has been found to have a shorter half-life than midazolam and is cleared 1.3 times more quickly than midazolam in healthy adults. This may be the reason why low concentrations of the metabolite have been found after intravenous administration of the parent compound. After intravenous administration concentrations of 1-OH were 8 times lower than midazolam and it was calculated that 1-OH would contribute approximately 10% to the observed effects of intravenous administration of midazolam (Mandema, Tuk et al. 1992). Pharmacodynamic effects were evaluated by carrying out saccadic velocity and electroencephalographic (EEG) measures.

In a study involving 187 neonates from 6 NICU centres the 1-OH midazolam plasma ratio was found to be less than 0.1 in 50% of samples, between 0.1 and 0.5 in 44% of samples and more than 0.5 in 6% of the samples. In 38 patients 1-OH was not detected (Burtin, Jacqz-Aigrain et al. 1994).

4-OH is not thought to contribute significantly to the pharmacodynamic effect of midazolam and has a shorter half-life than 1-OH. It disappears rapidly from the plasma and has been difficult to detect (Mandema, Tuk et al. 1992).

1.3.9 Drug interactions with midazolam

Midazolam has been shown to be metabolised predominately by the enzyme system cytochrome P450 3A4. However, recent studies have confirmed the involvement of P450 3A3 and P450 3A5 systems in the metabolism of midazolam (Wandel, Bocker et al. 1994). The enzyme systems cytochrome P450 3A3 and 3A4 have been shown to metabolise midazolam to the same extent. However cytochrome P450 3A5 has been reported to increase the metabolism of midazolam by 2.7. P450 3A3 and 3A4 are found predominately in the liver whereas P450 3A5 is found predominantly in the kidney.

Drugs that cause induction or inhibition of the CYP3A (cytochrome P-4503A) system have been shown to alter the metabolism of midazolam markedly (Dresser, Spence et al. 2000). Carbamazepine and phenytoin can both induce these enzymes and have been shown to increase the metabolism of midazolam significantly, shortening the half-life to 1.3 hours and reducing expected plasma levels of midazolam in patients taking these agents orally. (Backman, Olkkola et al. 1996). Fentanyl has been shown to inhibit the metabolism of midazolam by reducing its clearance and prolonging the half-life (Hase, Oda et al. 1997). Macrolide antibiotics, fluoroquinolones and azole antifungals all inhibit CYP mediated metabolism and can cause a reduction in the clearance of many agents used in the intensive care setting including midazolam (Pea and Furlanut 2001). Erythromycin and clarithromycin have been found to significantly increase the plasma levels of midazolam during co-administration, whereas azithromycin, an azalide antibiotic is thought to have little or no effect on the metabolism of midazolam (Yeates, Laufen et al. 1997). Propofol has been reported to decrease the clearance of midazolam by competitive inhibition of hepatic CYP3A4 (Hamaoka, Oda et al. 1999). Such clinically significant interactions can lead to toxicity or a reduced effect.

1.4 Sedation assessment in intensive care

'Appropriate assessment will lead to the appropriate use of sedation in the critically ill' (Murray 1997).

Maintaining an optimal level of comfort in critically ill patients is crucial and plays an important role in the road to recovery of these patients. There is increasing evidence to suggest that poorly controlled pain and anxiety may be associated with a worse outcome from critical illness (Schelling, Stoll et al. 1998). In order to achieve adequate sedation, appropriate and accurate assessment of the level of sedation is imperative. In current practice monitoring of plasma concentrations of the commonly used sedatives including benzodiazepines as a means to titrate sedative response remains unreliable. Other objective methods with which to assess levels of sedation including neurophysiological monitoring of the EEG remain in the early stages and as yet are not routinely used in practice (Berkenbosch, Fichter et al. 2002). Therefore the only method available to assess sedation is via sedation assessment scales.

A task force of the American College of Critical Care Medicine has produced guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Recommendations made in these guidelines about sedation assessment are (Jacobi, Gilles et al. 2002):

- A sedation goal or endpoint should be established and regularly redefined for each patient.
- Regular assessment and response to therapy should be systematically documented.
- The use of a validated sedation assessment scale is recommended.

No similar guidelines have been produced for children; however, the above recommendations are appropriate for sedation assessment in critically ill children.

A considerable amount of work has been undertaken to investigate the assessment of pain in children including critically ill children (McGrath and Craig 1989; Norden, Hannallah et al. 1991; Lawrence, Alcock et al. 1993). However, in comparison there is very little work

done in the area of sedation assessment, particularly in the field of PICU. A number of sedation scoring systems have been developed for use in adult intensive care but few have been validated. Moreover, assessment scales developed for use in adults may not be suitable for use in children. An example of this is the development and validation of the paediatric coma scale from the Glasgow Coma Scale that is used to assess level of consciousness in head injury patients (Tatman, Warren et al. 1997). The Glasgow Coma Scale was unsuitable for use in young children, as the verbal component was inappropriate. Therefore the verbal component of the assessment was replaced with a grimace score, thereby taking into consideration the developmental immaturity of young children.

1.4.1 Critical appraisal of available sedation assessment scales

It has been suggested that any sedation scale developed for use in the clinical setting should meet the following criteria (Hooper and George-Gay 1997; Quirke, Bowyer et al. 1997):

- Exhibit graded changes with sedation level
- Show similar changes independent of sedative agents
- Be easy to use, interpret and record
- Assess all components of patient comfort and sedation
- Be non-invasive
- Be sensitive to clinical changes
- Cause no discomfort to the patient
- Perform reliably with the concurrent use of neuromuscular blocking agents
- Be valid and reliable

Many of the subjective assessment scales available with which to measure sedation in intensive care have evolved from the Ramsay Scale (Ramsay, Savege et al. 1974).

1.4.1.1 The Ramsay Sedation Assessment Scale

The Ramsay scale was one of the first sedation scales to be developed that defined a more objective end point of therapy and has been used in many subsequent studies (Figure II). However, although extensively used in practice, the Ramsay scale has not been validated for use in critically ill children.

Figure II The Ramsay Assessment Scale

Awake levels:

1. Patient anxious and agitated or restless or both
2. Patient co-operative, orientated and tranquil
3. Patient responds to commands only

Asleep levels, depend on response to a light glabellar tap or loud auditory stimulus

4. Patient responds briskly
5. Patient responds sluggishly
6. Patient does not respond

Further criticisms of the Ramsay scale include the use of an extra external stimulus with which to distinguish between sleep and over sedation. In children it is currently considered unsatisfactory to use extraneous unpleasant stimuli in addition to those already experienced in PICU to assess sedation.

1.4.1.2 The Addenbrookes Sedation Scale

The Addenbrookes Sedation Scale has been developed from the Ramsay scale (Figure III). It consists of seven levels and has the advantage over the Ramsay scale that it uses endotracheal suction as a painful stimulus thereby reducing further discomfort to the patient

Figure III The Addenbrookes Sedation Scale

0	Agitated
1	Awake
2	Roused by voice
3	Roused by tracheal suction
4	Unrousable
5	Paralysed
6	Asleep

The Addenbrooke's scale also incorporates sleep into the design, highlighting the importance of sleep in the care of critically ill patients. It is simple and easy to use, however the scale still remains very subjective in its design.

1.4.1.3 The Observer's Assessment of Alertness/Sedation Scale

The Observer's Assessment Alertness/Sedation Scale (OAA/S Scale) was developed and validated to assess level of alertness in adults who were sedated (Figure IV) (Chernik, Gillings et al. 1990). The study was undertaken in healthy adults and compared this sedation scale with a visual analogue scale. It was found that the OAA/S Scale provided a reliable method with which to assess level of sedation. The scale is objective in design as it breaks down the assessment using four parameters - responsiveness, speech, facial expression and eyes. However this scale lacks the ability to assess agitation and has not been validated within intensive care. It is therefore inappropriate for use in the critically ill child as it relies on communication for assessment

Figure IV Observers Assessment of Alertness/Sedation Scale

Responsiveness	Speech	Facial Expression	Eyes	Score
Responds readily to name spoken in a normal tone	Normal	Normal	Clear, no ptosis	1
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	2
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognisable words	-	-	4
Does not respond to mild prodding or shaking.	-	-	-	5

1.4.1.4 The Sedation Agitation Scale

The Sedation Agitation Scale has been validated for the assessment of sedation in critically ill adults (Figure V) (Riker, Picard et al. 1999). It consists of seven levels each with a description associated with the level of sedation. The scale has an advantage over other assessment scales in that it assesses extent of agitation and therefore is not just a measure of consciousness. The scale does not take into account assessment of the sleeping patient. Moreover, the use of the Sedation Agitation Scale in children has not been validated and owing to the reliance of this technique on verbal commands to assess sedation, its use would be inappropriate for the pre-verbal child.

Figure V Sedation Agitation Scale

Score	Description	Example
+3	Immediate threat to safety	Pulling at endotracheal tube or catheters, trying to climb over bed rail, striking staff
+2	Dangerously agitated	Requiring physical restraints and frequent verbal reminding of limits, biting endotracheal tube, thrashing side to side
+1	Agitated	Physically agitated, attempting to sit up, calms down to verbal instructions
0	Calm and cooperative	Calm, arousable, follows commands
-1	Over sedated	Difficult to arouse or unable to attend conversation or commands
-2	Very over sedated	Awakens to noxious stimuli only
-3	Unarousable	Does not awaken to any stimuli

1.4.1.5 The Motor Activity Assessment Scale

The Motor Activity Assessment Scale is very similar in design to the Sedation Agitation Scale and has been validated in mechanically ventilated surgical adults (Devlin, Boleski et al. 1999). It was designed to assess agitation as well as level of sedation although it does not take into consideration the sleeping patient. Moreover, it uses an additional noxious stimulus to assess over sedation and therefore it would be inappropriate to be used in critically ill children.

1.4.1.6 The New Sheffield Sedation Scale

The New Sheffield Sedation Scale was developed and validated in critically ill adults (Figure VI) (Olleveant, Humphries et al. 1998). It consists of 6 levels each with a description of the levels of sedation. A further two levels of sedation where incorporated into the design of the assessment scale, namely an assessment for the sleeping patient and the paralyzed patient, which were denoted in the documentation by the letters 'S' and 'P' respectively. The advantages of this scale include the assessment of agitation rather than just the level of consciousness and also the importance that is given to sleep. However, this assessment scale has not been validated in children. In addition there appears to be some ambiguity with regard to levels 3 and 4, which appear to be very similar. The descriptions

of the levels of sedation score are in some cases quite lengthy and could be made more concise to improve ease of use.

Figure VI The New Sheffield Sedation Score

Awake. At this level patients should be awake and orientated requiring minimal or no sedation. They should be self-ventilating, either via a face mask or through an endotracheal tube which they are tolerating. This level should be reached by the patient prior to being extubated after having gone through the weaning process successfully. This level with no sedation is what may be aimed for in many patients who are ventilated and who have a tracheostomy or a particular neurological problem.

Agitation. At this level the patient is showing signs of agitation and restlessness, compromising ventilation, oxygenation and general condition. Observe for signs of distress on physiotherapy, suctioning of the endotracheal tube and oropharynx and on handling in general.

Optimum Level (i). This level of sedation should be where the patient is just asleep. The patient should respond to speech and to touch either by squeezing of the nurse's hand or by blinking. The patient may require bolus sedation as well as the background sedation cover prior to handling during care, also prior to physiotherapy sessions or invasive procedures.

Optimum Level (ii). This level of sedation should be where the patient is just asleep. The patient should respond to speech and to touch either by squeezing of the nurse's hand or by blinking. The patient should also handle well and tolerate care.

Sluggish Level. This level is where the patient has dull/ sluggish responses to any form of stimulation, i.e. glabellar tap, or on suction through the endotracheal tube

Flat level. This level is when the patient is showing no signs of response to stimulation of any kind.

1.4.1.7 The Vancouver Recovery Scale

The Vancouver Recovery Scale (VRS scale) was developed and validated to assess level of sedation after surgical or diagnostic procedures requiring general anaesthesia or sedation (Figure VII) (Macnab, Levine et al. 1991). It was used to assist staff to determine when it was safe and appropriate to allow paediatric patients to leave the post-anaesthetic recovery room. Although a robust method was used to validate the VRS scale, neonates and younger children were not included in the study. In addition the VRS scale could not be used in ventilated children and was therefore only suitable for non-intubated children. The VRS scale is also complex in design and takes an average of 4 minutes to complete. The time taken to complete any sedation scale is crucial and should be minimized where possible owing to the extensive amount of documentation currently required in intensive care. A follow up study investigated the usefulness of video taped assessments, which were subsequently used for training junior staff (Macnab, Glick et al. 1994).

Figure VII The Vancouver Recovery Scale for Children

A. Response		
i) Awake/alert		4
ii) Awake/drowsy		3
iii) Asleep/easily aroused		2
iv) Asleep/difficult to arouse		1
v) Asleep/unable to arouse		0
B. Note if child scores "0" on above, do not proceed		
i) Responds fully to stimuli in an age-appropriate manner		2
ii) Delayed response to stimuli		1
iii) Absent response to stimuli		0
C. Facial Expression		
i) "Alert" facial expression		1
ii) "Flat" facial expression		0
D. Eyes		
i) Bright eyes		1
ii) Dull eyes; glazed		0
E		
i) Looks "at you"		1
ii) Looks "through you"		0
F		
i) Accommodates		1
ii) Does not accommodate		0
G		
i) Recognition of stimuli		1
ii) Limited or no recognition of stimuli		0
H		
i) Purposeful and spontaneous eye movement		1
ii) Little or no spontaneous or purposeful eye movement		0
Movement		
I	i) Spontaneous and varied central activity	4
	ii) Spontaneous and varied peripheral activity	3
	iii) Central activity in response to stimuli	2
	iv) Peripheral activity in response to stimuli	1
	v) No movement	0
J	i) Absence of tremor or ataxia	2
	ii) Minor ataxia or tremor	
	iii) Major ataxia or tremor	0
K	i) Coordinated spontaneous movement	2
	ii) Weak/coarse spontaneous movement	1
	iii) No purposeful spontaneous movement	0
L	i) Shows age-appropriate manual dexterity	2
	ii) Awkward or clumsy hand movement	1
	iii) No fine hand movement	0

1.4.1.8 The Comfort Scale

The Comfort Scale is the only sedation assessment scale that has been developed and validated in critically ill mechanically ventilated children (Marx, Smith et al. 1994). The scale consists of 8 parameters with which to assess level of sedation, namely, alertness, calmness/agitation, respiratory response, physical movement, blood pressure, heart rate, muscle tone and facial tension. By breaking the assessment down into these parameters a degree of objectivity to the assessment was introduced and the scale was found to provide a reliable method of sedation assessment. However the scale has been heavily criticised for being too complicated and time consuming to use (Chernik, Gillings et al. 1990; Olleveant, Humphries et al. 1998).

1.4.2 Requirements of a sedation assessment scale for critically ill children

It is evident that there are a number of sedation scales that have been developed and validated for use in critical care but few have been validated for use in children. It is important that any sedation scale developed for use in children is not reliant on speech for any part of the assessment since is will be inappropriate for the pre-verbal child. Recovery sedation assessment scales that have been developed for use in children are only appropriate post extubation and again cannot be used in the critical care setting. Age related differences are important when considering sedation assessment in children. This is particularly relevant in the pre-verbal child where it is often difficult to distinguish pain from agitation (Voepel-Lewis and Malviya 1998). It is imperative to identify whether a child's distress is caused by pain or anxiety because, although there is some degree of overlap between the two, treatment is different. Many scoring systems use an additional stimulus such a glabellar tap or response to loud voice to assess level of sedation. These scoring methods have been criticised for causing unnecessary disruption and further anxiety in children who are already subject to numerous unpleasant procedures. Therefore any sedation score using this method to assess over sedation would not be appropriate in children.

Sleep is an important factor in the recovery of a child in intensive care and the fewer interruptions to their normal sleep/wake patterns has been shown to improve and hasten

recovery. Therefore it would be advantageous for any sedation assessment method developed for use in children to take into consideration the sleeping child.

Intensive care units tend to be very busy and nursing staff are required to complete extensive documentation, therefore any sedation assessment method needs to be both easy and practical to use. It is also essential that any sedation assessment scale used is reproducible and consistent when used by different members of staff.

The assessment of level of sedation in a patient receiving neuromuscular blocking agents poses a difficult problem. Neuromuscular blocking agents are often indicated as adjuncts for sedation of critically ill patients requiring mechanical ventilation. Neuromuscular blocking agents do not provide any sedation or analgesia. Therefore, monitoring the level of sedation in these patients is essential to avoid the development of under sedation, which is particularly distressing in the paralysed patient (Cheng 1996). Currently there are no validated methods to assess level of sedation in a paralysed patient. Neurophysiological monitoring of the electroencephalogram involving the bispectral index is being investigated as an objective measure with which to assess level of sedation (Berkenbosch, Fichter et al. 2002).

1.5 Drug administration in children

1.5.1 The use of unlicensed medicines in children

'With regard to the availability of drugs of proven quality and adequate license for paediatric patients in hospital, dramatic shortcomings exist' (t Jong, Vulto et al. 2001)

A large number of drugs prescribed in children have not undergone trials in children and therefore are not specifically licensed for use in children. In addition, licensed drugs are often prescribed outside the terms of the product license with regard, for example, to age, route of administration and dose and is commonly described as being used 'off label' (Turner, Nunn et al. 1999; Conroy and Peden 2001; Lifshitz, Gavrilov et al. 2001). This problem is widespread and has been shown to exist within Europe and the United States. A study carried out in 5 European countries found that over two thirds of children admitted to hospital received drugs prescribed in an unlicensed or 'off label' manner (Conroy, Choonara et al. 2000). The use of unlicensed medicines in children has been studied specifically in neonates where the problem seems to be more extensive than in other paediatric groups (Conroy, McIntyre et al. 1999). These studies found that over 70% of neonates were prescribed a medicine that was either unlicensed or off label to be used in this patient group.

It has been demonstrated that there is an increased risk of adverse drug reactions in children who are prescribed unlicensed or off label medicines (Turner, Nunn et al. 1999; Choonara and Conroy 2002). Adverse drug reactions can be extrinsic (caused by errors in manufacturing, supply or prescribing) or intrinsic (caused by inherent properties of drugs). Until more is known and understood about the intrinsic properties of the drug it has been recommended that as far as possible the minimum effective doses are prescribed (Asscher, Parr et al. 1995). However, the problem surrounding the most effective dose to be used in children is evident in the numerous variations documented in paediatric formularies for the same drug. The following are all commonly used formularies that contain paediatric dosing recommendations, but there is no one standard formulary that is universally used.

British National Formulary

Alder Hey Book of Children's Doses

Guy's St. Thomas' and Lewisham Hospitals Paediatric Formulary

Melbourne Children's Formulary

Pediatric Dosage Handbook by Taketomo, Hodding Kraus.

Data Sheet Compendium

Medicines for Children

Midazolam Hydrochloride injection is licensed in adults as an intravenous sedative. When midazolam is prescribed for a child by any route it is used off label. In PICU midazolam is usually administered as a bolus dose or as a continuous infusion for the purposes of sedation when a child is mechanically ventilated. Midazolam has been used for other indications in children including seizure control and procedural sedation and by many different routes including rectal, nasal, oral and intramuscularly. In all these situations midazolam is being used off label.

1.6 Research in Children

1.6.1 Informed consent in medical research

'I would think that of all the professions, only in medicine would there be any sort of debate about whether people need to be told that they, their bodies, their body fluids, their emotions, or whatever were to be subjects of research' (Bratt 1997)

The question of obtaining informed consent from patients prior to inclusion in medical research is one that has been much debated recently. There is no doubt that informed consent should be obtained in virtually all research studies, the difficulty arises when, to obtain informed consent poses a problem and therefore should it be waived.

The declaration of Helsinki states that:

'In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subjects freely given informed consent, preferably in writing'.
(World Medical Association 1997)

Obtaining informed consent from children presents a grey area since in most cases an informed opinion cannot be obtained. Alderson and Montgomery (1996) have suggested that children above the age of 5 can and should play a greater part in decisions about their own health care. They state that children who can express a view should be given information, listened to and have their views taken into consideration when decisions about their health treatment are being considered. At 5 years of age, compulsory school age, children should be presumed competent. Paul (1997) has pointed out that as in adults, competence in children is not something that is merely present or absent. It may vary in

children of the same age, depending on when, where and how the question is asked, the cognitive capacities of the child at that time and the level of competence required.

A suggestion made by Morley (1997) that babies should only be enrolled in to studies from which parents have given consent, was also associated with the comment that this is likely to result in bias because the most difficult acute cases will not be enrolled.

Recently guidelines for the ethical conduct of medical research involving children have been published by the Royal College of Paediatrics, Child Health: Ethics Advisory Committee (2000).
The guidelines are based on six principles:

1. Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner.
2. Children are not small adults; they have an additional, unique set of interests.
3. Research should only be done on children if comparable research on adults could not answer the same question.
4. A research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal.
5. All proposals involving medical research on children should be submitted to a research ethics committee.
6. Legally valid consent should be obtained from the child, parent or guardian as appropriate. When parental consent is obtained, the agreement of school age children who take part in research should also be requested by researchers.

The guidelines state that children are unique as a research group since they are the only people in British Law on whose behalf other individuals may consent to medical procedures. Many children are vulnerable, easily bewildered and frightened and unable to express their needs or defend their interests. The point is made that research in children should only be undertaken if work with adults is clearly not feasible and where a choice of age groups is possible, to involve older children as opposed to younger children. Assessment of potential benefits must be made before embarking on any proposed

research, including an assessment of the severity of the problem and, how likely is the research to achieve its stated aims.

The guidelines state that legal valid consent must be informed and given freely. For consent to be given freely researchers must:

- Offer families no financial inducement, although expenses should be paid.
- Exert no pressure on families.
- Give them as much time as possible (some days for a major study) to consider whether to take part.
- Encourage families to discuss the project with – for example, their relatives, or primary health carers.
- Tell them that they may refuse to take part, or may withdraw at any time, even if they have signed a consent form.
- Say that they need not give a reason for withdrawing, although their reason may help the researchers and other children in the study.
- Assure them the child's patient treatment will not be prejudiced by withdrawal from the research.
- Encourage parents to stay with their child during procedures.
- Respond to families' questions, anxiety or distress throughout the study.

For consent to be informed, researchers must discuss with families: -

- The purpose of the research.
- Whether the child stands to benefit directly and, if so how; the difference between research and treatment.
- The meaning of relevant research terms (such as placebos).
- The nature of each procedure, how often or for how long each may occur.
- The potential benefits and harms (both immediate and long term).
- The name of a researcher whom they can contact with inquiries.
- The name of the doctor directly responsible for the child.
- How children can withdraw from the project.

Children who are critically ill and in intensive care pose a particularly difficult problem with regard to informed consent. They are often heavily sedated as part of their routine treatment and as such not in a position to give their consent to be involved in clinical research. Moreover, relatives, parents and/or guardians may not be available or may themselves not be in a position to give informed consent owing to the stressful nature of the situation. However, research is lacking in these particular situations and as such is vital to be undertaken.

1.7 Aims and objectives of the present study

Sedation is an essential part of therapy delivered to critically ill children in intensive care. The most commonly prescribed intravenous sedative within PICU is midazolam. Although this drug has been used extensively in children it remains unlicensed for use in critically ill children and therefore dosage regimens prescribed are often based on past experience rather than researched evidence. It is widely recognised that administration of sedation to the critically ill child is often poorly managed leading to over or under sedation. This has arisen owing to a lack of knowledge of the pharmacokinetics and pharmacodynamics of midazolam in children of different ages with different medical complications. In addition sedation assessment is hampered by the absence of a validated sedation assessment scoring system that can be used in critically ill children. Without a robust method of assessment administration of safe and effective sedation is difficult.

1.7.1 Aims

- To develop and validate an observational sedation assessment scale that is appropriate for use in paediatric intensive care.
- To investigate the pharmacokinetic and pharmacodynamic characteristics of midazolam and its metabolites in critically ill children.
- To investigate the effect disease states have on the pharmacokinetics and pharmacodynamics of midazolam in critically ill children.

1.7.2 Objectives

- To compare and contrast two observational sedation assessment scales for reproducibility and practical use in critically ill children.
- To investigate any correlation between midazolam dose and level of sedation in critically ill children and quantify the effect that various disease states have on this relationship.

- To investigate any correlation between midazolam plasma concentration and level of sedation in critically ill children and the effect that various disease states have on this relationship.
- To investigate the clearance of midazolam in critically ill children and the effect that various disease states have on clearance.
- To investigate the production of midazolam metabolites in critically ill children and the effect of disease state upon metabolite production.

EXPERIMENTAL METHODS

1 Development and validation of a sedation assessment scale

1.1 Introduction

The development and validation of a sedation assessment scale was a prospective study, undertaken at the Paediatric Intensive Care Unit (PICU) at Birmingham Children's Hospital, Birmingham, England.

This part of the study was designed to develop, compare and validate two different types of observational sedation assessment scales and it consisted of four stages:

- Development of the sedation assessment scales.
- Assessment of the reproducibility of each sedation assessment scale.
- Assessment of the practicality of each sedation assessment scale.
- Assessment of the long-term reliability of the sedation assessment scale.

1.2 Sedation scales

1.2.1 Scale 1

The first assessment scale comprised five levels of sedation with a description of each level of sedation (Appendix 1). This scale was already in use at Birmingham's Children Hospital PICU prior to initiation of the study. This sedation scale however had not undergone any validation and had been developed from sedation scales used previously in adult critically ill patients. This sedation scale was simple in design and required a single overall assessment of the patient to produce a value of level of sedation. No development of this scale was felt necessary before inclusion into the study.

1.2.2 Scale 2

The sedation assessment scale 2 was developed as part of this project in collaboration with the nursing staff at Birmingham Children's Hospital. The design features that were to be included into the sedation assessment scale were as follows:

- Appropriate for the critically ill child
- Not reliant on verbal communication for assessment
- Appropriate for children receiving mechanical ventilation
- Suitable for use in all ages of children
- Exclusion of an additional painful stimulus
- Easy and practical to use
- Inclusion of parameters associated with sedation assessment previously cited in the literature
- Objective in its assessment
- Highlights the importance of sleep

In comparison to sedation assessment scale 1, scale 2 was more complicated in design (Appendix 2). It consisted of 5 patient parameters about which an assessment had to be made including; facial expression, eyes, body movement, agitation and respiration. To make an overall assessment using scale 2 it was necessary to make assessments of each individual parameter and produce an overall numerical score of sedation.

Each sedation assessment scale was studied consecutively for a period of 12 weeks, in children requiring sedation assessment as part of their routine monitoring. This part of the study was designed to assess the reproducibly of each sedation scale. At the end of this part of the study nursing staff were asked to complete a questionnaire regarding both sedation scales in order to evaluate the ease of use and practicality of each scale. In addition to the questionnaire a number of face-to-face interviews were held with members of the nursing staff and were undertaken to gain additional information about sedation assessment. A follow up study was undertaken 12 months after validation of the sedation scales to assess the long-term reproducibility of the scales.

1.3 Subjects

Male and female patients aged 0 days to 18 years were entered into the study. Patients receiving neuromuscular blocking agents were excluded from the study. The Local Ethical Committee was approached to seek advice regarding requirement of ethical approval for this study to proceed. Ethical approval was not deemed necessary as the study was purely observational in design and did not alter patient care or treatment. However, it was felt that information for parents and/or carers should be made available regarding the study's aims and objectives. An information leaflet was produced for parents and a poster displayed on the parent notice board providing additional information about the study if required (Appendix 3).

1.4 Reproducibility of sedation assessment scales

All PICU staff were informed of the study and written information was circulated to everyone incorporating study aims, objectives and design (Appendix 4). Sedation assessment scale 1 which had been in regular use on the unit prior to the study was placed at every bed station. Nursing staff were asked to carry out sedation assessments as frequently as was deemed necessary for individual patients. To validate the scales for reproducibility two people had to undertake a simultaneous independent sedation assessment. In all cases one assessor was the nurse responsible for the care of the patient and the second was either myself or a second nurse. After a period of 6 weeks sedation assessment scale 2 was introduced to the unit and scale 1 withdrawn. A two-week run in period of the second sedation scale was undertaken before commencement of data collection in order to allow staff to become familiar with the scale. The validation procedure was repeated as for the scale 1. For each sedation assessment made, patient age and reason for admission were recorded. Each sedation assessment scale was studied for a period of 6 weeks and was used in all children requiring sedation assessment as part of their routine monitoring. All information collected was entered onto a relational database (Access© Microsoft). Kappa and weighted kappa values were used to analyse the extent of agreement between assessors for each individual sedation assessment scale (Carletta 1996; Uebersax 2000). The kappa coefficient measures agreement among a set of raters making category judgements and corrects for chance agreement. Weighted kappa was developed to take into consideration the extent of disagreement between raters (Cohen 1968).

1.5 Assessment of practicality of sedation assessment scales

1.5.1 Nursing staff self-completion questionnaire

At the end of the 12 week validation period of the sedation scales, all PICU nursing staff were asked to complete a questionnaire (Appendix 5) about both observational sedation assessment scales. The questionnaire was designed to establish which assessment scale staff favoured and the reasons for this. The questionnaire was piloted in 5 members of the nursing staff, which included junior and senior members of staff. The 5 nurses were asked to critically appraise the draft questionnaire with regard to:

- Time taken to complete
- Clarity of question
- Suggest further questions, which would be useful to include
- Relevance of included questions

All 5 nurses said the questionnaire took no longer than 20 minutes to complete. Most questions were clear but a suggestion was made to move the sedation assessments scales, which were located at the end of the questionnaire nearer to the appropriate questions. The questionnaire was therefore split into 2 sections, part 1 regarding scale 1 and part 2 regarding scale 2 and the relevant sedation scale was relocated at the beginning of the appropriate section. Most questions were thought to be relevant but again a suggestion was made to include a question about nurses PICU experience.

The questionnaire included 33 questions of which 20 involved selecting a single answer from preset options. A further 7 questions required multiple answers and included a total of 62 potential questions. The remaining 5 questions were open questions and were included to give the nurses an opportunity to express comments about the scales with regard to any modifications that would make the scales easier to use or aid clarification.

The questionnaire included in its design some repetition of questions to confirm consistency of answers, for example questions 4 and 16 were repeated using the lickert scale in questions 8a and 18l. One other design feature in the questionnaire was to alter similar questions to ensure accurate reading on behalf of the person completing the questionnaire, for example questions 7 and 17 were very similar. Questions were included about the time taken to make an assessment; clarity of the wording used in each scale and the usefulness of each in ventilated, self-ventilating and paralysed children. Staff were also asked to comment on the subjectivity of each scale and the accuracy of each in the measurement of level of sedation. Individuals were encouraged to make comments in the questionnaire with reference to any modifications that could be made to the scales to improve for example accuracy, clarity or ease of use.

A 3-week deadline to complete the questionnaire was detailed in the covering letter sent out with the initial questionnaire. All questionnaires were coded and a second questionnaire was sent out to members of staff who had not completed the initial questionnaire by the dead line. A reminder was sent out to all members of staff after a further two weeks to encourage staff to complete the questionnaire.

All information collected was entered onto a relational database (Access© Microsoft).

1.5.2 Face-to-face nursing staff interviews

The questionnaire was followed up, by conducting short semi-structured face-to-face interviews (Appendix 6) with a representative sample of the nursing staff at Birmingham Children's Hospital. The purpose of the interviews was two fold:

- Firstly to gain further information about sedation assessment in PICU.
- Secondly to establish an opinion from the non-responders of the questionnaire regarding preference of sedation scale.

The interviews were designed to take no more than 10minutes to complete. It was intended to repeat only a very few questions from the questionnaire. The interview consisted of 9 questions of which 5 where closed questions. The remaining 4 questions were open in design, encouraging an opinion to be expressed and were not included in the questionnaire. The subject matter in these questions included; particular children who were difficult to sedate effectively, training needs regarding sedation assessment perceived necessary, the influence of parents/carers upon effective sedation and further research required in the area of sedation assessment.

1.6 Assessment of the long-term reproducibility of sedation assessment scale 2

From the results of the sedation assessment validation study, the questionnaire and the interviews, it was decided that sedation assessment scale 2 should be incorporated into standard nursing protocol and should be used regularly at Birmingham Children's Hospital PICU. Therefore, a follow up study was conducted 12 months after the inclusion of scale 2 into Birmingham Children's Hospital PICU protocol to assess the reproducibility of sedation scale 2 over time. The validation of the sedation assessment scale study was repeated using only scale 2 and independent, blinded sets of sedation scores were collected as previously described. Data was collected over a 6 week period.

2 Midazolam pharmacokinetic and pharmacodynamic study

2.1 Introduction

This study was a prospective pharmacokinetic and pharmacodynamic study undertaken at the Birmingham Children's Hospital, Paediatric Intensive Care Unit. The study involved children who were critically ill receiving mechanical ventilation. The study consisted three stages:

- Recruitment of patients to the study after obtaining informed consent.
- Collection and analysis of blood samples to measure plasma concentration of midazolam and its metabolites.
- Analysis of the data and correlation of midazolam plasma concentration with level of sedation.

Data collection for the study was undertaken over a 12 month period.

2.2 Patient population

Critically ill male and female mechanically ventilated patients aged 0 days to 18 years receiving midazolam as part of their routine medication, were entered into the study. The Local Ethics Committee granted ethical approval for the study. Informed consent was obtained from a parent or legal guardian before patients were entered into the study. Patients were excluded from the study, who were:

i) obese i.e. patients who were more than 10% over their ideal body weight.

ii) patients who had already been recruited to another study.

2.3 Study procedures

The study was explained to all medical and nursing staff working within PICU using a combination of written information (Appendix 7) and verbal information presented at meetings. The researcher identified patients for the study on a daily basis. Initially it was hoped that patients would be recruited on day 1 of admission to PICU. However, it soon became apparent that this was a most stressful time for parents and carers. Therefore, it was decided to approach most parents/carers from day 2 post admission. The study and

procedures were explained in full to parents/carers before the children were entered into the study.

A copy of the signed consent form (Appendix 8) and the information sheet (Appendix 9) were given to parents/carers. A child consent form (Appendix 10) and a child information leaflet (Appendix 11) were also produced for the study. Once a patient had been recruited to the study the nurse and doctor responsible for the care of the child was informed of their inclusion into the study by verbal communication by myself.

The pharmacokinetic study coexisted with patient care. That is, midazolam was prescribed as part of a patient's routine care and recruitment to the study was made after the decision to initiate midazolam therapy. The midazolam infusion rate and any supplemental midazolam bolus doses were recorded. There was no restriction upon change of midazolam dose or the use of bolus dosing in patients recruited to the study and there was no restriction on the administration of additional sedative agents to the patient's drug regimen if deemed necessary. However, all changes in midazolam infusion rate and additional drugs administered to the patient were documented in full.

2.4 Documentation

Concomitant medication received during the study was recorded including route of administration, frequency and dosage. Weight (kg) was recorded for each patient. Heart rate and blood pressure were recorded at least 6 times a day. Midazolam infusion rate and any bolus doses administered to the patient were recorded together with sedation scores. Biochemistry results were recorded together with haemoglobin count and any drug levels taken. All of the above were routinely documented by the nursing staff as part of their daily observations.

2.5 Sampling

Blood samples were taken from patients in order to measure plasma concentrations of midazolam using High Performance Liquid Chromatography (HPLC). It was hoped that blood samples could be taken at the start of a midazolam infusion in every patient recruited to the study. This proved very difficult to achieve for a number of reasons. Midazolam infusions are usually started on day 1 of admission and as previously stated it was decided to approach parents about the study from day 2 of admission. Secondly, it was necessary for the researcher to be present to arrange blood samples to be taken on commencement of the midazolam infusion. This proved impractical. Therefore samples were taken on a daily basis after a patient had been recruited to the study. The sample size was 1ml of blood. In patients younger than 1 month, 1 sample was taken each day. In patients over one month of age up to two samples could be taken each day. In patients receiving a continuous midazolam infusion samples were taken after a period of 6 hours without a dose alteration and in the absence of any bolus doses. This was in order to calculate midazolam clearance, which requires an assumed steady state for calculation. On discontinuation of the midazolam infusion two samples were taken within a 24 hour period. Where possible a sample was also taken at 48 hours if access was still available. Samples were taken from the arterial line by the nurse caring for the patient. If arterial access was unavailable samples were not taken from any other line. The blood samples were collected in heparinised tubes. The samples were centrifuged to separate off the plasma at approximately 1500G for 10 minutes at 4°C. The plasma was stored at -70°C until analysis. All samples were analysed within an eight week period of being taken.

2.6 Data analysis

Data base

All information collected was entered onto a relational database (Access© Microsoft). The database consisted of six forms, which were all linked by a unique identification reference. The individual forms contained information as follows:

- Demographic data about each patient
- Medications that were prescribed as required

- Intravenous medications that were prescribed on a regular basis
- Other medications prescribed on a regular basis
- Information about an individual blood sample
- Biochemistry results for individual patients

Statistical tests

The statistical tests used during the pharmacokinetic analysis included non-parametric tests. The Pearson coefficient was used to investigate correlations between :

- midazolam plasma concentration and level of sedation
- midazolam plasma concentration and dose of midazolam
- dose of midazolam and level of sedation

The Mann U Whitney test was used to investigate significant differences between midazolam clearance and the extent of production of the metabolites of midazolam with respect to different ages of children and different disease state.

Units used in documentation

Plasma concentrations measured in nanograms /millilitres (ng/ml)
Midazolam infusion rate prescribed in micrograms/kilogram/minute (mcg/kg/min)
Morphine infusion rate prescribed in micrograms/kilogram/hour (mcg/kg/hr)
Midazolam clearance measured in millilitres/kilogram/minute (ml/kg/min)

3 Analytical methods and materials

3.1 General introduction

The overall aim of the analytical part of this study was to investigate the pharmacokinetic and pharmacodynamic parameters of midazolam in critically ill children and in particular, the effect that disease states had on the metabolism of midazolam in this patient group. Analysis was carried out on patient's plasma using High Performance Liquid Chromatography (HPLC). The metabolites of midazolam 1-hydroxymidazolam and 4-hydroxymidazolam were also investigated.

3.2 Analytical techniques

Analytical methods for the quantification of drugs and their metabolites in biological samples play a crucial role in the interpretation of pharmacokinetic data. Therefore it is imperative to validate any analytical method used with regard to selectivity, precision, accuracy, recovery, limit of detection, and limit of quantification (Bressolle, Bromet-Petit et al. 1996). Determination of the pharmacokinetic and pharmacodynamic properties of midazolam in critically ill children required a suitably selective and sensitive technique owing to the restriction in blood volume available and the comparatively smaller doses of midazolam administered. Previous techniques for the determination of midazolam and its metabolites include, gas chromatography (GC), HPLC and mass spectrometry (MS).

De Vries, Rudi et al. (1990) compared HPLC, GC and GC-MS for the determination of midazolam in human plasma and concluded that GC was the preferred routine plasma assay with a sensitivity of 20ng/ml. However, the present study required the investigation of both midazolam and its metabolites. Compounds that are to be studied by GC methods need to be thermally stable as substances are examined in the vapour phase (Lindsay 1997). Metabolites are generally not only unstable in comparison to the parent compound but they are generally more polar than the parent compound and therefore show poor chromatographic behaviour by GC, being prone to tailing. HPLC is a more versatile method than GC because both the stationary phase and the liquid phase can interact with the sample molecules and as such can achieve much more difficult separations. It was

therefore concluded that the HPLC technique using ultra violet (UV) detection was the preferred method for use in the present study.

Puglishi, Pao et al. (1985) used HPLC for the analysis of midazolam and it metabolites. An isocratic mobile phase of methanol-acetonitrile-0.01M potassium phosphate buffer (pH 7.4) – tetrahydrofuran (30:28:40:2) was employed with UV detection at 254nm. Drug recovery using this method was 94.5± 7.1% and greater than 89% for the metabolites. The sensitivity of the assay was 50ng/ml of plasma for all compounds. The extraction method used diethyl ether-methylene chloride. However, this technique required 1ml of plasma for analysis and therefore was inappropriate for the present study.

Eeckhoudt, Desager et al. (1998) used HPLC for the analysis of midazolam and 1-hydroxymidazolam from human biological samples. However, again the assay required 1ml of plasma, which made it inappropriate for use in small children. In addition a gradient mobile phase was used making the assay more complex. Kanazawa, Nishimura et al. (1995) used HPLC mass spectrometry to determine the pharmacokinetic behaviour of midazolam in pig plasma. The method was very sensitive having a lower limit of detection from plasma of 1 to 2ng/ml. However, 5ml of pig plasma was required for the assay and again inappropriate for this study.

The quantitative HPLC analysis eventually adopted was based upon a previous method developed by Lee and Charles (1996), which used HPLC for the routine monitoring of midazolam and 1-hydroxymidazolam in premature neonates. The quantity of plasma used by Lee for the analysis was only 100µl and the assay's limit of detection was 25ng/ml. The method used an isocratic mobile phase of acetonitrile:tetrahydrofuran:phosphate buffer (0.01M pH6.7) (35:5:60) and UV detection at 220nm. Extraction of plasma was performed using 10% isopropanol in dichloromethane (DCM) followed by a back extraction into phosphoric acid. The internal standard used was climazolam.

3.3 Determination of midazolam and its metabolites in plasma by reverse phase HPLC

3.3.1 Introduction

The following section describes the method developed to separate midazolam and its metabolites, following the extraction of these compounds from small sample volumes of human plasma.

3.3.2 Chromatography.

The method was developed on a HPLC - Spectra Physics liquid chromatograph. The system consisted of a degasser SCM 400, a pump P2000, an autosampler AS3000 and a fixed length ultra-violet absorption detector 1000. A Chromquest 3 W-060 workstation and a Dell 600PC, 600MHz Intel Pentium III processor was used for integration.

Reverse phase chromatography allows a number of advantages over normal phase chromatography. The method has a broad scope and allows samples with a wide range of polarity to be separated. Moreover, metabolites are generally more water-soluble than the parent drug and therefore elute earlier without interfering with the separation of the parent drug. One of the disadvantages with reverse phase chromatography is that many of the columns using a silica-bonded phase are stable only at pH ranges between 3 and 8. Therefore a Phenomenex Luna 5μm C18 (2) 150 x 4.60mm column together with a guard column C18 (ODS octadecyl) 4mm x 3.00mm ID was chosen for the stationary phase, which is stable from pH 1.5 to 10. Other stationary phases were tested including a Hypersil 5ODS C18 25cm x 4.6mm column but were found to give poor peak shape and greater peak tailing in comparison to the Luna column.

The mobile phase consisted of ammonium acetate 0.01M (pH 7.01): acetonitrile:tetrahydrofuran (60:27.5:12.5). Originally a mobile phase consisting of ammonium acetate (1M):acetonitrile:THF (60:35:5) was tested but it was found that the metabolites did not achieve full separation. Therefore the following mobile phases were tried to separate the metabolites completely:

Ammonium acetate 0.01M:acetonitraile:THF (60:37.5:2.5), (60:32.5:7.5), (60:30:10) and (60:27.5:12.5). By increasing the amount of THF the metabolites were completely separated and peak shape was not affected by reducing the amount of acetonitrile.

3.3.3 Selection of internal standard

The use of the internal standard method has a number of advantages, in that any variations in injection volume, detector sensitivity or chromatographic changes are accounted for by the internal standard. This method does not require an exact volume to be injected each time and therefore produces better precision than the external standard method. A number of internal standards were evaluated for use in the present study, including diazepam, flurazepam, clonazepam and alprazolam (Figures IX, X, XI and XII respectively). The chemical structure of these potential internal standards can be compared with that of the chemical structure of midazolam (Figure VIII). Under the chromatography conditions developed for the separation of midazolam, 1-hydroxymidazolam and 4-hydroxymidazolam; only clonazepam and alprazolam, were shown to have good separation, resolution and peak shape. However, during the extraction from plasma it was found that clonazepam was not removed by this process, therefore alprazolam was found to be the most suitable internal standard.

Figure VIII Chemical Structure of Midazolam.

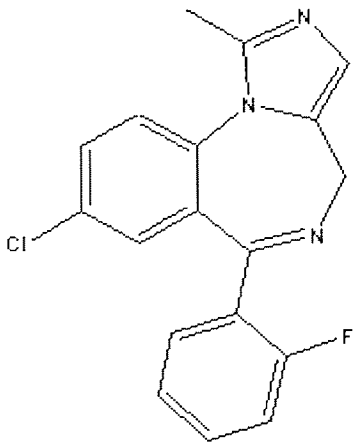


Figure IX Chemical Structure of Diazepam

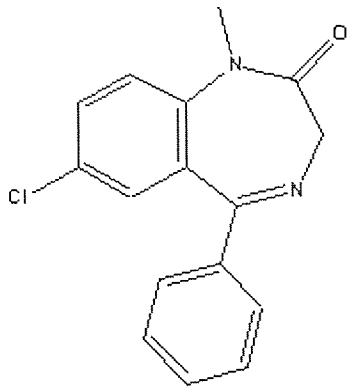


Figure X Chemical Structure of Flurazepam

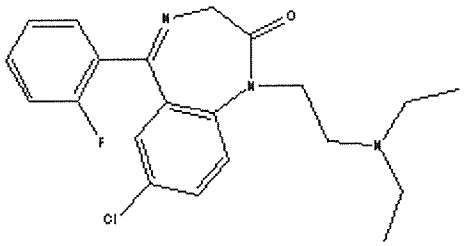


Figure XI Chemical Structure of Clonazepam

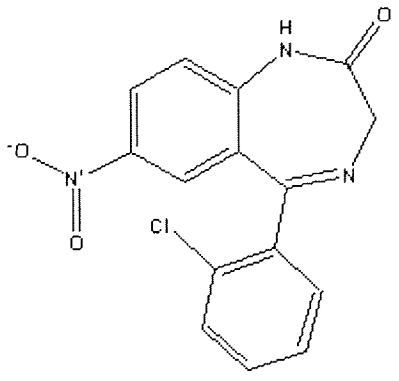
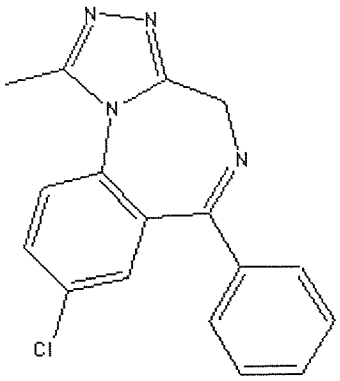


Figure XII Chemical structure of Alprazolam



3.3.4 Extraction of midazolam and metabolites from human plasma

The extraction method was based on a method developed by Lee and Charles (1996). The plasma was initially extracted using isopropanol (10%) and DCM followed by a second extraction using hexane. However, preliminary experiments found that drug recovery was reduced using hexane and this part of the Lee and Charles extraction was omitted. This HPLC technique was to be applied to the assay of small volume samples and as such it was essential to ensure maximum sensitivity by achieving a high recovery extraction. Preliminary experiments also determined that isopropanol did not improve or reduce the recovery process and therefore DCM was used as a sole extracting solvent in the present study. This simplified the process and the number of potentially contaminating materials.

3.3.5 Sample treatment procedure

The aim of extracting a plasma sample is to recover maximum quantities of the components of interest in a suitable solvent solution that is free from interfering compounds such as proteins. The use of a guard column not only preserves the life of the column it can prevent larger compounds entering the column and interfering with the analysis.

Extraction of midazolam and its metabolites from 0.5ml plasma was undertaken by the addition of 100µl of 1M sodium hydroxide and 20µl of internal standard (10mcg/ml) to

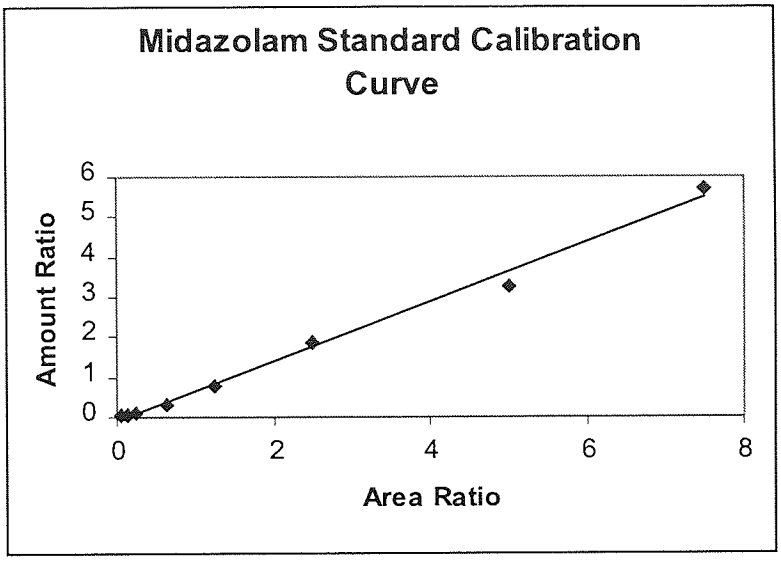
15ml capacity glass screw capped tubes. The mixture was extracted twice using 2mls and 3mls of DCM respectively by vortex mixing for 2 minutes each. After centrifugation (2000g for 5 minutes) the organic layer was decanted into a conical tube. A white flocculant material appeared in the organic layer after mixing. This has also been described previously and was thought to be due to minor emulsification of the two liquid phases and was removed after centrifugation steps (Odou, Robert et al. 1997). The organic layer was evaporated to dryness under a steady stream of nitrogen. In preliminary experiments the residue was dissolved in 1ml of 0.02M orthophosphoric acid and 7µl 1M sodium hydroxide was then added to the residue. However, it was found that this method opened up the imidazole ring and gave a split peak of midazolam on the resulting chromatogram. Therefore in the method adopted for this study the residue was dissolved in 175µl of mobile phase and this eliminated the split peak effect. A 50µl aliquot was injected onto the column. Generally if a solvent other than the mobile phase is used to re-dissolve the residue loss of efficiency and broadening of peaks is seen. This occurs because as the sample injected moves down the column, sample molecules at the edges of the injected band are in contact with the mobile phase that has a composition different to that of the bulk sample. This can result in the molecules at the band edge travelling at a different speed to that of the rest of the sample, resulting in spreading or splitting of the peaks.

3.3.6 Standard calibration curves

Standard calibration curves in the range of 25ng/ml to 3000ng/ml were prepared by adding known amounts of midazolam, 1-hydroxymidazolam and 4-hydroxymidazolam to drug free plasma. Samples were analyzed as described and the peak area ratios of all compounds to the internal standard were plotted against the corresponding concentrations. A typical specimen standard curve is presented in figure XIII.

The recovery of midazolam, its metabolites and the internal standard were estimated by comparing the peak area obtained from the injection of an extracted sample with that of a solution containing the same amount of compound. The inter and intra assay precision were determined for all compounds. Coefficients of variation (CV) for calculation of assay precision were determined from the ratio of the standard deviation to the mean.

Figure XIII. Typical standard calibration curve for midazolam over the concentration range 25ng/ml to 3000ng/ml



The Amount Ratio (y axis) is the ratio of the amount of midazolam to internal standard.

The Area Ratio (x axis) is the ratio of the area of midazolam to internal standard.

The gradient of the line is 1.342

The intercept of the line is 0.132

Multiple correlation coefficient (coefficient of determination) r^2 = 0.993

3.3.7 Assay Specifications

Chromatograms of drug free plasma, spiked plasma and plasma from patients receiving midazolam are shown in figures XIV, XV, XVI and XVII respectively.

Midazolam, 1-hydroxymidazolam, 4-hydroxymidazolam and the internal standard were all well resolved, with retention times of 10.9, 7.8, 6.9 and 6.1 respectively. The minimum detectable concentration (defined as a peak height, three times baseline noise) in a 50ul sample was 25ng/ml for each compound. All calibration curves showed linearity for midazolam 1-hydroxymidazolam and 4-hydroxymidazolam in plasma (r^2=0.99). The inter and intra assay precision data for drug and metabolites in plasma are summarized in tables IV, V and VI which include their coefficients of variation.

The assay developed for the present study was shown to be selective, as it was free from chromatographic interference from endogenous materials and other drugs administered regularly to critically ill children including the following:

Dobutamine hydrochloride
Dopamine hydrochloride
Rocuonium bromide
Adrenaline acid tartrate
Milrinone (as lactate)
Sodium nitropruside
Gentamicin (as sulphate)
Vancomycin (as hydrochloride)
Amoxycillin (sodium salt)
Cefuroxime (sodium salt)
Cefotaxime (sodium salt)
Ceftazidime (as pentahydrate) with sodium carbonate
Amphoteracin (as a complex with sodium chloesteryl sulphate)
Frusemide (as hydrochloride)
Ranitidine (as hydrochloride)
Flucloxacillin (sodium salt)
Propofol (emulsion)
Atracurium besylate
Morphine sulphate
Heparin sodium
Metronidazole sodium salt
Phenytoin sodium
Erythromycin (as lactobionate)

Table IV Intra and inter day assay coefficients of variation for midazolam (n=5)

Concentration (ng/ml)	Intra assay (CV)	Inter assay (CV)
50	8.29	9.55
500	9.36	9.30
2000	3.55	6.27

Table V Intra and inter day assay coefficients of variation for 1-OH (n=5)

Concentration (ng/ml)	Intra assay (CV)	Inter assay (CV)
50	11.37	11.88
500	11.51	10.91
2000	2.77	5.00

Table VI Intra and inter day assay coefficients of variation for 4-OH (n=5)

Concentration (ng/ml)	Intra assay (CV)	Inter assay (CV)
50	20.55	11.32
500	12.2	15.91
2000	4.32	6.55

3.3.8.Materials and equipment

The following is a list of all the materials and equipment used in the assay.

Column – Phenomenex Luna 5Um C18 (2) 150x 4.60mm
Phenomenex Guard column C18 (ODS octadecyl) 4mmx3.00mm ID

Solvents obtained from CEAC solvent stores
Methanol HPLC grade
Acetonitrile HPLC grade
Tetrahydrofuran HPLC grade
Dichloromethane HPLC grade

Standards
Midazolam and Alprazolam forensic grade obtained from Sigma

Metabolites:

1-hydroxymidzolam-8-chloro-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine-1-methanol
Molecular formula C18H13ClFN3O
Molecular weight 341.8

4-hydroxymidazolam-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-4-ol.
Molecular formula C18H13ClFN3O
Molecular weight 341.8
donated by Roche Pharmaceuticals, Roche Products Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire.

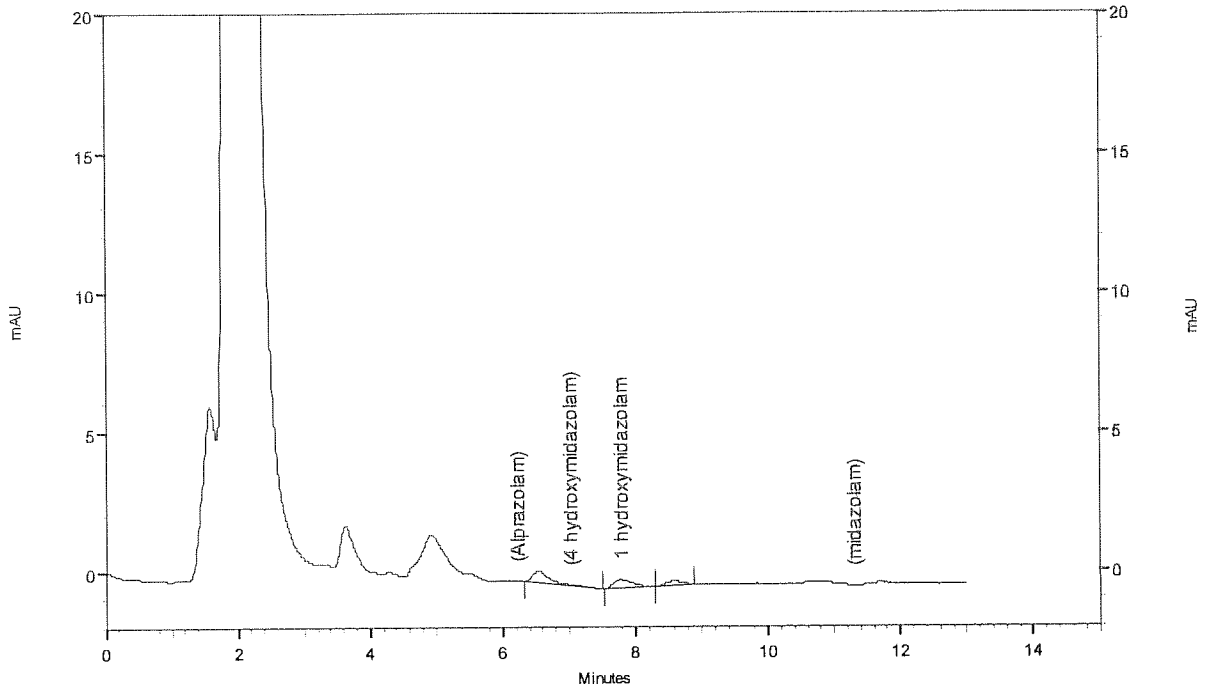
Reagents
Ammonium acetate crystals from Sigma
Sodium hydroxide crystals from Sigma
Double distilled water

Equipment
Jenway pH meter
Stuart Scientific Blood Tube Rotator SB1 from Fisher
Sanyo Gallenkamp Mistral 3000i centrifuge
Tecam SC3 Sample concentrator
Glass screw capped testubes 100x16mm fitted with rigid plastic caps with inert PTFE liners and rubber discs from Fisher
Clarified PP Conical glass drying tubes 115x16mm screw cap non sterile
Disposable glass pastuer pipettes 230mm from Fisher
Autosampler vials from Chromacol 03FISV 300ul fixed insert screw top vial
9SC (B) 8Rti lids – 8mm screw cap – blue w/neck Teflon/ rubber.
Gilson pipettes 20,100, 200, 1000, 5000.
Lithium heparin 2ml vials for blood collection.

3.3.9 Examples of chromatogram

Figure XIV is an example of a chromatogram obtained from a blank plasma extraction.

Figure XIV An example of HPLC chromatogram for a blank plasma extraction



Figures XV, XVI and XVII are examples of chromatograms obtained from spiked plasma containing 50ng/ml, 500ng/ml and 2000ng/ml each of midazolam, 1-hydroxymidazolam and 4-hydroxymidazolam respectively.

Figure XV HPLC chromatogram for plasma containing 50ng/ml of midazolam 1-hydroxymidazolam and 4-hydroxymidazolam and 400ng/ml of alprazolam

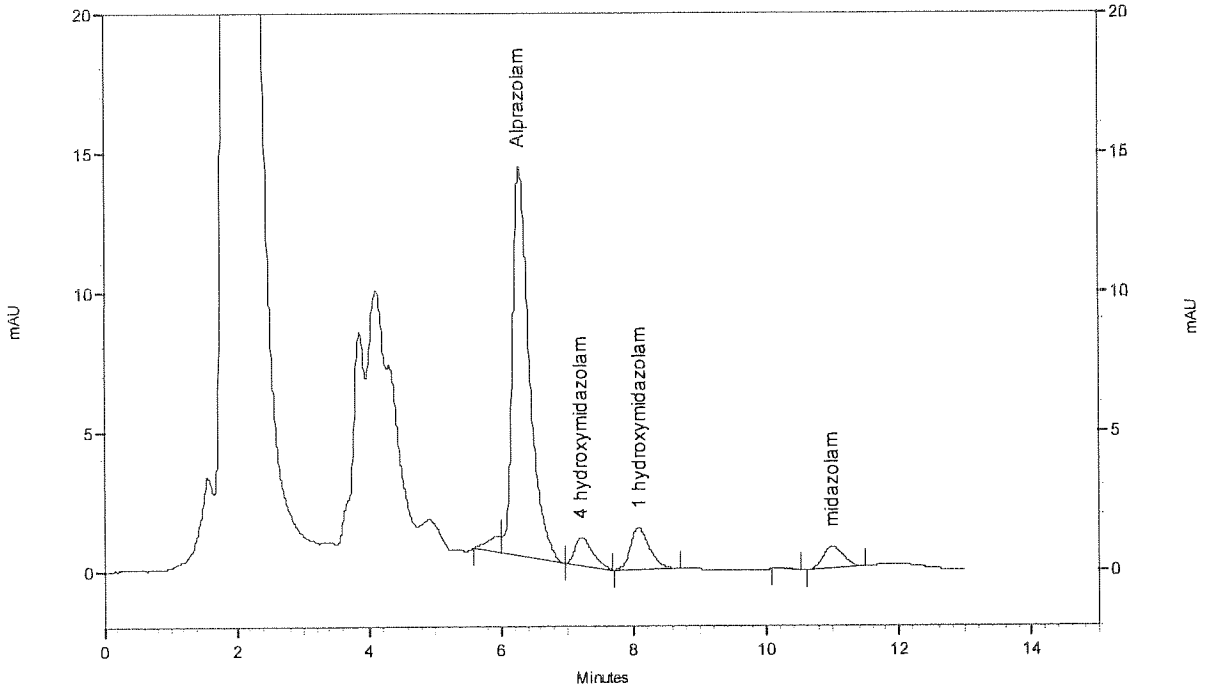


Figure XVI HPLC chromatogram for plasma containing 500ng/ml of midazolam 1-hydroxymidazolam and 4-hydroxymidazolam and 400ng/ml of alprazolam

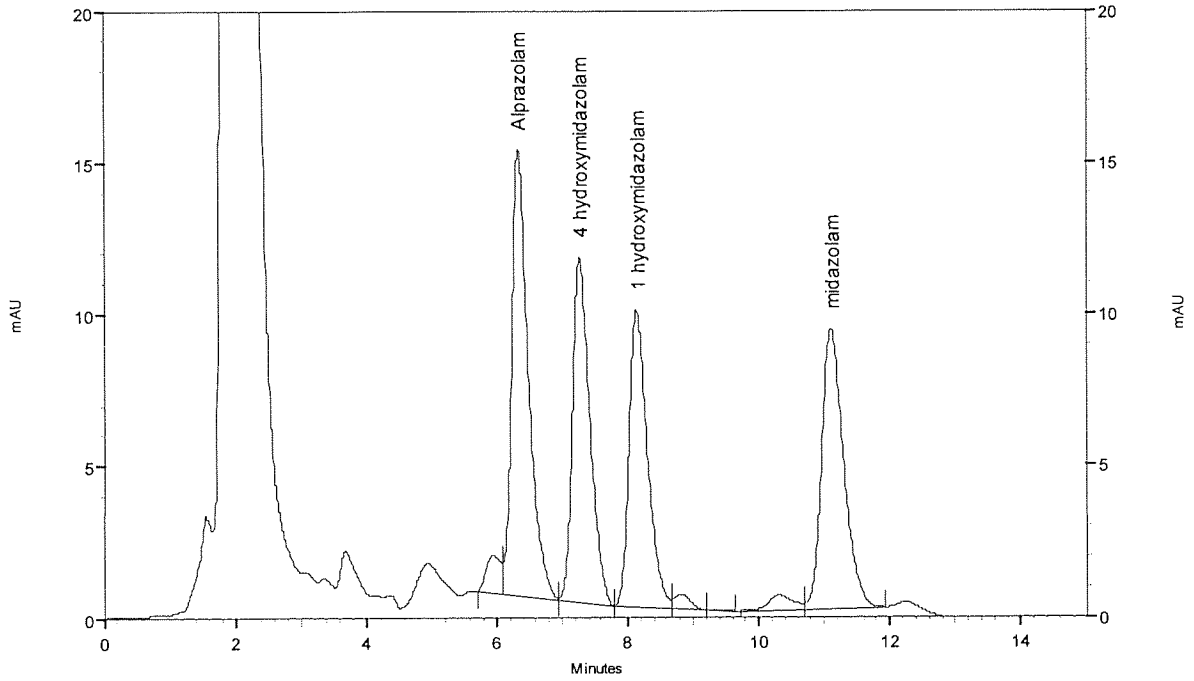


Figure XVII HPLC chromatogram for plasma containing 2000ng/ml of midazolam 1-hydroxymidazolam and 4-hydroxymidazolam and 400ng/ml of alprazolam

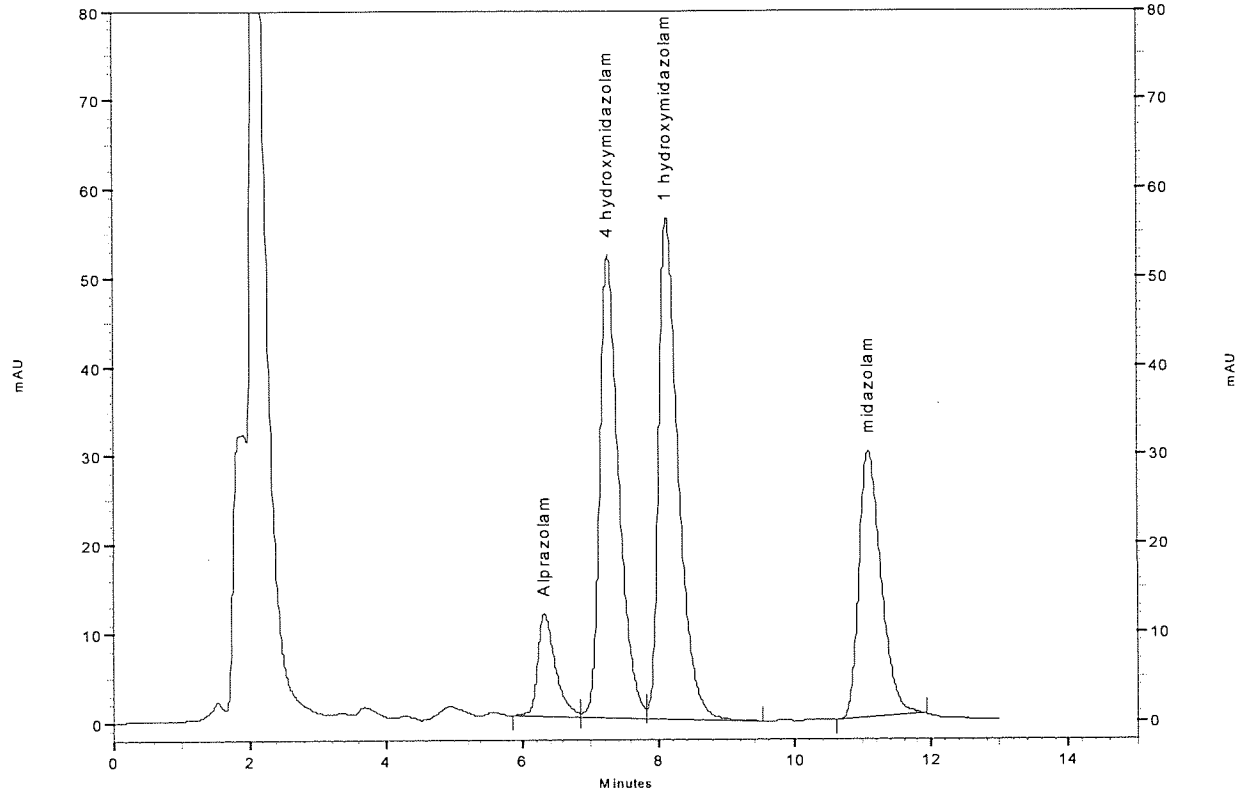


Figure XVIII (a and b) are examples of chromatograms obtained form patient plasma containing midazolam, 1-hydroxymidazolam and 4hydoxymidazolam.

Figure XVIIIa Examples of HPLC chromatograms for patient plasma containing midazolam, 1-hydroxymidazolam and 4-hydroxymidazolam and 400ng/ml of alprazolam as internal standard

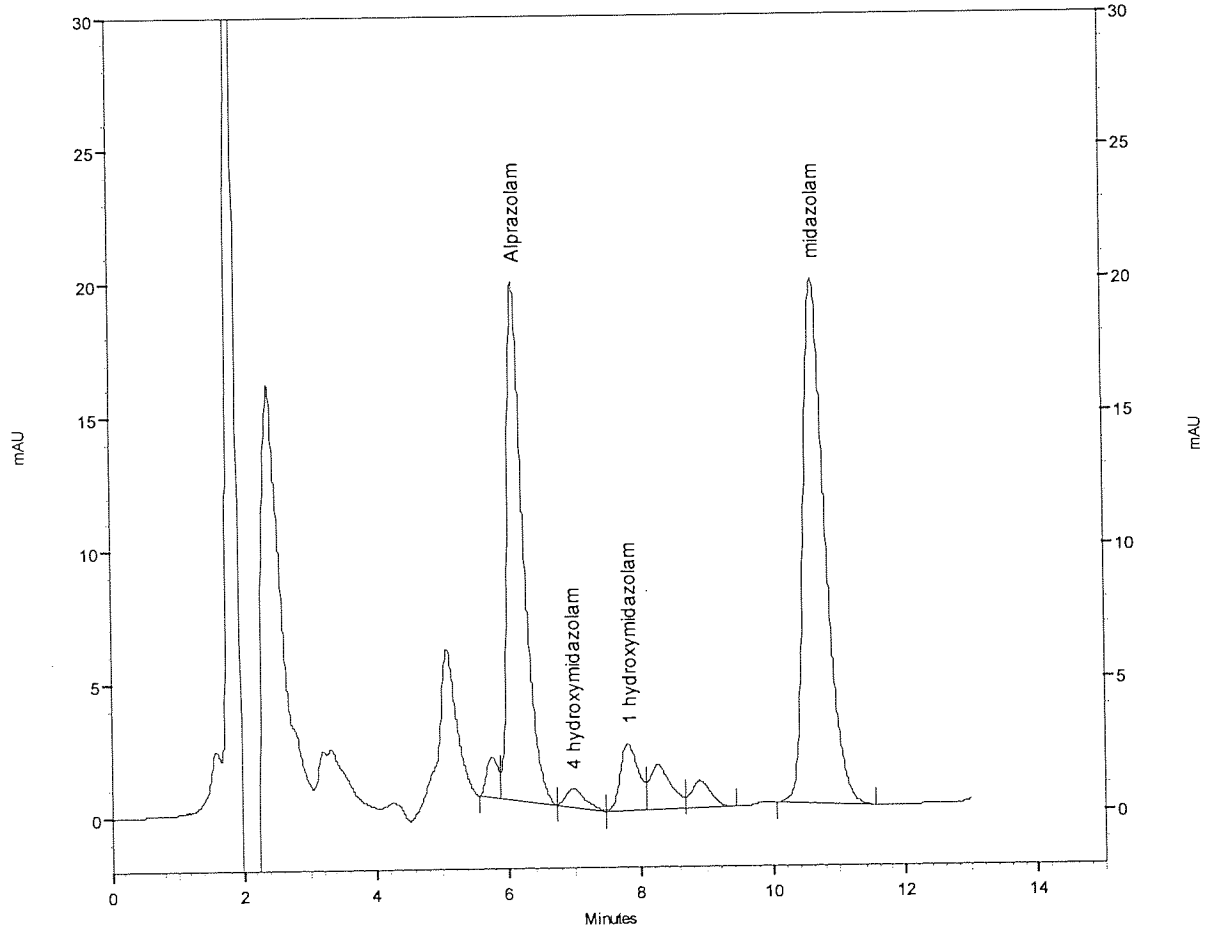
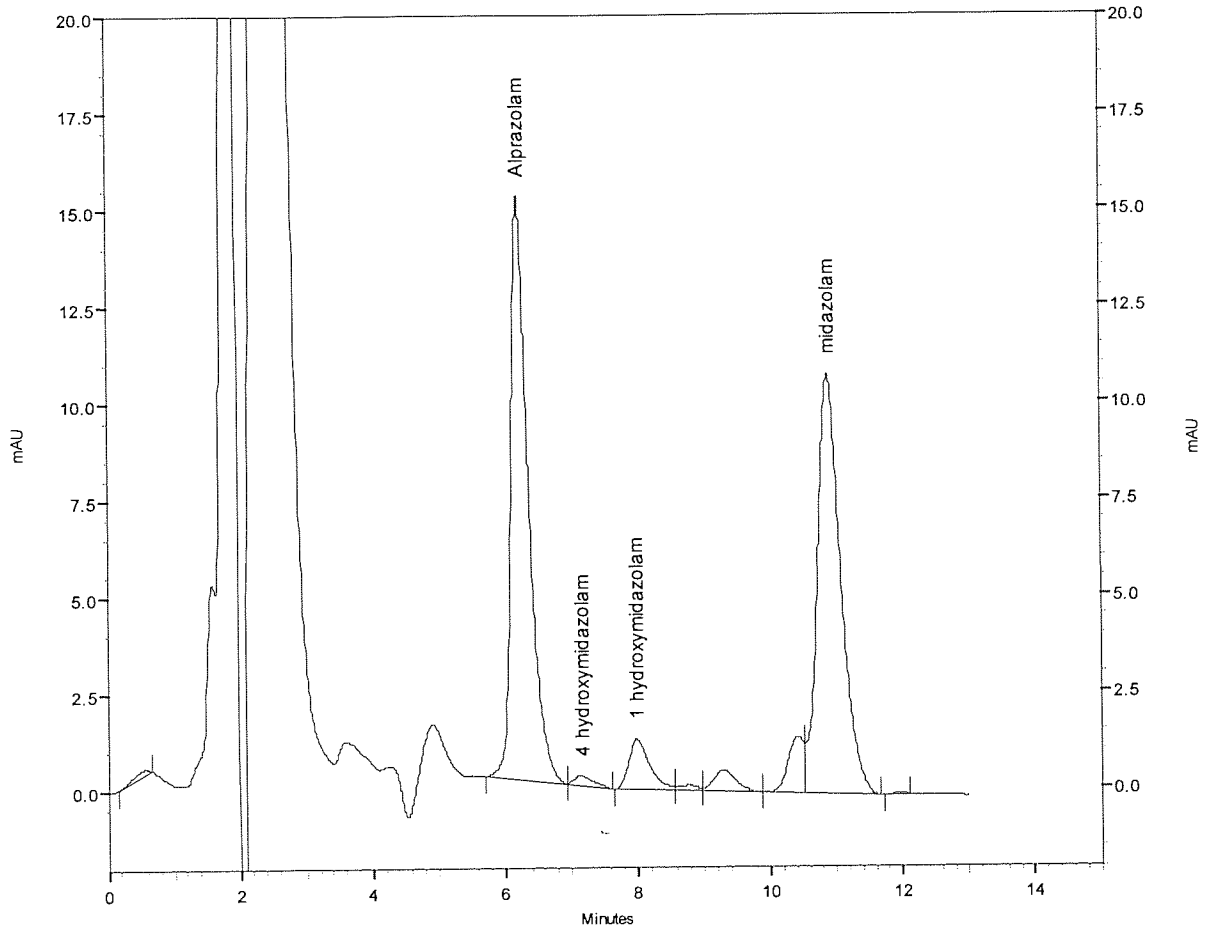


Figure XVIIIb Examples of HPLC chromatograms for patient plasma containing midazolam, 1-hydroxymidazolam and 4-hydroxymidazolam and 400ng/ml of alprazolam as internal standard



3.3.10 Suitability of assay for the quantification of midazolam and its metabolites

This assay for midazolam and it metabolites possesses a number of advantages over other published methods.

- Small samples of plasma can be assayed rapidly, reproducibly and reliably using a simple extraction method.

- The assay is selective and enables simultaneous quantification of midazolam together with its 1-hydroxymidazolam and 4-hydroxymidazolam metabolites.

Thus the assay is ideally suited to the quantification of midazolam and its metabolites derived from the plasma of critically ill children.

CHAPTER ONE

THE DEVELOPMENT AND VALIDATION OF A SEDATION ASSESSMENT SCALE FOR USE IN CRITICALLY ILL CHILDREN

CONTENTS

1.1 Introduction

Sedation assessment is considered to be essential in critically ill children receiving mechanical ventilation since children who are not effectively sedated can experience numerous problems. Under sedation can leave a child aware of their surroundings and anxious and has been associated with unplanned extubations and the removal of indwelling cannulae (Chevron, Menard et al. 1998). In contrast, over sedation can result in a delayed awakening and extend the time spent in intensive care and can cause unnecessary side effects owing to withdrawal symptoms on discontinuation of the sedative (Fonsmark, Rasmussen et al. 1999). In practice however, it is very difficult to carry out effective and accurate sedation assessment for a number of reasons:

- sedation is very difficult to define and its assessment can be very subjective.
- level of sedation has not been directly correlated to specific objective parameters which can be measured such as heart rate, blood pressure, oxygen requirement.
- many sedation assessment scales used in clinical practice have not been validated for use in critically ill children.

This part of the study was designed to validate a sedation assessment scale for use in critically ill children. The study compared two different types of observational sedation assessment scales. The first sedation scale was simple in design and was already in use at the Birmingham Children's Hospital PICU. The second sedation scale was more complicated in design and was devised as an alternative assessment scale. It was developed from a number of sedation scales used in critically ill adults and designed to be used specifically in children. Each sedation scale was tested for reproducibility and practicality.

1.2 Results of the reproducibility of the sedation scales

Over a 12-week period two observational sedation assessment scales were investigated consecutively and tested for reproducibility and practicality. A total of 100 blinded independent sedation scores were collected for scale 1, which involved 46 patients. A total of 87 blinded independent sedation scores were collected for scale 2, which involved 45 patients.

1.2.1 Analysis of the extent of reproducibility of sedation scales

The number of sedation assessments where perfect agreement was obtained between assessors was calculated as a percentage for each scale. Perfect agreement between assessors was obtained in 61% and 69% of cases for scale 1 and 2 respectively.

Although this gives an indication of the comparative reproducibility of the two sedation scales, it does not take into consideration that agreement between assessors could occur by chance. In order to take chance agreement into consideration kappa values were calculated. Kappa is a statistic that indicates the level of agreement between assessors above that expected by chance alone. However, the degree of disagreement is not estimated by kappa alone. Weighted kappa takes into account the magnitude of disagreement. Therefore, both kappa and weighted kappa were calculated for the purposes of this study. A kappa value of one indicates perfect agreement and a kappa value of zero indicates no agreement better than chance. There are no absolute definitions of kappa between zero and one but table 1.1 provides a guide to strength of agreement.

Table 1.1 A guide to the strength of agreement for different kappa values

Value of kappa	Strength of agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 –1.00	Very good

1.2.1.1 Kappa and weighted kappa values for scale 1

The value of kappa for sedation scale 1 was 0.50. This result indicates that the level of agreement between assessors for scale 1 is moderately good. The value of weighted kappa for sedation scale 1 was 0.87. The weighted kappa value indicates that the agreement between assessors was very good. The relative improvement in agreement using weighted kappa indicates that the margin of disagreement between assessors is small for scale 1.

1.2.1.2 Kappa and weighted kappa values for scale 2

The value of kappa for sedation scale 2 was 0.62. This result indicates that the level of agreement between assessors for scale 2 is good. The value of weighted kappa for sedation scale 2 was 0.94. The weighted kappa value indicates that the agreement between assessors was very good. Again the relative improvement in agreement using weighted kappa indicates that the margin of disagreement between assessors is small for scale 2.

1.2.1.3 Analysis of agreement for individual parameters in scale 2

Scale 2 comprised 5 components that each required an individual assessment. Therefore it was possible to calculate individual kappa values for each component as shown in table 1.2.

Table 1.2 Kappa values calculated for individual patient parameters during a sedation assessment using sedation scale 2

Parameter	Kappa
Facial expression	0.84
Eyes	0.80
Body movement	0.66
Agitation	0.79
Respiration	0.85

Kappa values for individual parameters in sedation assessment scale 2 ranged from 0.66 to 0.84 and indicates a good level of agreement between assessors.

1.2.2 Sedation scores achieved using sedation scales

1.2.2.1 Sedation scale 1

Scores from sedation scale 1 ranged from 1 to 5. A score of 1 indicated an awake state and a score of 5 indicated a heavily sedated state. Table 1.3 indicates the number of sedation assessments made by individual assessors at a given level of sedation.

Table 1.3 Sedation scores for assessor 1 (a^1), assessor 2 (a^2) and the total number of sedation scores for both assessors 1 and 2 (a^{total}) using scale 1

	Sedation Score	a^1	a^2	a^{total} (%)
	1	11	12	23 (11.5)
	2	16	14	30 (15.0)
	3	30	31	61 (30.5)
	4	21	14	35 (17.5)
	5	22	29	51 (25.5)
Total		100	100	200

The results indicate that the numbers of sedation scores made at each level when using scale 1 by each assessor are very similar. The majority of sedation scores are made at level 3 (30.5%), which indicates patients are satisfactorily sedated and level 5 (25.5%), which indicates patients are heavily sedated. The smallest number of sedation scores are made at level 1 (patient awake) for both assessors.

1.2.2.2 Sedation scale 2

Scores from sedation scale 2 ranged from 0 to 10. A score of 0 indicated an anxious and agitated state and a score of 10 indicated a heavily sedated state. Table 1.4 indicates the number of sedation assessments made by individual assessors at a given level of sedation. A total of 87 paired sedation scores were collected for scale 2, which involved 45 patients.

Table 1.4 Sedation scores for assessor 1 (a^1), assessor 2 (a^2) and the total number of sedation scores for both assessors 1 and 2 (a^{total}) using scale 2.

	Sedation Score	a^1	a^2	a^{total} (%)
	0	1	2	3 (1.7)
	1	3	3	6 (3.4)
	2	6	8	14 (8.0)
	3	4	8	12 (6.9)
	4	6	2	8 (4.6)
	5	16	12	28 (16.1)
	6	3	3	6 (3.4)
	7	5	7	12 (6.9)
	8	3	4	7 (4.0)
	9	31	29	60 (34.5)
	10	9	9	18 (10.3)
Total		87	87	174

The results indicate that the numbers of sedation scores made at each level when using scale 2 by each assessor are very similar. The majority of sedation scores are made at level 5 (16.1%), which indicates satisfactory sedation, and levels 9 and 10 (34.5% and 10.3% respectively), which correspond, to a heavily sedated patient. The smallest number of sedation scores are made at level 0 and 1 (1.7% and 3.4% respectively) which correspond to a very agitated and anxious.

1.2.3 Sedation assessment and patient age

Level of agreement of sedation scores between assessors was calculated according to the age of the child. Age categories were used as follows:

Neonates
Less than 1 year of age
1-3 years
4-7 years
more than 7 years of age.

Table 1.5 indicates the extent of agreement between assessors in relation to the patient's age using sedation scale 1.

Table 1.5 Level of agreement of sedation scores as a function of patient age using sedation scale 1

Age category	Total number of sedation scores	Number that agree
Neonate	41	24
Less than 1 year	35	25
1-3 years	7	4
4-7 years	6	4
More than 7 years	11	4

These results indicate that the majority of assessments were made in neonates and patients aged less than 1 year. Table 1.6 indicates the extent of agreement between assessors in relation to the patient's age using sedation scale 2.

Table 1.6 Level of agreement of sedation scores as a function of patient age using sedation scale 2

Age category	Total number of sedation scores	Number of sedation scores that agree
Neonate	19	13
Less than 1 year	22	14
1-3 years	31	21
4-7 years	4	4
More than 7 years	11	8

From these results it can been seen that the majority of sedation assessments were made in neonates, patients aged less than 1 year and those aged between 1 and 3 years. Numbers for children aged 4 years and above are small in both groups. The extent of agreement between assessors was 50% or above for both sedation scales for all age groups except for children above the age of 7 years.

1.2.4 Relationship between assessment agreement and disease state of the child

Level of agreement between assessors was investigated for both sedation scales according to different disease states. Tables 1.7 and 1.8 indicate the levels of agreement between assessors in patients with the same disease state using scales 1 and 2 respectively.

Table 1.7 Relationship between assessment agreement as a function of disease state using scale 1

Disease state	Total number of sedation scores	Number of sedation scores that agree
Cardiac	61	40
Infection	5	3
Liver	4	3
Neurology	10	5
Post-operative	14	7
Respiratory	6	3

It can be seen that most sedation scores were undertaken in cardiac patients.

Table 1.8 Relationship between assessment agreement as a function of disease state using scale 2

Disease state	Total number of sedation scores	Number of sedation scores that agree
Cardiac	33	20
Infection	3	2
Liver	17	11
Metabolic	1	1
Neurology	3	2
Oncology	2	1
Post-operative	9	6
Respiratory	16	15
Trauma	3	3

Again it can be seen that most sedation scores were undertaken in patients with cardiac impairment. For both sedation scores the extent of agreement between assessors was 50% or above in all disease states.

1.2.5 Level of agreement between assessors during a baseline and responsiveness sedation assessment

Sedation scale 2 incorporated a baseline and responsiveness sedation assessment in its design. Table 1.9 indicates the total number of sedation scores undertaken for a baseline sedation score and responsiveness sedation score and the agreement between assessors.

Table 1.9 Extent of agreement between assessors during baseline and responsiveness assessments using sedation scale 2

	Total	Number of sedation scores that agree
Baseline score	70	52 (74.3%)
Responsiveness score	17	8 (44.4%)

The results indicate that there are more baseline sedation scores undertaken than responsiveness scores. It was found that for over 70% of the baseline sedation scores carried out, assessors agreed on the level of sedation. Whereas, for only 44% of the responsiveness sedation assessments undertaken, assessors agreed on a level of sedation.

1.3 Discussion of the reproducibility of the sedation scales

The two observational sedation assessment scales investigated in the present study were very different in design. Sedation assessment scale 1 was very simple in design and required a single assessment of the patient, which resulted in a sedation score. In contrast, sedation scale 2 was more complex in design requiring an assessment of facial expression, body position/movement, presence of agitation and assessment of respiratory function. One of the important features of this study was the development of sedation scale 2. The aim of this scale was to produce a sedation assessment method that was appropriate to be used in critically ill children that would assess agitation as well as level of sedation. The sedation scale was not reliant on verbal communication and therefore was suitable to be used in all ages of children who were ventilated. Sleep is often disrupted in PICU and it has been shown that by

improving natural sleep the outcome of critically ill patients can be improved (Cureton-Lane and Fontaine 1997). Therefore the importance of sleep was highlighted in the design of sedation scale 2 and staff encouraged to reduce disruption to the sleeping patient wherever possible. Sedation assessment is inherently difficult to undertake accurately because it is usually subjective. The purpose of sedation scale 2 was to reduce the degree of subjectivity by compartmentalising the assessment, thereby making it more objective.

Comparison of Sedation Scales

The present study is unique in comparing two different types of sedation assessment scales for reproducibility and practical use in critically ill children. Moreover, no other studies have investigated age-related or disease-related influences upon sedation assessment. The present study is also unique in determining the long-term reproducibility of a sedation assessment scale to consider if it is affected by time.

Sedation scale 1 consisted of 5 levels where level 1 indicated an awake state and level 5 indicated a heavily sedated state. A score of 3 represented satisfactory sedation: that is asleep but moves spontaneously. Sedation scale 2 consisted of 11 levels, where level 0 represented an anxious and agitated state and level 10 a heavily sedated state. A score of 5 represented a satisfactory level of sedation. It is interesting to note that the majority of sedation scores for scale 1 were at levels 3 and 5 and for scale 2 at levels 5 and 9. Therefore even using different types of sedation assessment scales, similar results were obtained. These results also indicate that although a significant number of patients appear to be satisfactorily sedated there are a number of patients who appear to be heavily sedated and are possibly at risk of over sedation.

Measure of Reproducibility of Sedation Scales

To test the reproducibility of both sedation scales it was necessary to investigate the extent of agreement between assessors undertaking simultaneous sedation assessments. Inter-observer agreement is often used as a method of assessing the reliability of a subjective classification or assessment procedure and gives an indication of internal consistency. The simplest approach

to the measurement of agreement is to calculate the number of exact agreements by assessors (proportional agreement).

61% of paired sedation assessments made by assessors, using scale 1 were identical. Whereas, 69% of paired sedation assessments made by assessors using scale 2 were identical. These results give a rapid and simple indication that both sedation scales investigated in the present study produce similar results with good reproducibility. However, the weakness in this simple assessment is that agreement between assessors can occur purely by chance, which has not been taken into consideration.

The second measurement of agreement was extended by undertaking Cohen's kappa statistic. Cohen's kappa is the leading measure in agreement and is used to assess the extent of agreement in rating procedure. There are three versions of Cohen's kappa:

- Kappa - which measures a simple agreement between raters; that is a simple agree/disagree method.
- Fleiss and Light developed a more generalized kappa, which can be used when there are more than two raters.
- Weighted kappa - which was developed to allow for degrees of agreement and takes into consideration the extent of disagreement.

In this study kappa and weighted kappa values were calculated to assess the extent of agreement between assessors for each sedation scale.

Kappa and weighted kappa values for scale 1 were 0.5 and 0.87 respectively. Kappa and weighted kappa values for scale 2 were 0.62 and 0.94 respectively.
A kappa value of 1 represents perfect agreement, whereas, a kappa value of 0 indicates no better agreement than chance. A negative kappa value would indicate a worse than chance agreement. The results indicate that both sedation scales give a good level of agreement and, therefore internal consistency.

It should be noted that there have been a number of criticisms of the use of Cohen's kappa. Firstly, kappa values cannot usually be compared across studies, procedures or populations, unless the options are identical. For example, the kappa values from scale 1 and 2 in the present study cannot be directly compared since the number of intervals for each scale was not identical. The number of options in scale 1 was five and in scale 2 was eleven. Therefore, the kappa values obtained can only be considered with regard to each sedation scoring system in isolation. For kappa values to be calculated assessors must use the same rating categories. There maybe occasions when an investigation involves raters using different categories. Kappa itself does not take into consideration any degree of disagreement. Consequently, weighted kappa was developed in order to address this deficiency. It should be noted however, that if weighted kappa is to be calculated, the weights are selected arbitrarily. These criticisms aside, kappa is still used extensively in studies to evaluate assessor agreement and until further research is conducted to develop an alternative method, is likely to remain the leading measure of agreement.

Relationship between level of agreement and age

One of the reasons why children's medicine stands apart from adult medicine is the developmental stages of the child from the neonatal stage to the mature adult. Changes occur in size, weight and maturity of organs including the kidneys and liver two of the most important organs with respect to drug metabolism. There is not only major physiological differences between adults and children but also psychological differences in the mental development of children. This becomes very apparent when developing a sedation assessment scale for the critically ill child. Many sedation scales have been developed in adults where the ability to understand verbal commands and communicate is evident. Adult scales are therefore not appropriate for use in pre-verbal children and in many cases where children are receiving mechanical ventilation. A sedation assessment scale effective in PICU must take into consideration the constraints imposed by all ages of children for it to be practical.

In the present study differences in the level of agreement with respect to the age of the critically ill child were investigated. Assessed children were banded into age groups in order

to aid analysis. The age groups included neonates, those less than 1 year of age, those between the ages of 1 and 3 years, those between the ages of 4 and 7 years and those above the age of 7 years. For scale 1 the majority of assessments were made in children of neonatal age and those under the age of 1 year. With the exception of children above the ages of 7 years agreement between assessors exceeded disagreement in all cases. For sedation scale 2 the majority of assessments were made in children aged less than 1 year and those aged between 1 and 3 years. The extent of agreement between assessors exceeded disagreement in all cases.

Many studies have highlighted the difficulty of assessing the level of sedation in the neonatal population. One of the reasons put forward for this is the difficulty in distinguishing pain from anxiety in this age group. The present study indicates that both sedation scales indicate good reproducibility in neonates. As a result of insufficient numbers of patients further work is required to clarify reproducibility of sedation assessment in children above the ages of 4 years. However, the evidence from this study suggests that good reproducibility using both sedation scales is achieved across all ages of children.

Relationship between level of agreement and disease state

This study attempted to investigate the relationship between sedation assessment and disease state. The only previously reported sedation assessment scale to specifically consider a particular disease/injury is the Glasgow Coma Score, developed to assess level of consciousness in patients with head injuries (Teasdale and Jennett 1974). The present study is limited by the small numbers of patients in disease categories other than cardiac patients. This makes it difficult to draw any reliable conclusions. However, there are no significant differences between scale 1 and 2 with regard to the assessment of cardiac patients in the present study.

One of the groups of children potentially causing difficultly with regard to sedation assessment are those with neurological disorders because the injury can complicate normal sedation assessment. Another group of children that present difficulties with regard to sedation assessment are those admitted with status epilepticus since they may be prescribed a number of anticonvulsants that cause sedation as a side effect. Patients with learning difficulties can

also be difficult to assess as they may respond differently to other children with regard to facial expression and body movement. This is also true of patients suffering spasticity, where normal appropriate body movement is different to that seen in other children. In all these conditions as well as in normal children it is imperative where possible to seek advice from parents and carers with regard to the normal behaviour and attitude of their child. All children respond and behave differently and parents should be able to help nursing staff determine the normal patterns of behaviour and movement.

Level of agreement using baseline and responsiveness scores for sedation scale 2

Sedation scale 2 incorporated a baseline sedation score and a responsiveness sedation score. The baseline score required the nursing staff to undertake a sedation assessment without any prior disruption to the patient. This method of sedation assessment will not distinguish between a child who is merely asleep and a child who is heavily sedated. Therefore, a responsiveness sedation assessment was incorporated into the design of the sedation assessment scale. A responsiveness sedation assessment could be carried out when the child was undergoing a routine procedure such as physiotherapy, daily care procedures or suctioning, all of which usually take place at least once or twice a day. All these procedures cause a degree of discomfort and disruption to the patient and would be expected to cause a sleeping child to wake but not affect an over sedated child. Using this method additional discomfort is not caused to the patient as with other sedation assessment scales which include an additional external stimulus with which to assess possible over sedation.

The results from the present study indicate that the extent of agreement between assessors for a baseline score is very good (74%). However, the extent of agreement between assessors falls to around 44% for a responsiveness sedation assessment. Baseline assessments require only an observational assessment and nursing staff can do so generally without any interruptions. To carry out a responsiveness assessment the nurse maybe involved in another activity, for example aiding with physiotherapy or suctioning and therefore, the assessment will be done retrospectively after finishing the procedure. This may be one reason for the lower level of agreement seen between assessors carrying out responsiveness scores. In addition numbers of responsiveness assessments performed were limited and therefore, it

would be useful to carry out further work in this area to clarify the situation and identify further problems

1.4 Results of the self-completion questionnaire to nursing staff on the sedation scales

The questionnaire was designed to obtain nursing staff opinion about both sedation scales. The questionnaire included 33 questions of which 20 required circling a single stated answer. A further 7 questions required multiple answers and included a total of 62 potential questions. The remaining 5 questions were open questions and were included to give the nurses an opportunity to express comments about the scales with regard to any modifications that would make the scales easier to use or aid clarification.

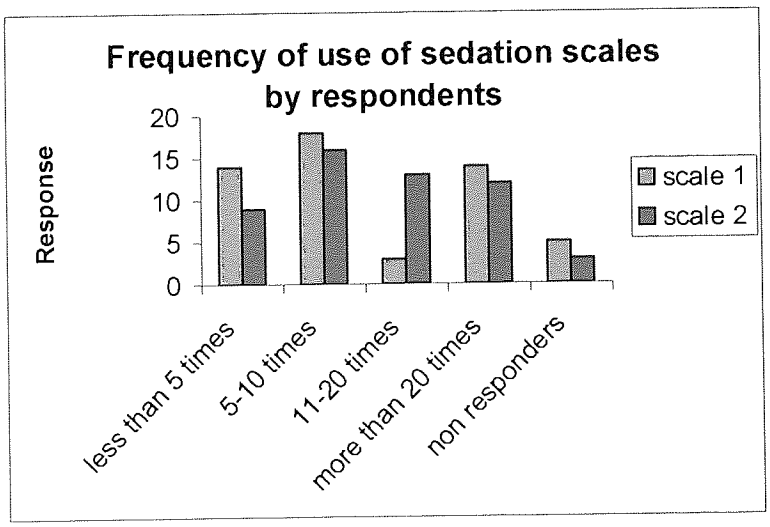
A total of 108 self completion questionnaires were sent to PICU nursing staff, of which 54 were returned (50% response rate) after two follow ups. Evaluation of the questionnaire has been undertaken by considering a number of specific issues relating to the answers made by the respondents. These will be documented below under individual headings. A response rate from the total number of respondents will be indicated, for example as 48/54. A complete set of the results form the questionnaire can be found in Appendix 12.

Use of the sedation scales by respondents

Respondents were asked if they had used each sedation scale in the 3 months prior to completing the questionnaire. The question required a simple yes/no response (Q1 scale 1, Q11 scale 2). The results indicated that 48/54 respondents had used scale 1 and that 41/54 respondents had used scale 2.

The respondents were then asked how often they had used each scale in the 3 months prior to completing the questionnaire. The question gave the respondents four options ranging from less than 5 times to more than 20 times (Q2 scale 1, Q12 scale 2). The results indicated that in the 3 months prior to completing the questionnaire, 35/54 respondents had used scale 1 more than 5 times and that 41/53 respondents had used scale 2 more than 5 times. The response for questions 2 and 12 are summarized in figure 1.1.

Figure 1.1



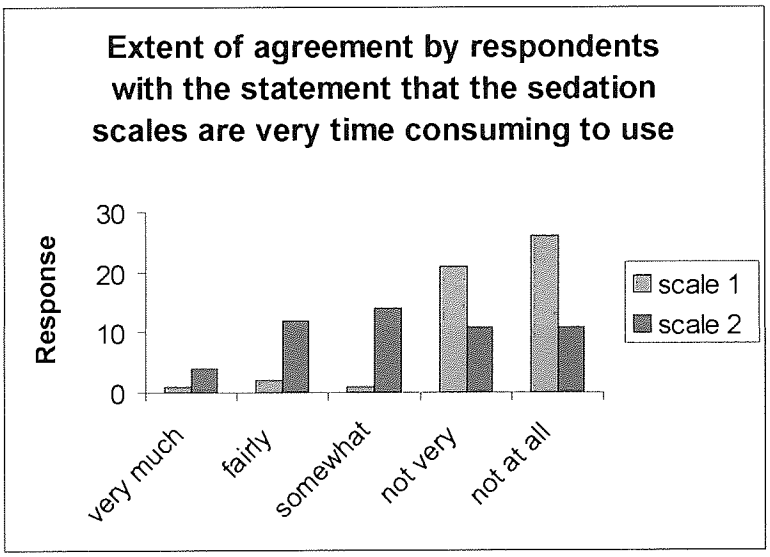
Time taken to make an assessment using both scales.

Respondents were asked on average how long it took to make an assessment using each sedation scale. Respondents were given 4 options ranging from, less than 1 minute to more

than 5 minutes (Q3 scale 1, Q13 scale 2). The results indicated that 40/54 respondents took less than 1 minute to make a sedation assessment using scale 1. Whereas, 48/54 respondents took 1-3 minutes to make an assessment using scale 2. These results indicate that respondents were taking longer to make an assessment using sedation scale 2.

The respondents were also asked how time consuming each scale was to use. The question was asked in the form of a Likert scale (Q8H scale 1 Q18H scale 2). The responses are summarized in figure 1.2.

Figure 1.2



From the results it can be seen that the majority of respondents thought that sedation scale 1 was less time consuming to use in comparison to scale 2.

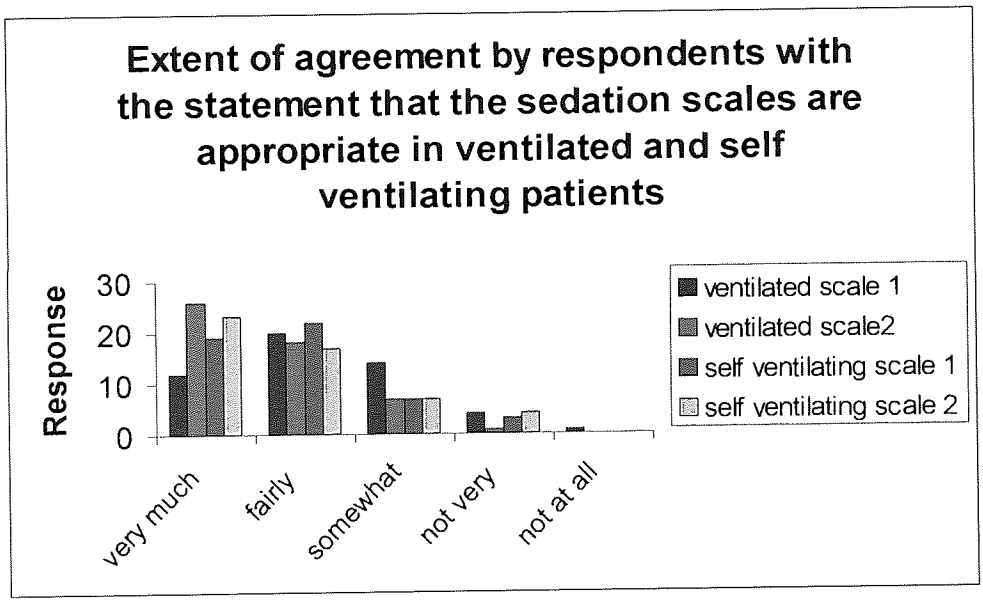
Suitability of sedation scales for patients receiving different types of ventilation

Respondents were asked if they would use each sedation scale in patients receiving mechanical ventilation with no sedation. The question required a simple yes/no response (Q5

scale 1 Q15 scale 2). The results indicated that 40/54 respondents would use scale 1 in patients receiving ventilation but no sedation and 46/54 respondents would use scale 2 in this group of patients.

A similar question was also asked as part of a Likert response (Q8E, Q8F scale 1, Q18E, Q18F scale 2). In this case respondents were asked to indicate the extent of agreement to the statement 'the scale is appropriate for patients receiving mechanical ventilation' and 'the scale is appropriate for self ventilating patients'. The responses are summarized in figure 1.3.

Figure 1.3



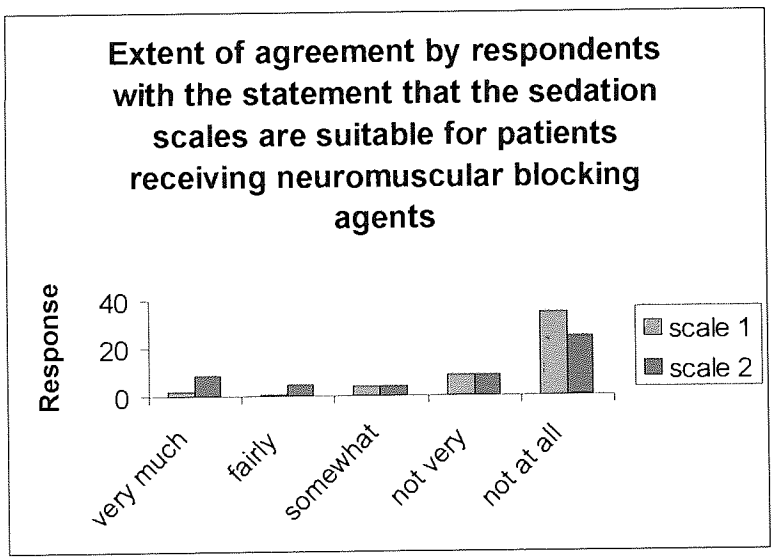
The results suggest that the majority of respondents thought that both sedation scales would be appropriate for use in patients who were ventilated as well as those who were self-ventilating.

Suitability of sedation scales for patients receiving neuromuscular blockade.

Respondents were asked about whether they would use each sedation scale in patients receiving neuromuscular blockade. The question required a simple yes/no response (Q4 scale 1 Q14 scale 2). The results indicated that 44/54 respondents would not use scale 1 in patients receiving neuromuscular blocking agents and 37/54 respondents would not use scale 2 in this group of patients.

A similar question was also asked as part of a Likert response (Q8J scale 1, Q18J scale 2). In this case respondents were asked to indicate the extent of agreement to the statement 'the scale is suitable for patients receiving neuromuscular blocking agents'. The responses are summarized in figure 1.4.

Figure 1.4

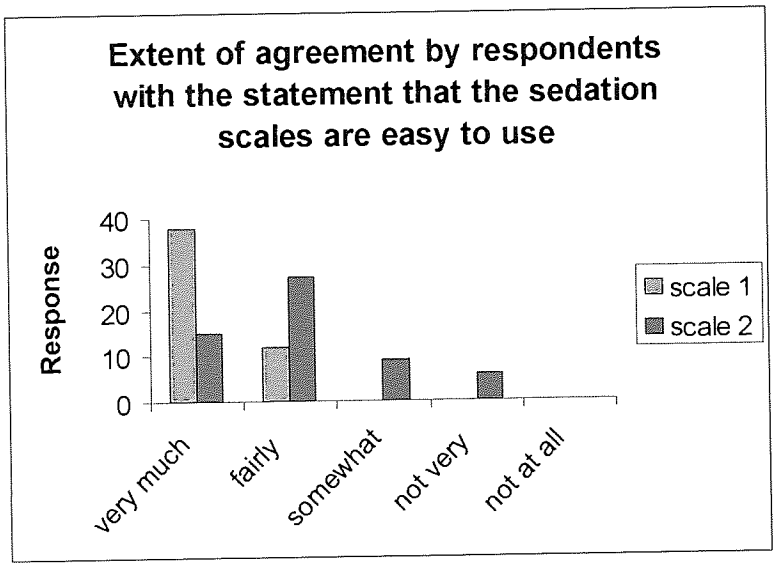


The results indicate that the majority of respondents thought that neither of the sedation scales were suitable to be used in patients receiving neuromuscular blocking agents.

Ease of Use and Understanding of Sedation Scales.

Respondents were asked how easy each sedation scale was to use. The question was asked as part of a Likert response (Q8A scale 1, Q18A scale 2) and respondents were asked to indicate the extent of agreement to the statement 'the scale is very easy to use'. The responses are summarized in figure 1.5.

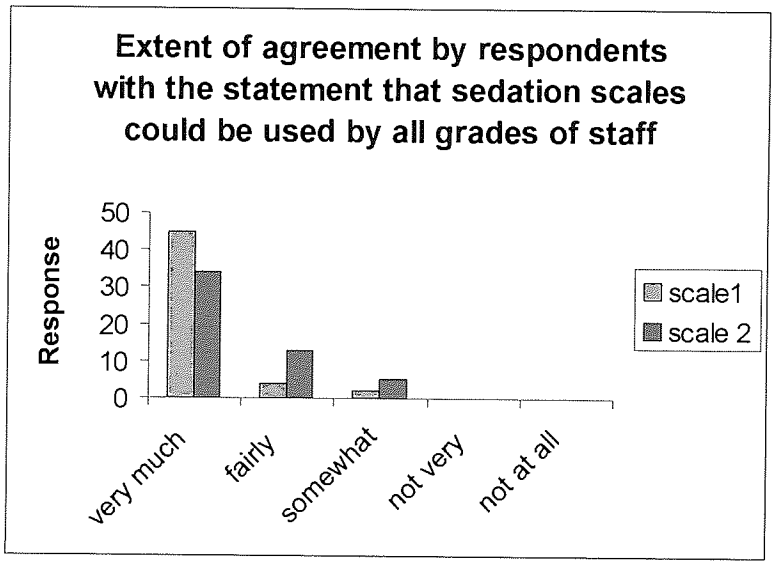
Figure 1.5



The results suggest that respondents found scale 1 easier to use compared to scale 2. 50/50 respondents gave a positive response about scale 1, whereas 42/55 respondents gave a positive response about scale 2 to this statement.

Respondents were asked whether the sedation scales could be used by all grades of nursing staff. The question was asked as part of a Likert response (Q8K scale 1, Q18K scale 2) and respondents were asked to indicate the extent of agreement to the statement that 'the scales can be used by all grades of nursing staff'. The responses are summarized in figure 1.6.

Figure 1.6

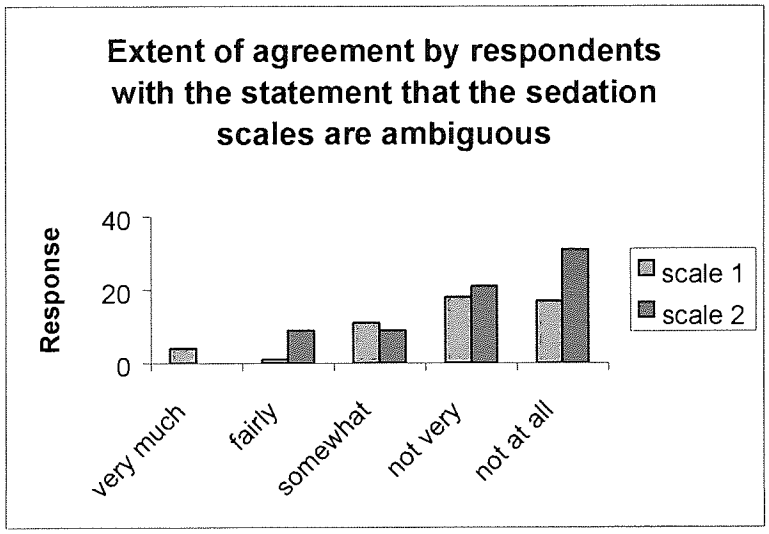


The results suggest that the majority of respondents thought that both scales could be used by all grades of staff.

Suitability of the wording used in sedation scales.

Respondents were asked whether the wording used in the sedation scales was appropriate. The question was asked as part of a Likert response (Q8I scale 1, Q18I scale 2). In this case respondents were asked to indicate the extent of agreement to the statement that 'the wording used in the assessment scale is ambiguous'. The responses are summarized in figure 1.7.

Figure 1.7



The results suggest that respondents thought that the wording in both scales was not ambiguous.

Respondents were then asked to choose words or phrases that they thought best described the different levels of sedation in each assessment scale. Respondents were allowed to choose more than one phrase if necessary and the results are summarized in table 1.10 (scale1), table 1.11 (scale 2) and figure 1.8 (scale 2).

Table 1.10 Words chosen by respondents to describe different sedation levels in scale 1

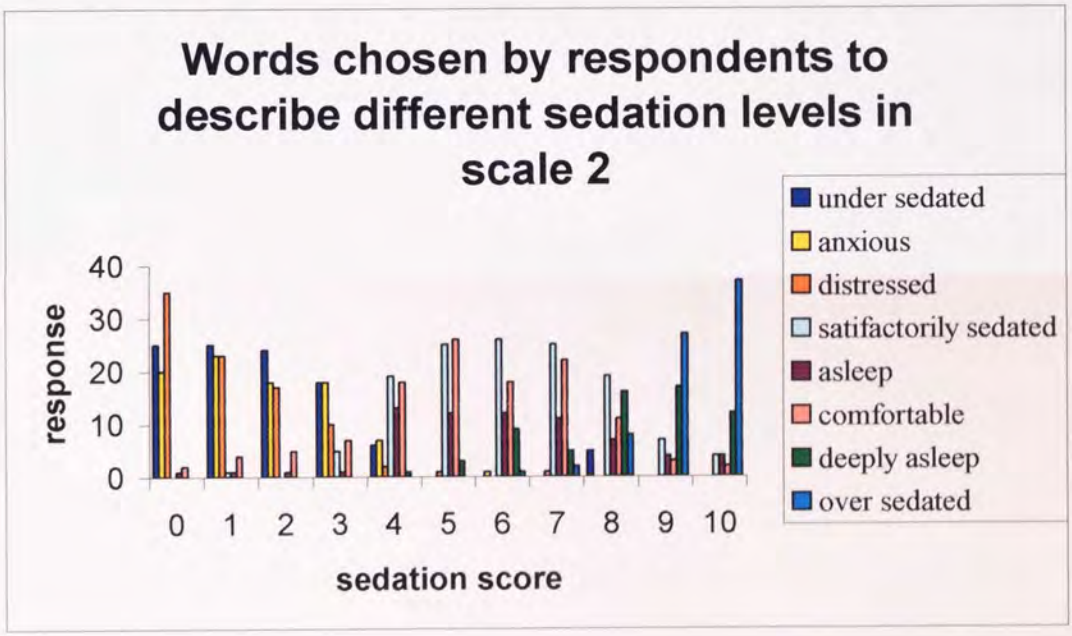
	1 Wide awake	2 Awake but sleepy	3 Asleep but moves spontaneously	4 Asleep but responds to stimulation	5 Hard to rouse
Under sedated	29	8	4	4	1
Over sedated	0	0	0	9	44
Satisfactorily sedated	6	28	38	27	2
Asleep	1	6	30	17	0
Anxious	29	8	4	1	0
Distressed	28	8	3	0	0
Deeply asleep	0	0	1	29	22
Comfortable	27	31	28	23	3

In scale 1 sedation level 1 indicated that the patient is awake. It is interesting to note that respondents associated the words – 'under sedated', 'anxious', 'distressed' and 'comfortable' with this level of sedation. These results suggest that there is a degree of ambiguity with this level of sedation in this scale. In addition level 4 indicates that the patient although asleep will respond to stimulation. From the results respondents associated the words 'satisfactorily sedated', 'deeply asleep' and 'comfortable' with this level of sedation. Again the results suggest a degree of ambiguity with this level of sedation

Table 1.11 Words chosen by respondents to describe different sedation levels in scale 2

	0	1	2	3	4	5	6	7	8	9	10
Under sedated	25	25	24	18	6	0	0	0	5	0	0
Over sedated	0	0	0	0	0	0	1	2	8	27	37
Satisfactorily sedated	0	1	0	5	19	25	26	25	19	7	4
Asleep	1	1	1	1	13	12	12	11	7	4	4
Anxious	20	23	18	18	7	0	1	0	0	0	0
Distressed	35	23	17	10	2	1	0	1	0	0	0
Deeply asleep	0	0	0	0	1	3	9	5	16	17	12
Comfortable	2	4	5	7	18	26	18	22	11	3	2

Figure 1.8



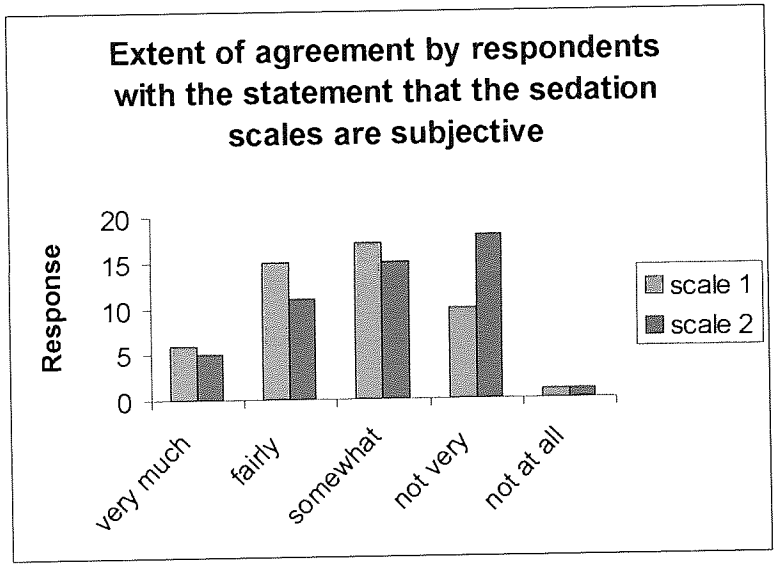
From the results it can be seen that respondents associate the words 'under sedation', 'anxious' and 'distressed' with sedation levels 0, 1, 2 and 3 of scale 2. Respondents associate the words 'satisfactorily sedated', 'comfortable' and 'asleep' with sedation levels 4, 5, 6 and 7. Respondents associate the words 'over sedated' and 'deeply asleep' with sedation levels 9 and 10 of scale 2. The words that respondents associate with sedation level 8 of scale 2 are

somewhat conflicting and include 'satisfactorily sedated', 'comfortable', 'asleep', 'deeply asleep' and 'over sedated'.

The subjectivity of sedation scales

Respondents were asked to state how subjective or objective they thought each sedation scale was. The question formed part of a Likert scale and respondents were asked to indicate the extent of agreement to the statement that 'the assessment scale is very subjective'. (Q8L scale 1, Q18L scale 2). The responses are summarized in figure 1.9.

Figure 1.9

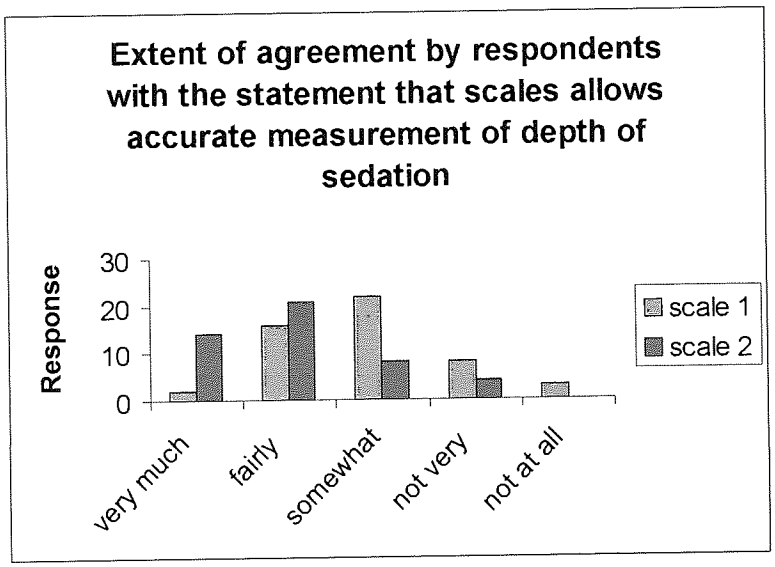


From the results it can be seen that there is considerable disagreement between respondents regarding the subjectivity of both scales. 21/49 respondents gave a positive answer to the statement and 11/49 respondents gave a negative answer regarding scale 1. Whereas, 16/50 respondents gave a positive answer to the statement and 19/50 gave a negative answer regarding scale 2.

Assessment accuracy and usefulness of sedation scales.

Respondents were asked whether they thought each sedation scale gave an accurate assessment of the level of sedation. The question was asked as part of a Likert response (Q8B scale 1, Q18B scale 2). In this case respondents were asked to indicate the extent of agreement to the statement that the 'sedation assessment scale allows accurate measurement of depth of sedation'. The responses are summarized in figure 1.10.

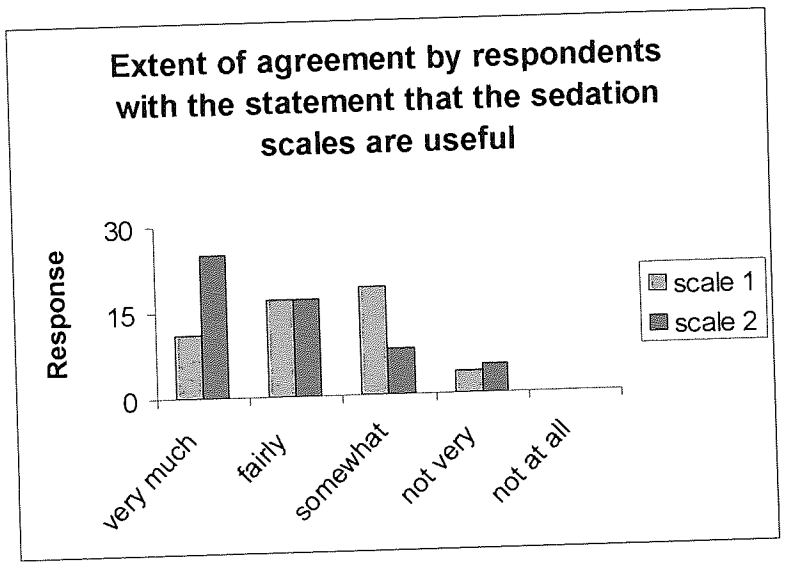
Figure 1.10



The results suggest that the majority of respondents thought that scale 2 provided a more accurate measurement of the depth of sedation compared to that obtained from scale 1.

Respondents were asked about the usefulness of each sedation scale. The question was asked as part of a Likert response (Q8D scale 1, Q18D scale 2). In this case respondents were asked to indicate the extent of agreement to the statement that the 'sedation assessment scale is very useful'. The responses are summarized in figure 1.11.

Figure 1.11

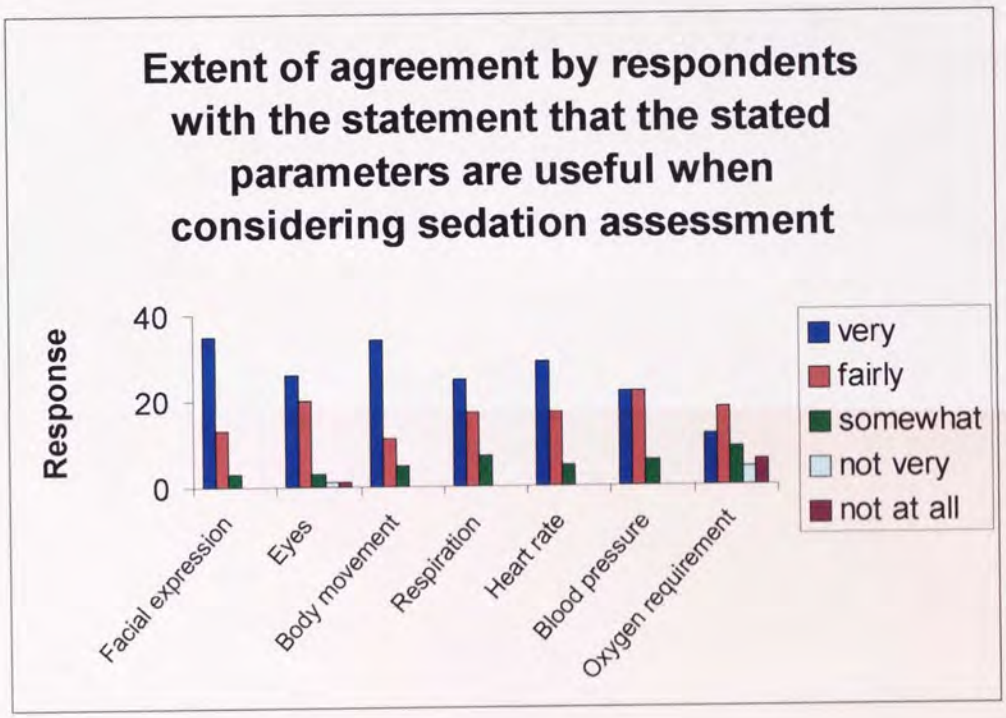


From the results it can be seen that the majority of respondents thought that both sedation scales were useful. However, the results suggest that respondents thought that scale 2 was more useful in comparison to scale 1.

Parameters relevant to assessment of sedation

Respondents were asked about the usefulness of considering a number of parameters during sedation assessment. The respondents were given a number of parameters and the question was asked as part of a Likert scale (Q23). The respondents were asked to indicate the extent of agreement to the statement 'how would you rate the usefulness of the following parameters in sedation assessment.' The results are summarised in figure 1.12.

Figure 1.12

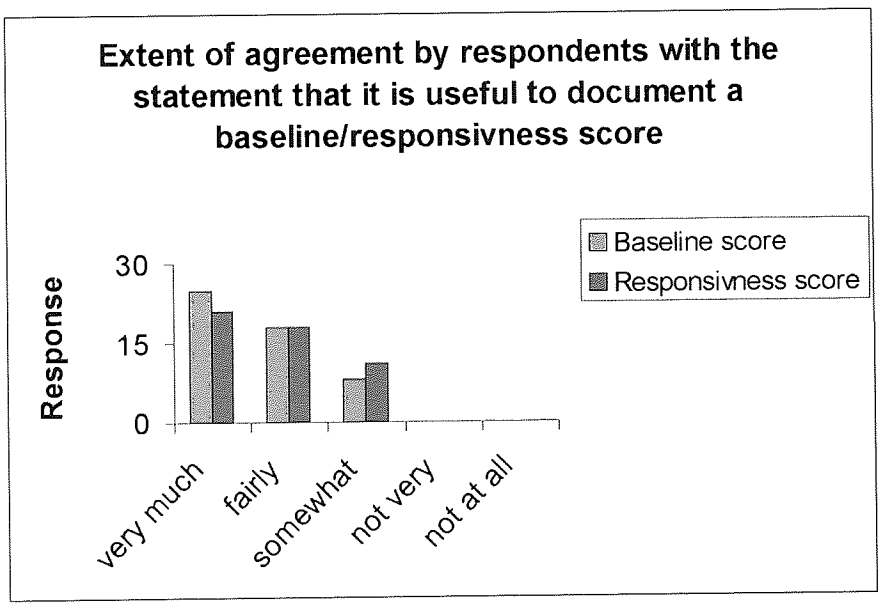


From the results it is clear that the majority of respondents thought that facial expression, eyes, body movement, respiration, heart rate and blood pressure were all parameters that were useful when considering level of sedation in patients. There was a mixed response from respondents regarding the usefulness of considering a patients oxygen requirement when assessing a patients level of sedation.

Usefulness of documenting a baseline and responsiveness score in scale 2.

Part of the design of sedation scale 2 incorporated a facility for the nursing staff to document a baseline sedation score or a responsiveness sedation score. Respondents were asked to indicate the usefulness of this design feature. The question was asked as part of a Likert scale and respondents were asked to indicate the extent of agreement with the statement that 'documenting a baseline score is useful' (Q18M) and 'documenting a responsiveness score is useful' (Q18N). The results are summarized in the figure 1.13.

Figure 1.13



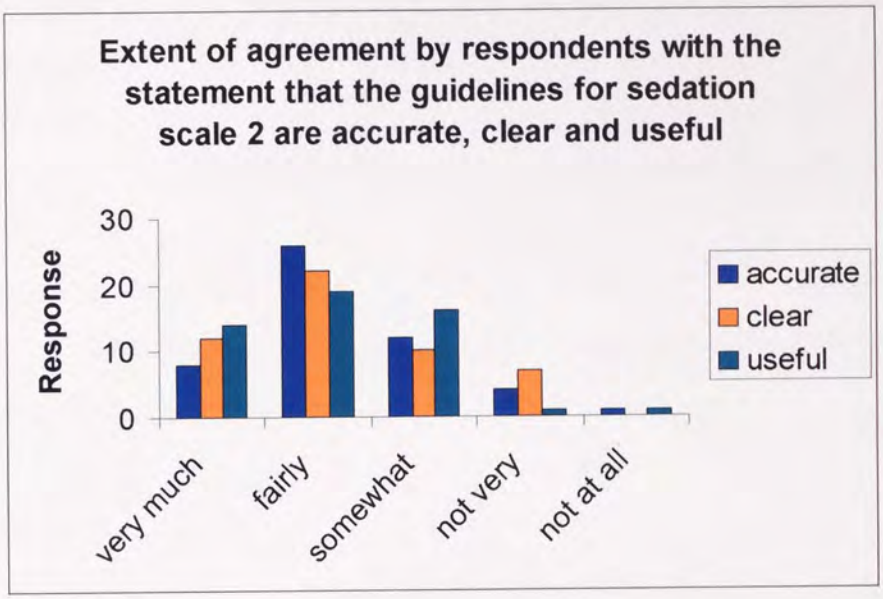
The results suggest that the majority of respondents thought that documenting baseline and responsiveness sedation scores were useful.

Usefulness of the guidelines to review sedation in scale 2

Part of the design of sedation scale 2 incorporated guidelines that could be used by the nursing staff to indicate the need for a child's sedation to be reviewed. Respondents were asked to indicate the usefulness of this design feature. The question was asked as part of a Likert scale and respondents were asked to indicate the extent of agreement with the statements that 'the guidelines to review sedation are useful' (Q18Q) and 'the guidelines for the need to review

sedation are accurate' (Q18O) and 'the wording of the guidelines to review sedation are clear' (Q18P). The results are summarised in the figure 1.14.

Figure 1.14



The results suggest that the majority of respondents thought that the guidelines were accurate, clear and useful. 34/51 respondents gave a positive response regarding the accuracy of the guidelines. 34/51 respondents gave a positive response regarding the clarity of the guidelines. 33/51 respondents gave a positive response regarding the usefulness of the guidelines.

1.5 Results from face to face nursing staff interviews

A total of 31 short semi-structured interviews were conducted with a sample of the nursing staff of which 26 had not previously completed a questionnaire. The interviews were designed to take no more than 10 minutes to complete. The aim was to ascertain principally preference of the respondent between the two sedation assessment scales used and their reasons for this. Consequently, it was intended to repeat only a very few questions from the questionnaire. The interview consisted of 10 questions of which 6 where closed questions. The remaining 4 questions were open in design, encouraging an opinion to be expressed and these had not been previously included in the questionnaire. The subject matter in these questions included:

- The appropriateness of sedation assessment on PICU in different children.
- Particular children who were perceived as difficult to sedate effectively.
- Perceived training needs in the area of sedation assessment.
- Further research required in the area of sedation assessment.

A set of results from the interviews can be found in Appendix 13.

Appropriateness of sedation assessment on PICU in different children.

Respondents were asked if they thought that sedation assessment on PICU was relevant in the following types of children:

- Ventilated children
- Recently extubated children
- Self ventilating children
- Paralysed children

The question was a simple yes/no response (Q1). The results are summarized in table 1.12 and indicate that most of the nursing staff interviewed thought that sedation assessment was relevant in all children.

Table 1.12. Extent of agreement by respondents with the statement that sedation assessment was relevant for different ventilated and non-ventilated children

	yes	no
Ventilated children	31	0
Recently extubated children	28	3
Self ventilating children	28	3
Paralysed children	30	1

Particular children who were difficult to sedate effectively

Respondents were asked if they could identify particular children in whom a safe level of sedation was difficult to achieve (Q4). The following groups of children were highlighted by the staff as posing a particular problem with regard to achieving adequate sedation:

- patients with Down syndrome
- neonates
- children aged over 15 years
- children aged between 1-3 years
- patients with neurological problems.

Training needs for nurses in sedation assessment

Respondents were asked if they thought that training in sedation assessment was necessary (Q6). The question required a simple yes/no response. The results indicated that 27/31 respondents thought that training in sedation assessment was necessary.

Identified areas of research required in sedation assessment.

Respondents were asked if they could identify any areas where research might be useful in the field of sedation assessment (Q8). Two areas highlighted by the nursing staff that were thought to require further research into sedation assessment included:

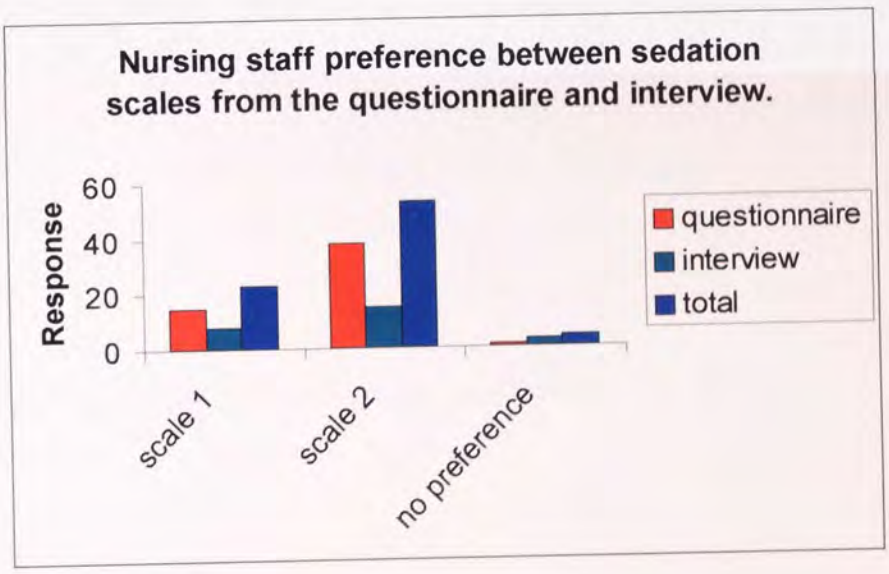
- paralysed patients
- patients with neurological problems

1.6 Nursing staff preference between sedation scales from the questionnaire and interviews

Respondents of the questionnaire were asked which sedation assessment scale would they prefer to use in PICU. The question gave four options, scale 1, scale 2, another sedation scale or no sedation scale. 15/53 respondents preferred scale 1 whereas, 38/53 respondents stated they preferred scale 2. 1/53 respondents stated that they had no preference of sedation scale used.

A total of 26 members of the nursing staff that were interviewed had not previously completed a questionnaire. 8/26 interviewees stated they preferred sedation scale 1, 15/26 interviewees stated they preferred scale 2 and 3 interviewees stated they did not have a preference. In total 80 members of the nursing staff expressed a preference between the two sedation scales either via the questionnaire or the interview. The results are summarized in figure 1.15.

Figure 1.15



In total 23/80 (28.8%) nursing staff stated they preferred sedation scale 1, 53/80 (66.3%) stated they preferred scale 2 and 4/80 (5.0%) did not have a preference.

1.7 Discussion of nursing staff self-completion questionnaire and interviews

As described 54 questionnaires were finally returned out of 108 sent out. A total of 31 short interviews were conducted with members of the nursing staff of which 26 had not completed a questionnaire. In total 80 members of the nursing staff (74.1%) expressed an opinion about the sedation assessment scales either via a questionnaire or short interview.

In total 53 (66.3%) members of the nursing staff that expressed an opinion preferred sedation assessment scale 2 compared to scale 1. A total of 23 (28.8%) preferred scale 1 and 4 (5.3%) had no preference of a scale to be used in PICU regularly.

From the results of the study it was evident that both sedation scales were found to be useful in assessing sedation in critically ill children. Nursing staff thought that both scales were useful in assessing sedation in mechanically ventilated children whether they were receiving sedation or not, as well as patients that were self-ventilating. However both sedation scales were thought not to be useful in patients receiving neuromuscular blocking agents.

One of the important aspects to establish about any sedation assessment scale is how practical it is to use. From the results it was found that nursing staff thought that scale 1 was slightly easier to use compared to scale 2, but that both scales could be used by all grades of nursing staff. The fact that nursing staff found scale 1 easier to use than scale 2 is not surprising as scale 1 is much simpler in design compared to scale 2. Nursing staff also stated that scale 1 took less time to use compared to scale 2. Again this was not entirely unexpected owing to the more complex design of scale 2. From these results it might be expected that the nursing staff would prefer to use scale 1 regularly in PICU because it appears simpler to use and less time consuming. However, the results from the study found that nursing staff preferred sedation scale 2. The reasons for this are clear from the remaining questions from the questionnaire.

From the results of the study nursing staff thought that scale 2 gave a more accurate assessment of the level of sedation compared to scale 1, even though scale 2 was more complicated in design and consequently took slightly longer to use. The parameters used in scale 2 with which to assess sedation included, facial expression, eyes, body movement, and respiration, all of which nursing staff thought were useful and appropriate to consider during

sedation assessment. Objective parameters such as these are not included in scale 1 and therefore make scale 1 more subjective in design compared to scale 2. In addition one of the problems highlighted with scale 1 was in the wording. It was clear from the results that there was some ambiguity in the meaning of level 1 of scale 1. Respondents of the questionnaire chose words to describe level 1 including comfortable, distressed, anxious and under sedated. These descriptions are clearly conflicting and require some clarification. In direct contrast to this respondents clearly describe different sedation levels in scale 2 and associate a score of between 0 and 3 with under sedation, anxiety and distress; a score of between 4 and 7 with satisfactory sedation and being comfortable and a score of 9 or 10 with over sedation. Scale 1 was criticised by a number of nursing staff that it did not assess anxiety but merely level of consciousnesses. This is a very important point to consider as the principal aim of providing sedation to critically ill children is to reduce fear and anxiety in the intensive care unit and not just to keep patients asleep and easily managed.

Further reasons highlighted by the nursing staff preferring sedation scale 2 were the inclusion of baseline and responsiveness assessments. The reason for including this facility in scale 2 was to reduce disruption to patients. A baseline score could be conducted merely by observing the patient. A responsiveness score could be conducted if necessary to distinguish between a patient who was heavily sedated and unresponsive to stimulation, or a patient who was merely sleeping and would wake upon stimulation. Many sedation scales have been criticised for using the response to an additional stimulus on a regular basis. This is inappropriate in critically ill children where it has been shown that encouraging natural sleep improves and aids recovery. Therefore disruption to patients should be kept to a minimum if possible.

The guidelines incorporated in sedation scale 2 that provided advice to the nursing staff about reviewing sedation, were also found to be useful. This design was included to draw attention to nursing staff about patients who were either under sedated or over sedated and therefore might require review of their sedation. From the results of the study these guidelines were thought to be useful, clear and accurate.

From the results of the questionnaire and interviews several modifications were made to sedation scale 2. The wording in the descriptions of sedation scale 2 was changed to be more concise. Also a suggestion was made by respondents to incorporate into the sedation policy, a requirement on the part of the medical staff and nursing staff to agree a required level of sedation for a particular child at least twice daily. Each child is likely to require different levels of sedation depending on their severity of illness and level of respiratory support. Therefore, a child may be required to be kept heavily sedated for a period of time and this should not be necessarily regarded as over sedation. Conversely, if a child is nearing extubation minimal sedation is required to avoid respiratory depression and this should not be regarded as under sedation. All of these modifications were implemented into the design of sedation scale 2 and the latter was incorporated into regular use at Birmingham Children's Hospital PICU.

From the results of the nursing staff interviews further information was obtained about sedation assessment in PICU. Children highlighted by the staff as being difficult to sedate effectively included, patients with Down syndrome, neonates, children aged over 15 years, children aged between 1-3 years and patients with neurological problems. Reasons for this remain unclear but these groups of patients will be discussed in the following chapters. Nursing staff also thought that further research was required with regard to sedation and its assessment in paralysed patients and patients with neurological problems. Nursing staff thought that both sedation assessments scales were inappropriate for sedation assessment in patients receiving neuromuscular blocking agents. There is a lack of suitable methods of sedation assessment for this group of patients and therefore the need for further research in this area is essential. Again the reasons why it is imperative to undertake appropriate sedation assessment in the paralysed patient will be developed in this study and discussed in further detail in the following chapters.

1.8 Long-term assessment of the reproducibility of sedation scale 2

A total of 80 paired sedation assessment scores were collected for scale 2, which involved 50 patients. Table 1.13 shows the range of sedation scores obtained from each assessor. The proportion of agreement of all assessments made by the raters was found to be 62.5%. Kappa was calculated to be 0.60.

Table 1.13. Range of sedation scores for both assessors using sedation scale 2.

Sedation score	Assessor 1.	Assessor 2	Total No.
0	0	0	0
1	4	1	5
2	2	5	7
3	1	1	2
4	5	6	11
5	27	23	50
6	7	15	22
7	9	4	13
8	5	4	9
9	9	9	18
10	11	12	23

Discussion of the sedation assessment scale follow up study

After a period of 12 months sedation assessment scale 2 had been in regular use at Birmingham Children's Hospital PICU. A follow up study was undertaken in order to investigate reproducibility of the scale over time. The follow up study was identical in design to the original study where two independent assessors made a sedation assessment of a child simultaneously and remained blind to each others scores. It was found that in a total of 62.5% of cases the two assessors agreed. Kappa was found to be 0.60, which indicates good agreement between assessors. This was very similar to previous findings in the present study for the level of agreement found between assessors using scale 2 and suggests that the reproducibility of scale 2 remained constant over time. The range of sedation scores (table 1.1.3) can be compared to the range of scores obtained in the initial experiment (table 1.4). The majority of scores were made at level 5 and levels 9 and 10 which were similar to the results found previously in the present study.

1.9 Summary

The aim of the sedation assessment scale evaluation was to compare and contrast two different types of observational sedation assessment scales for reproducibility and practical use in critically ill children. Few studies have fully validated a sedation assessment scale in PICU patients and no other study has compared two different types of scales. Sedation scale 1 was simple in design requiring a single assessment of the patient by the nursing staff. This scale was in use at Birmingham Children's Hospital PICU prior to the study being undertaken. Scale 2 was more complicated in design and required the nursing staff to make an assessment of five patient parameters to achieve a sedation score. Scale 2 was developed as part of the present study, by considering other sedation assessment scales used in critically ill patients. Due to the subjective nature of sedation assessment it was important to assess each scale for reproducibility. This was undertaken by comparing the extent of inter rater agreement for each sedation scale. Both sedation scales investigated in this study were found to achieve good reproducibility. In addition to investigating reproducibility however, it was imperative to seek and obtain the opinions of the nursing staff using the scales. This was important for several reasons. Firstly, nurses using the scales could highlight any shortcomings in the scales identified with regular use. Secondly, involvement in the decision about which sedation scale should be used regularly in PICU gives a sense of ownership of the sedation scale and encouragement to use it effectively. Both sedation assessment scales were found to be useful in assessing the level of sedation in critically ill children by the nursing staff. However, sedation scale 2 was thought to provide a more accurate measure of the level of sedation and anxiety, rather than merely sedation compared to scale 1 and was considered to be less ambiguous to use in comparison. Although scale 2 was found to be slightly more time consuming to use than scale 1 it was preferred by the majority of the nursing staff. The long-term reproducibility of scale 2 was investigated after a period of 12 months regular use at Birmingham Children's Hospital PICU. It was found that the reproducibility of scale 2 remained constant over time. Therefore as a result of this study sedation scale 2 was incorporated into Birmingham Children's Hospital PICU sedation policy.

CHAPTER 2

THE INVESTIGATION OF MIDAZOLAM PLASMA CONCENTRATION AND LEVEL OF SEDATION IN CRITICALLY ILL CHILDREN

CONTENTS

2.1 Introduction

This chapter describes an investigation into the correlation between midazolam plasma concentration in critically ill children and level of sedation. The sedative effect of midazolam was monitored in patients using the sedation assessment scale developed and validated in the present study. An investigation into the correlation between dose of midazolam infusion and midazolam plasma concentration was also undertaken.

Previous studies have found large inter-individual variations in midazolam plasma concentration in critically ill adults and few have been able to identify any correlation between midazolam plasma concentration and level of sedation (Oldenhof, de Jong et al 1988). Midazolam plasma concentrations in the region of 300-400ng/ml have been found to produce satisfactory anaesthesia during major surgery in adults (Nilsson, Tamsen 1986). In adults recovering from surgery midazolam plasma concentrations in the region of 50-75ng/ml have been associated with effective postoperative sedation (Perrson, Nilsson 1987). This work is supported by a study undertaken by Somma, Donner et al (1998) that found midazolam plasma concentrations of 71ng/ml to provide satisfactory sedation in surgical intensive care adults. However, few studies undertake in critically ill children have been able to establish such a correlation with sedation (Hughes, Gill et al 1996; Nahara, McMorrow et al 2000). Hartwig, Roth et al. (1991) found a correlation between midazolam plasma concentration and level of sedation in critically ill children during the first 72 hours of therapy, after which time any correlation was lost.

Attempts to correlate midazolam plasma concentration with corresponding levels of sedation are complicated by the frequent addition of opioid analgesics to achieve pain control in critically ill children. Morphine itself produces a degree of sedation and it is difficult to directly correlate sedation and midazolam plasma concentration accurately when opioid analgesia has been administered. This problem will also be addressed within this part of the study.

2.2 Results

2.2.1 Patient number and reason for admission to PICU

The total number of patients recruited to the pharmacokinetic study was 57. In two of these patients arterial access was lost before blood samples could be taken. In a further 3, patients blood samples were lost during analysis owing to technical problems. Therefore, in total, blood samples were collected and analyzed from 52 patients (22 female and 30 male). The age of patients recruited to the study ranged from 0 to 18 years. Table 2.1 indicates the number of patients recruited to the study in the defined age bands.

Table 2.1 Numbers of patients recruited to the pharmacokinetic study within the defined age bands

Age bands	Patient number (n=52)
Premature neonates	2
Neonates	6
Less than 1 year	20
1-3 years	9
4-7 years	5
More than 7 years	10

Table 2.2 indicates the reasons for admission to PICU for the patients recruited to the study

Table 2.2 Numbers of patients recruited to the pharmacokinetic study within each specified admission category

Reason for admission	Patient number (n=52)
Burns	1
Cardiac surgery	23
Infection	3
Liver failure	4
Neurological	7
Postoperative	2
Respiratory	11
Spinal tumours	1

2.2.2 Sample number and summary of midazolam plasma concentrations

A total of 303 blood samples were taken from patients recruited to the study and the plasma was analyzed for midazolam, 1-hydroxymidazolam (1-OH) and 4-hydroxymidazolam (4-OH). The findings relating to plasma concentrations of the metabolites 1-OH and 4-OH will be presented and discussed in Chapter 4. Midazolam plasma concentrations ranged from 0-9306ng/ml. The length of time patients recruited to the study received a continuous midazolam infusion ranged from 1-23 days.

Figure 2.1 Midazolam plasma concentration (ng/ml) in critically ill patients versus the corresponding day after admission on which the blood sample was taken

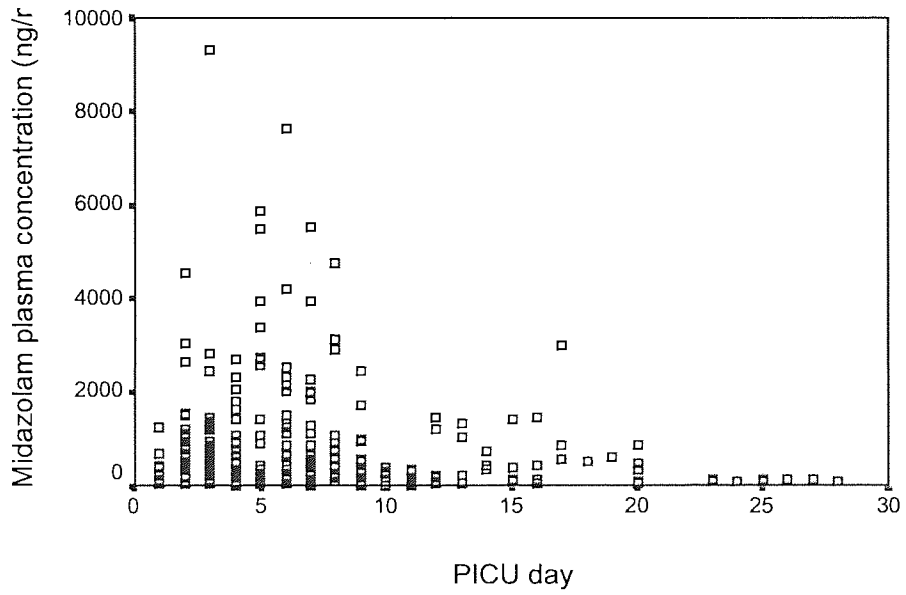


Figure 2.1 indicates that the majority of blood samples were taken from patients after day 1 of admission to PICU. It was difficult to obtain consent from relatives to recruit patients to the study on day 1 of admission to PICU for a number of reasons, which will be discussed. Therefore the majority of patients were recruited after day 1 of admission. Midazolam infusion rate ranged from 0.5-15mcg/kg/min. However only 1 patient received high dose midazolam during which 9 blood samples were taken. The remaining patients received a midazolam infusion rate between 0.5 and 6.4mcg/kg/min. It can be seen from the results that there is a wide range in midazolam plasma concentrations achieved.

A total of 76 blood samples were taken from patients after the midazolam infusion had been discontinued. The midazolam plasma concentrations in these patients are presented in table 2.3

Table 2.3 Midazolam plasma concentrations in patients after discontinuation of midazolam infusion.

PICU Day	No. of patients	No. of samples (n=76)	Midazolam plasma concentration (ng/ml)
1	1	1	28
2	2	2	18, 158
3	16	19	0-1233
4	18	22	0-2557
5	6	8	43-2570
6	4	5	30-874
7	2	4	534, 2017
9	3	4	0-982
10	1	1	314
11-28	5	10	0-163

It can be seen from the results that the majority of patients had the midazolam infusion discontinued on days 3 and 4 after admission to PICU, indicating a relatively short duration of midazolam therapy. It is interesting to note that in some cases, even after the midazolam infusion had been discontinued the midazolam plasma concentration has remained high.

2.2.3 Summary of sedation assessment scores

All blood samples (n=303) taken from patients recruited (n=52) were associated with a sedation score. The sedation assessment scale ranged form 0 to10, a score of 0 indicating light sedation and 10 indicating heavy sedation. There was also a facility within the sedation assessment scale to assess a patient as sleeping and this would be indicated in the documentation using the letter 'A'. Patients that were receiving neuromuscular blocking agents and paralysed could not be assessed for level of sedation using the sedation assessment scale and this would be indicated in the documentation using the letter 'P'. Table 2.4 gives a breakdown of the number of samples taken with an individual sedation score together with the number of patients in each case.

Table 2.4 Number of samples taken from patients and the corresponding sedation score.

Sedation score	0	1	2	3	4	5	6	7	8	9	10	A[a]	P[b]
Number of samples	3	3	4	3	6	50	11	10	7	34	39	22	111
Number of patients	2	3	4	3	6	25	9	7	4	17	21	11	29

a-denotes patients assessed as asleep
b-denotes patients that were paralysed.

The sedation assessment scale was subdivided into three sections. A sedation score between 0 and 3 indicated light sedation and/or under sedation, a score between 4 and 7 indicated a satisfactory level of sedation and a score between 8 and 10 indicated heavy sedation and/or over sedation. Table 2.5 shows the number of samples associated with a sedation score within these categories.

Table 2.5 Number of samples taken from patients within the different categories of the sedation assessment scale

Sedation score range	0-3	4-7	8-10
Number of samples (%)	13 (7.6)	77 (45.3)	80 (47.1)

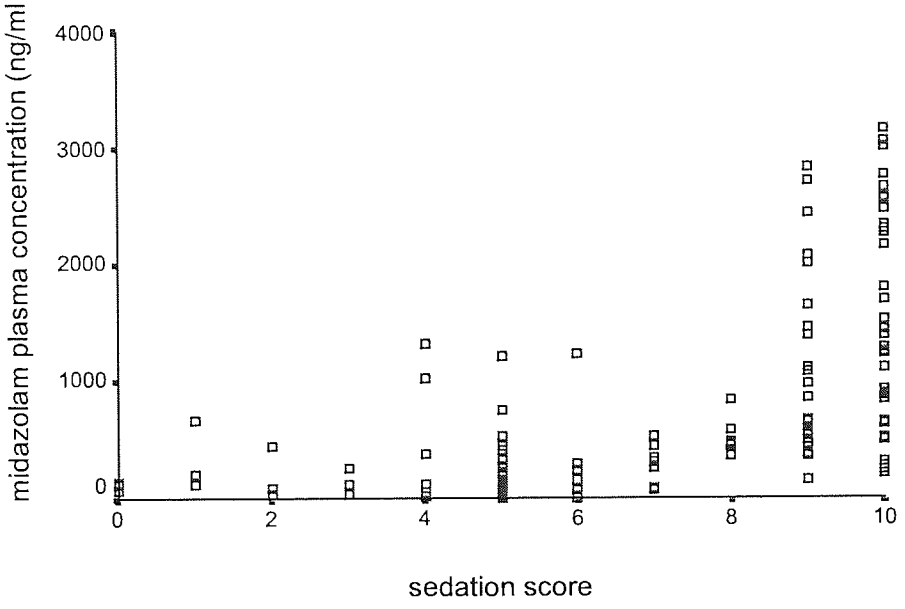
The results suggest that only 45.3% of samples taken from patients were associated with a satisfactory level of sedation. A similar number of samples taken from patients (47.1%) were associated with a heavily sedated state. Patients assessed as sleeping were considered as satisfactorily sedated as they were clearly not agitated or in any distress. Patients assessed as asleep were not heavily sedated as a responsiveness score was carried out at least daily to distinguish between patients who were merely asleep from those that were heavily sedated.

2.2.4 Level of sedation and midazolam plasma concentration

The correlation between midazolam plasma concentration and sedation score was investigated where a midazolam concentration was associated with a sedation score between 0 and 10. Blood samples that had been taken from patients who had been assessed as sleeping or paralysed at the time of taking the blood sample were not included in this analysis. The number of midazolam plasma concentrations used in this analysis was 170 and the results are shown in figure 2.2

A number of midazolam plasma concentrations (n=18) were found to be outside the midazolam calibration curve concentration range (25-3000ng/ml) and can be found in Appendix 14 and have been excluded from this analysis.

Figure 2.2 Midazolam plasma concentrations (ng/ml) taken from patients in which a sedation score was made between 0-10 of the sedation assessment scale.



The correlation between midazolam plasma concentration and sedation score was undertaken using the Pearson coefficient, which was found to be 0.598 (the correlation was significant at a level of 0.01). The results indicate a positive correlation between midazolam plasma concentration and sedation score. However, there was a wide range in midazolam plasma concentrations associated with a sedation score of 9 and 10, which represent a heavily sedated patient.

In order to investigate further different levels of sedation, the sedation score was subdivided into three sections as previously described. A score between 0 and 3 represented light sedation, a score between 4 and 7 represented a satisfactory level of sedation and a score between 8 and 10 represented heavy sedation. Figure 2.3 shows the mean midazolam concentrations associated with these three levels of sedation as well as those obtained in patients assessed as sleeping and those that were paralysed at the time of blood sample. Table 2.6 shows the range of midazolam plasma concentrations associated with the different ranges of sedation level. Midazolam plasma concentrations found to be outside the standard

calibration curve (25-3000ng/ml) have been excluded from the analysis and can be found in Appendix 14.

Figure 2.3 Midazolam plasma concentration (±s.e.mean) taken from patients in which a sedation score was made using the sedation assessment scale. Sedation scores have been subdivided into light sedation, satisfactory sedation and heavily sedated.

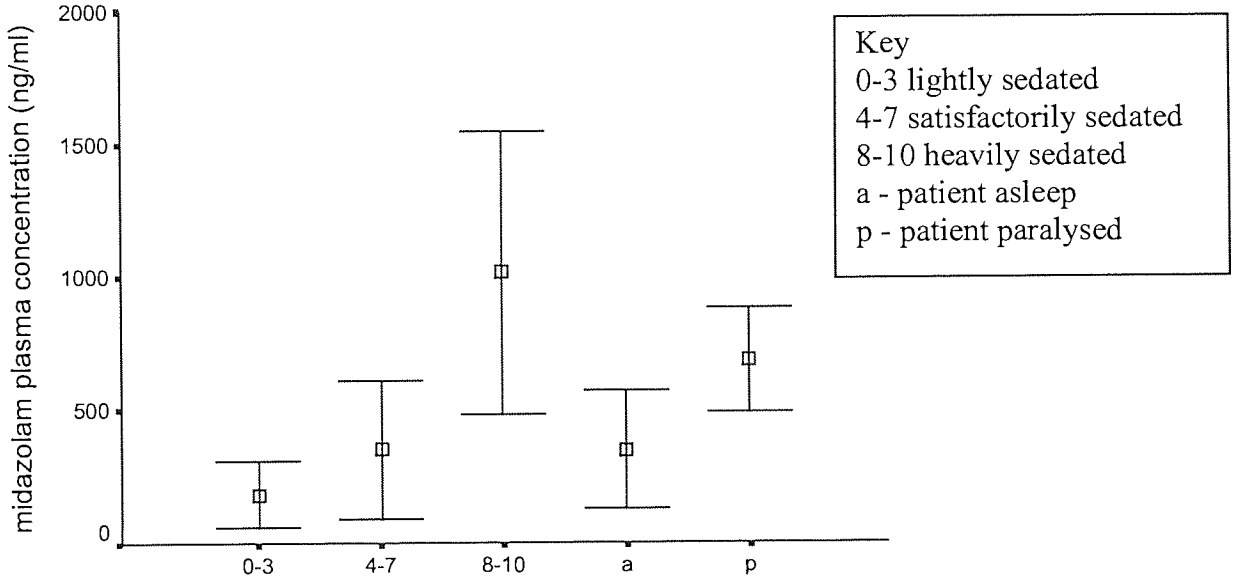


Table 2.6 Midazolam plasma concentration (±s.e.mean) taken in patients and the corresponding sedation scores made using the sedation assessment scale

Sedation score range	No. samples	Mean midazolam plasma concentration (ng/ml) (±s.e.mean)	Midazolam plasma concentration range (ng/ml)
0-3	13	179 (52.5)	28-672
4-7	77	223 (31.9)	25-1319
8-10	71	1227 (105.5)	147-3154
A [a]	22	248 (62.4)	25-1011
P [b]	102	759 (64.1)	0-3371

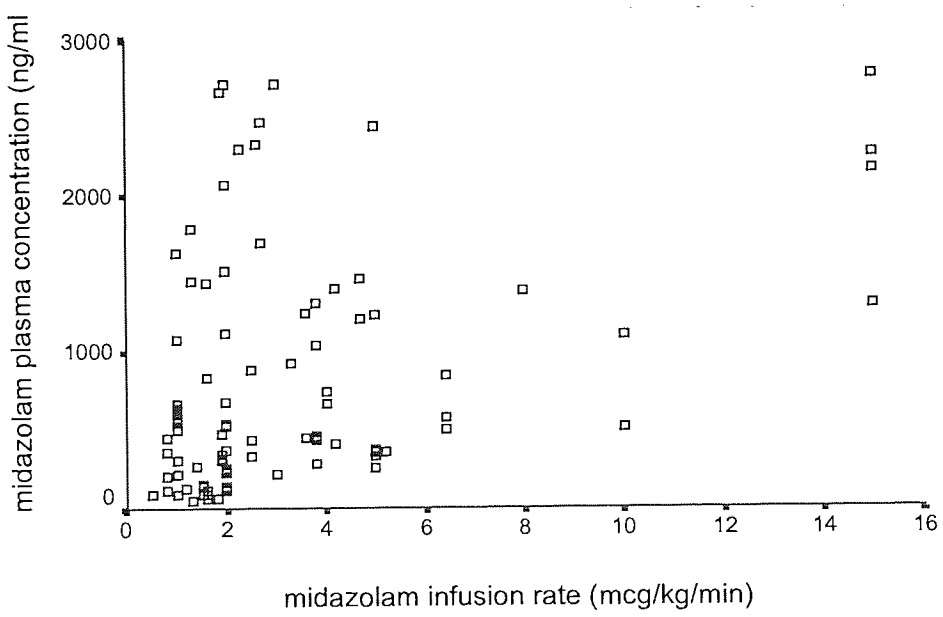
a-denotes patients assessed as asleep
b-denotes patients that were paralysed.

These results show that a mean midazolam plasma concentration of 223ng/ml provided a satisfactory level of sedation. It is interesting to note that the mean midazolam plasma concentration achieved in patients who were satisfactorily sedated and those assessed as sleeping were found not to be significantly different. A mean midazolam plasma concentration of 1227ng/ml was associated with a heavy level of sedation, which was found to be significantly different ($p=0.0001$) from the mean midazolam concentration found in patients satisfactorily sedated. The difference in the mean midazolam concentration between patients lightly sedated and those that were satisfactorily sedated was found not to be significantly different but this may be due to the small numbers in the lightly sedated group. It can be seen from the range in midazolam plasma concentration that there is a degree of overlap between different levels of sedation and midazolam concentration.

2.2.5 Midazolam plasma concentration and dose of midazolam infusion

The relationship between midazolam plasma concentration and midazolam dose was also investigated. A total of 9 midazolam plasma concentrations were found to be outside the midazolam plasma calibration curve range of 25-3000ng/ml and were excluded from this analysis. Using the Pearson coefficient only a weak correlation was found between midazolam plasma concentration and midazolam dose (0.304 which was significant at a level of 0.01). The results are summarized in figure 2.4. It can be concluded that no significant correlation was found between midazolam plasma concentration and dose of midazolam.

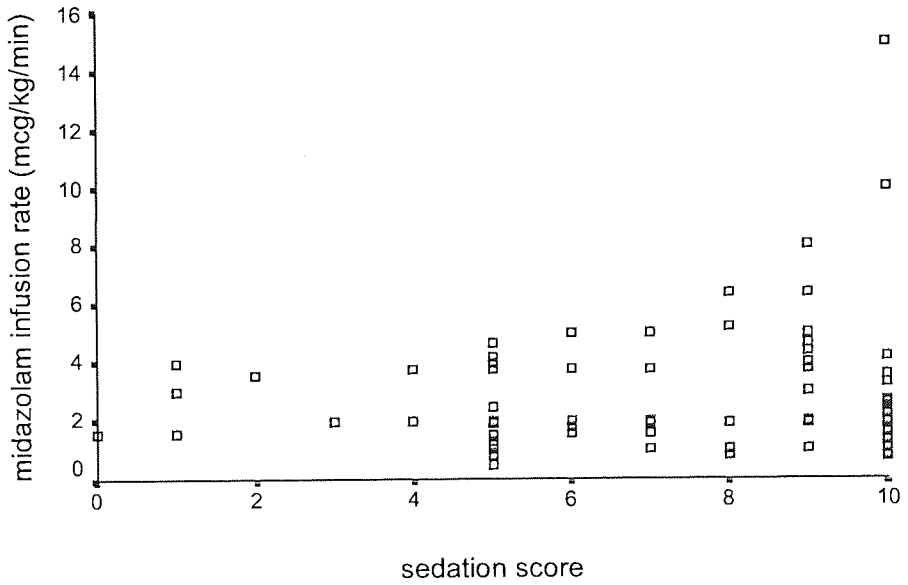
Figure 2.4 Midazolam plasma concentrations (ng/ml) taken from patients and the corresponding dose of midazolam (mcg/kg/min)



2.2.6 Level of sedation and midazolam plasma concentration in patients receiving a midazolam infusion

A total of 110 blood samples were taken that were associated with a sedation score whilst patients were receiving a continuous midazolam infusion i.e. in patients in whom the midazolam infusion had not been discontinued. The relationship between sedation score and dose of midazolam was investigated and the results are shown in figure 2.5.

Figure 2.5 Dose of midazolam (mcg/kg/min) in patients receiving a continuous midazolam infusion and the corresponding sedation score



Using the Pearson coefficient only a weak correlation was found between midazolam dose and sedation score (0.216 at a level of significance of 0.05). The results indicate that there is no significant correlation between midazolam dose and level of sedation.

2.2.7 The effect of age on midazolam plasma concentration and sedation assessment

Further analysis was undertaken investigating the mean midazolam plasma concentration as a function of patient age. Table 2.7 indicates the mean midazolam plasma concentrations associated with a sedation score between 4 and 7 in different ages of children. No significant differences were found between the mean midazolam plasma concentration associated with a sedation score between 4 and 7 in different ages of children.

Table 2.7 Mean midazolam plasma concentrations taken in patients who were assessed as satisfactorily sedated (sedation score between 4 and 7) using the sedation assessment scale as a function of patient age.

Age group	Sample number	Mean midazolam plasma concentration (ng/ml)	Midazolam plasma concentration range (ng/ml)
Neonates	4	176	46-536
Less than 1 year	39	173	25-751
1-3 years	11	364	64-1231
4-7 years	5	137	25-308
More than 7 years	18	278	25-1319

Table 2.8 indicates the mean midazolam plasma concentrations associated with a sedation score between 8 and 10 in different ages of children. The results suggest that children of all of ages achieved high concentrations of midazolam in the plasma and were therefore at risk of over sedation.

Table 2.8 Mean midazolam plasma concentrations taken in patients who were assessed as heavily sedated (sedation score between 8 and 10) using the sedation assessment scale as a function of patient age

Age group	Sample number	Mean midazolam plasma concentration (ng/ml)	Midazolam plasma concentration range (ng/ml)
Neonates	15	1261	158-3012
Less than 1 year	17	630	147-1525
1-3 years	7	1397	203-2715
4-7 years	5	1755	478-3154
More than 7 years	25	1410	237-3056

2.2.8 The effect of concurrent morphine infusions on sedation assessment

The majority of patients admitted to PICU required analgesia and in many cases a strong opioid analgesic was needed. The most routinely prescribed analgesic is morphine. Morphine has sedative properties as well as analgesic properties. Therefore in patients prescribed midazolam and morphine the level of sedation may be due to the combination of drugs. When investigating any correlation between the sedative effects of midazolam with plasma concentration, co-administration of morphine is likely to cause complications. The following analysis investigates the effect of morphine on the sedation score.

Figure 2.6 represents midazolam plasma concentrations taken during the administration of a range of morphine infusions (0-40mcg/kg/hr). There is a wide range of midazolam plasma concentrations achieved in patients, which is independent of the dose of morphine infusion patients were receiving.

Figure 2.6 Midazolam plasma concentrations (ng/ml) taken from patients receiving a concomitant morphine infusion (mcg/kg/hr)

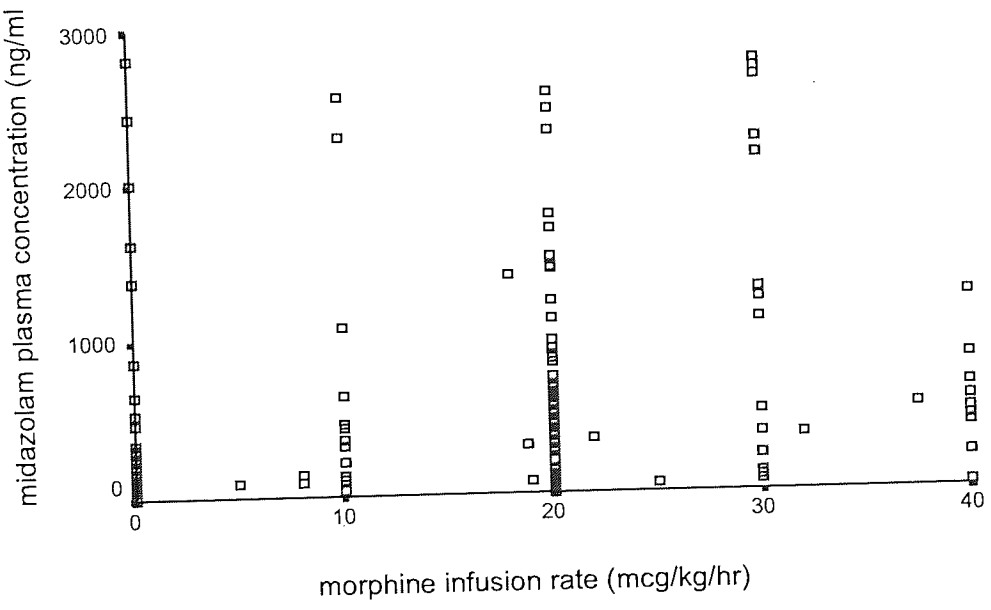


Figure 2.7 shows mean midazolam plasma concentrations in patients administered no morphine compared to those receiving a morphine infusion. The results are subdivided into the three levels of sedation described previously that is lightly sedated, satisfactorily sedated and heavily sedated. Tables 2.9 and 2.10 summarize these results and the number of blood samples taken in each group.

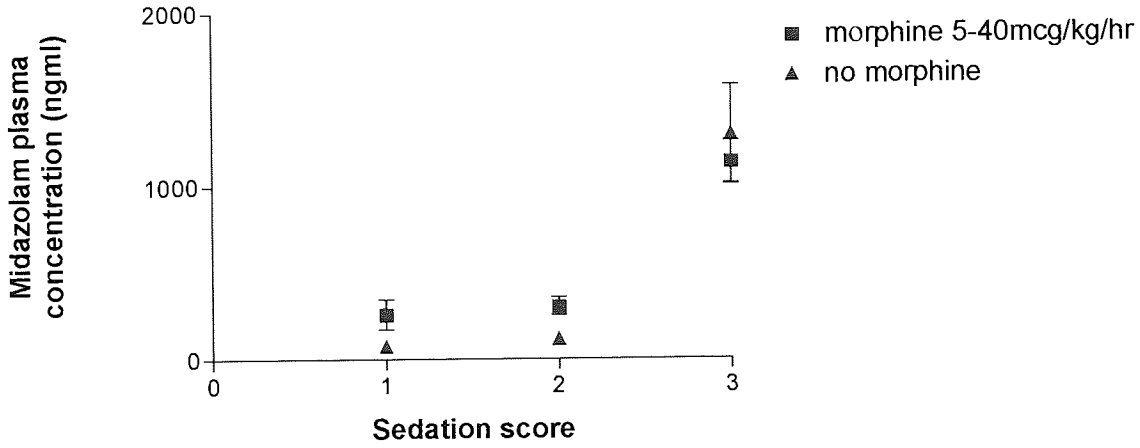
Table 2.9 Mean midazolam plasma concentrations in patients administered no morphine and the corresponding sedation score

Sedation score range	Number of samples	Mean midazolam plasma level (ng/ml)
0-3	4	79
4-7	33	117
8-10	10	1297

Table 2.10 Mean midazolam plasma concentrations in patients administered a concomitant morphine infusion (5-40mcg/kg/hr) and the corresponding sedation score

Sedation score range	Number of samples	Mean midazolam plasma level (ng/ml)
0-3	9	224
4-7	44	303
8-10	61	1215

Figure 2.7
Midazolam plasma concentrations (mean ± s.e.mean) in patients administered midazolam as a single agent and in patients administered concomitant morphine versus the patients sedation score.



1- light sedation (sedation score 0-3)
2- adequate sedation (sedation score 4-7)
3- heavy sedation (sedation score 8-10)

It was found that there were insufficient numbers of patients receiving midazolam as a single agent to draw any valid conclusions. However it can be seen that the plasma concentrations of midazolam in patients who are satisfactorily sedated are slightly higher in patients receiving both midazolam and morphine compared to patients only administered midazolam.

2.2.9 Midazolam plasma concentrations in patients receiving neuromuscular blocking agents

A total of 41 patients out of 52 were paralysed using neuromuscular blocking agents including rocuronium or atracurium. Patients were paralyzed for an average of 4.2 days and table 2.11 shows the length of time patients of different ages were paralysed in the study.

A mean midazolam plasma concentration of 223ng/ml has been found in this study to achieve a satisfactory level of sedation. In the present study it was found that in 84% of samples taken from patients receiving paralysis, a midazolam plasma concentration above 250ng/ml was observed. Out of these samples, 29% were found to have a midazolam plasma concentration above 1000ng/ml.

Table 2.11. Length of days patients received a neuromuscular blocking agent as a function of age.

Age band	Patient number	Total length of time (days) (average per patient)
Neonates	7	19 (2.7)
Less than 1 year	13	61 (4.7)
1-3 yrs	8	42 (5.3)
4-7 yrs	5	20 (4)
More than 7 years	8	30 (4)

These results suggest that patients receiving neuromuscular blocking agents are at risk of achieving high concentrations of midazolam. It is interesting to note that out of the 18 blood samples taken that were subsequently omitted from analysis as a result of the concentrations being outside the calibration range of 25-3000ng/ml; 8 of these samples were taken from patients receiving neuromuscular blocking agents. The plasma concentration for these samples was found to be in the range of 3938-6302ng/ml.

2.3 Discussion

The aim of providing sedation to critically ill children whilst in the intensive care unit is to alleviate anxiety and distress. The difficulty lies in providing the correct amount of sedation to achieve satisfactory sedation without causing under sedation or over sedation. In the present study a total of 170 blood samples were taken that were associated with a sedation score between 0 and 10. It was found that satisfactory sedation, which was represented by obtaining a sedation score between 4 and 7, was achieved in 45.3% of samples taken from patients. In 47.1% of samples, patients were assessed as heavily or over sedated, achieving a sedation score between 8 and 10. Under sedation, which was represented by achieving a sedation score between 0 and 3, was evident in only 7.6% of samples. The reasons why under sedation in patients recruited to the study appeared to a lesser extent than over sedation remain unclear. However, a patient who is under or lightly sedated can become very anxious and distressed and can lead to in some cases unplanned extubations and the removal of lines. Under sedation is therefore immediately obvious and is often dealt with quickly. Over sedation by contrast is not instantly obvious and can occur gradually. It is perhaps easier to over look than under sedation and maybe the reason why it was found more frequently than under sedation in the present study. Many studies investigating sedation in the intensive care setting have concentrated on the problems associated with under sedation rather than over sedation (Rosen and Rosen 1991; Little, Koenig et al. 1990). Other studies have reported the problems associated with long term infusions of midazolam and the potential problem of withdrawal effects after the midazolam has been discontinued (van Engelen, Gimrere et al. 1993; Fonsmark, Rasmussen et al. 1999). The present study found that over sedation was evident across all ages of children. The present study has found that high plasma concentrations of midazolam can be achieved very quickly even within the first 24-48 hours of therapy which can lead to a heavily or over sedated state. Over sedation can cause numerous problems including an increased risk of side effects from unnecessary exposure to the drug, prolonged weaning from the ventilator and as a consequence delayed discharge from PICU.

Few published studies have been able to correlate sedation level with midazolam plasma concentration stating that the diversity of plasma concentrations achieved, made any correlation impossible (Oldenhof, de Jong et al. 1988; Jacqz-Aigrain, Daoud et al. 1994; Hughes, Gill et al. 1996). Booker, Beechey et al (1986) investigated the use of midazolam infusions (2-6mcg/kg/min) in 50 children in PICU from which blood samples were taken from 10 patients to analyse plasma levels. However, it was found that concentrations were so variable that no conclusions could be drawn. Assessment of sedation was not undertaken according to a set protocol but was left to the discretion of the nursing staff who adjusted the rate of the midazolam infusion as required.

Jacqu-Aigrain, Daoud et al (1994) conducted a placebo controlled trial of midazolam in 48 mechanically ventilated neonates. The study found no correlation between sedation score at 24 and 48 hours and corresponding midazolam concentrations and found only that midazolam gave a better sedative effect than placebo. Again a validated sedation scoring method was not used in the study but one that had been adapted for the assessment of pain in children.

Hartwig, Roth et al. (1991) found a correlation between midazolam plasma concentration and level of sedation in patients during the first 24-72 hours of midazolam therapy. A desirable sedation score could be achieved during this time at a plasma concentration between 100-500ng/ml with a midazolam infusion rate between 1.6-6.7mcg/kg/min. After which time period, however, correlation was no longer evident between sedation score and midazolam plasma concentration. A total of 26 patients were entered into this study aged between 26 days and 5 years. Reasons for admission varied but respiratory support following cardiac surgery was the principal reason.

In the present study a total of 303 blood samples were taken that were associated with a sedation score. In a total of 52 patients, 227 blood samples were taken whilst the patient was receiving a midazolam infusion. The remaining samples (n=76) were taken after the midazolam infusion had been discontinued. The correlation between midazolam plasma concentration and sedation score was investigated in a total of 170 samples that were associated with a sedation score between 0 and 10. A positive correlation ($r=0.598$ $p=0.01$) was found between sedation score and midazolam plasma concentration (figure 2.2). The

correlation between these parameters was explored further by investigating midazolam plasma concentration at specified levels of sedation that is lightly sedated, satisfactorily sedated and heavily sedated. The sedation assessment scale was subdivided into three sections. Figure 2.3 shows the mean midazolam plasma concentration achieved at the three different levels of sedation. The results indicate that a satisfactory level of sedation was achieved at a mean midazolam plasma concentration of 223ng/ml (±31.9). This result compares favourably with work undertaken by Hartwig, Roth et al (1991) who found that a midazolam plasma concentration between 100-500ng/ml achieved a desirable sedation level. It is interesting to note that in the present study patients that were assessed as sleeping and did not therefore have a numerical sedation score associated with the midazolam concentration, achieved a mean midazolam plasma concentration of 248ng/ml. This finding supports the theory that patients who are asleep are not in any distress and are therefore adequately sedated. To reduce disruption to patients, assessment of sedation level is avoided where possible in patients who appear to be asleep.

It has been reported that in adults reliable sedation can be achieved with relatively small plasma concentrations of midazolam as low as 40ng/ml. Above a plasma concentration of 100ng/ml of midazolam adults tend to fall asleep if unstimulated (Gudgeon and Hindmarch 1983; Persson, Nilsson et al. 1987). However Lloyd-Thomas (1986) suggested that a midazolam plasma concentration of at least 250ng/ml was required to achieve adequate sedation in children. In the present study it was found that patients achieved an adequate level of sedation over a wide midazolam plasma concentration range (25-1319ng/ml). These results suggest that some patients can be maintained at a satisfactory level of sedation at very low plasma levels of midazolam. Therefore a minimum midazolam concentration cannot be defined, that will be associated with adequate sedation in all patients and this underlines the importance of accurate clinical sedation assessment using a validated scale in individual patients.

The dose of midazolam infused in patients in this study was very variable and ranged from 0.5-15mcg/kg/min. However only 1 patient received a high dose midazolam infusion from which 9 blood samples were taken. The remaining patients received a dose of midazolam

infusion that ranged from 0.5-6.4mcg/kg/min. The relationship between midazolam plasma concentration and dose of midazolam was also investigated. Only a weak correlation was found ($r=0.304$ $p=0.01$) (figure 2.4). The relationship between the dose of midazolam administered to patients and level of sedation achieved was also investigated (figure 2.5). Again only a weak correlation was found ($r=0.216$ $p=0.05$). Consequently, these results suggest that adjustment of midazolam dose is not an accurate and safe method to obtain satisfactory levels of sedation in critically ill children. The reasons for this remain unclear but further investigation into possible complicating factors including the effects of concurrent medication, the effect of age and disease state on sedation requirements are required.

No significant differences were observed in the midazolam plasma concentrations required to achieve adequate sedation in children of different ages. Although it must be pointed out that numbers of samples in some of the groups were very small. Further work is needed to investigate any age related differences in midazolam plasma concentrations required to achieve adequate sedation.

An important influence on the assessment of sedation is the use of concurrent sedative medication. It has been suggested that it is difficult to correlate level of sedation with midazolam plasma concentration because many patients receive a concomitant morphine infusion for pain relief. Morphine does have sedative properties and it is therefore difficult to distinguish between the sedative effects of analgesia and midazolam if both are administered concurrently. To investigate the effect morphine has on sedation assessment in critically ill children, the midazolam plasma samples associated with a sedation score were divided into two groups. Samples taken from patients receiving a morphine infusion between 5-40mcg/kg/hr and samples taken from patients not receiving a morphine infusion.

A total of 44 blood samples were taken from patients receiving midazolam as a single sedative (table 2.8). Patients in this group who were satisfactorily sedated achieved a mean midazolam plasma concentration of 117ng/ml. A total of 144 blood samples were taken from patients receiving a morphine infusion between 5-40mcg/kg/hr. Patients in this group who were satisfactorily sedated achieved a mean midazolam plasma concentration of 303ng/ml.

Numbers of patients receiving midazolam as a single agent were too small to draw any conclusive results. However, patients who were satisfactorily sedated who were receiving midazolam as a single agent achieved slightly lower midazolam concentrations than those receiving both midazolam and morphine. The reasons for this remain unclear but maybe as a consequence of severity of illness. Patients nearing extubation may be receiving midazolam as a single agent to reduce the respiratory depressant effects of a combination of morphine and midazolam. These patients would be adequately sedated at a lighter level of sedation and would therefore require a lower midazolam plasma concentration.

A total of 41 patients out of 52 were paralysed at some time during their admission to PICU. The average time patients were paralysed in PICU was 4.2 days. Neonates were paralysed for the shortest average time (2.7 days). Neurology patients were paralysed for the longest average time (6.7 days). Patients who are paralysed pose a difficult problem with regard to sedation assessment, however it does appear that this group of patients are at particular risk of achieving high concentrations of midazolam. It was found that 84% of samples taken from patients receiving paralysis had a midazolam plasma concentration above that required to achieve a satisfactory level of sedation (250ng/ml). A total of 29% of samples taken from patients receiving paralysis were found to have a midazolam concentration above 1000ng/ml. One of the reasons why these patients may be achieving high midazolam plasma concentrations is the lack of an accurate method by which sedation assessment can be undertaken in this group of patients.

Summary

In contrast to previous studies this study has established a significant correlation between midazolam plasma concentration and level of sedation in critically ill children. One of the shortcomings in other studies is a lack of a suitable sedation assessment scale that has been specifically designed for use in critically ill children. The sedation assessment scale used in this study was specifically designed for this purpose and was validated to ensure reproducibility. This part of the study has underpinned the pharmacokinetic and pharmacodynamic elements of the study and has played a crucial role in determining the correlation between plasma concentrations of midazolam and level of sedation. In the present study a mean plasma concentration of midazolam of 223ng/ml produced a satisfactory level of sedation. However, the range of midazolam plasma concentrations achieving adequate sedation was found to be between 25ng/ml and 1319ng/ml. This indicates that some patients can be managed on much lower midazolam plasma concentrations. We investigated patients who were assessed as sleeping and therefore adequately sedated. The mean midazolam plasma concentration in this group of patients was also similar at 248ng/ml. This finding confirms the correlation between adequate sedation and midazolam plasma concentration. As in previous studies, only a weak correlation was found between the dose of midazolam administered and midazolam plasma concentration. Also no significant correlation was found between the dose of midazolam administered and sedation level. Previous studies have stated that sedation assessment is difficult in patients receiving concomitant sedative therapy such as morphine. This study investigated patients receiving midazolam as a single agent and those receiving additional regimens of morphine. However numbers of patients receiving midazolam as a single agent were too small to draw any valid conclusions. In the present study over sedation appeared to be more of a problem than under sedation. Previous studies have concentrated on the problems arising from under sedation and also problems associated with the long term administration of midazolam compared to problems arising from over sedation. The consequences of over sedation can culminate in delayed discharge from ITU and over exposure to sedative medication with resultant side effects. This problem requires further research and confirms the need to adequately assess the level of sedation in all patients.

Patients receiving neuromuscular blocking agents pose a difficult problem with regard to effective sedation assessment. The results from this study have highlighted that these patients

are at risk of achieving considerably high plasma concentrations of midazolam. There is an urgent need to develop a method by which level of sedation can be assessed in these patients to avoid unnecessary and excessive exposure to sedative agents.

Summary of major findings

- Significant correlation between midazolam plasma concentration and level of sedation.
- Poor correlation between midazolam plasma concentration and midazolam dose.
- Poor correlation between midazolam dose and level of sedation.
- Patients receiving neuromuscular blocking agents are at risk of achieving high midazolam plasma concentrations.

It is apparent from this work that there is a wide range in midazolam plasma concentrations achieved in critically ill children. To investigate this further it is necessary to consider the clearance of midazolam in different ages of children and to take into consideration different disease states. Investigation of clearance will uncover if there are particular children that are accumulating midazolam and therefore achieving comparatively higher plasma concentrations. This will be discussed in the following chapter.

CHAPTER 3

THE INVESTIGATION OF MIDAZOLAM CLEARANCE IN CRITICALLY ILL CHILDREN

CONTENTS

3.1 Introduction

Many drugs are eliminated from the body at a rate that is proportional to their plasma concentration. Drugs that behave in this way are said to demonstrate first-order kinetics. The clearance of a drug is the volume of blood or plasma that is completely cleared of the drug in unit time. Clearance can be calculated when the drug has reached a steady state plasma concentration and the dose is known.

The clearance of midazolam in this study was calculated in order to investigate the elimination of midazolam in critically ill children. It has been demonstrated in adult studies that the half-life of midazolam is prolonged in critically ill patients (Taburet, Tollier et al 1990; Malacrida, Fritz et al. 1992). A number of studies investigating midazolam clearance in neonates have found a reduced clearance compared to healthy children (Jacqu-Aigrain, Wood et al 1990). However, studies in older children are lacking and give rise to conflicting results. The effect of disease state on the clearance of midazolam is also investigated in this study. It has been demonstrated in adult studies that particularly liver impairment and cardiac impairment can cause a reduced clearance of midazolam. Studies looking specifically at the effect certain disease states have on the clearance of midazolam in children are limited.

There is some evidence to suggest the development of auto-induction of midazolam with continued intravenous use (Lloyd-Thomas and Booker 1986). However, studies again are limited and require further research to clarify this position.

It is hoped that the results from this study will help clarify some of the findings from previous studies and further the knowledge of pharmacokinetics in critically ill children.

3.2 Results

A total of 303 arterial blood samples were taken from 52 patients. 227 blood samples were taken whilst patients were receiving a continuous midazolam infusion. Of these samples 224 were taken at an assumed steady state, that is, a change in infusion rate did not occur within six hours of taking a blood sample and no bolus doses were administered within six hours of taking a blood sample (see experimental methods 2.5 page 63).

It was found that in 18 blood samples taken during the study, the midazolam plasma concentrations were outside the standard calibration curve range of midazolam (25-3000ng/ml). The results of these midazolam plasma concentrations can be found in Appendix 14. Throughout this chapter it is stated when the results of these outliers have been included in the analysis.

Midazolam Clearance Calculation

The clearance of midazolam was calculated using the following formula (Young and Koda-Kimble1995):

$$Cl = \frac{\text{maintenance dose}(S)(F)}{\text{Cpss ave}(\tau)}$$

S and F represent the fraction of the dose reaching the systemic circulation
Cpss - average plasma concentration at steady state
τ is the dosing interval
Using a constant infusion rate S, F and τ can all be considered equal to 1.

A mean midazolam clearance was calculated for each set of patients and disease state investigated. Alteration of midazolam clearance with time was investigated. Duration of midazolam therapy was subdivided into days of treatment as follows:

- days 1 - 2
- days 3 - 4
- days 5 - 7
- above 7 days

3.2.1 Calculation of Midazolam Clearance

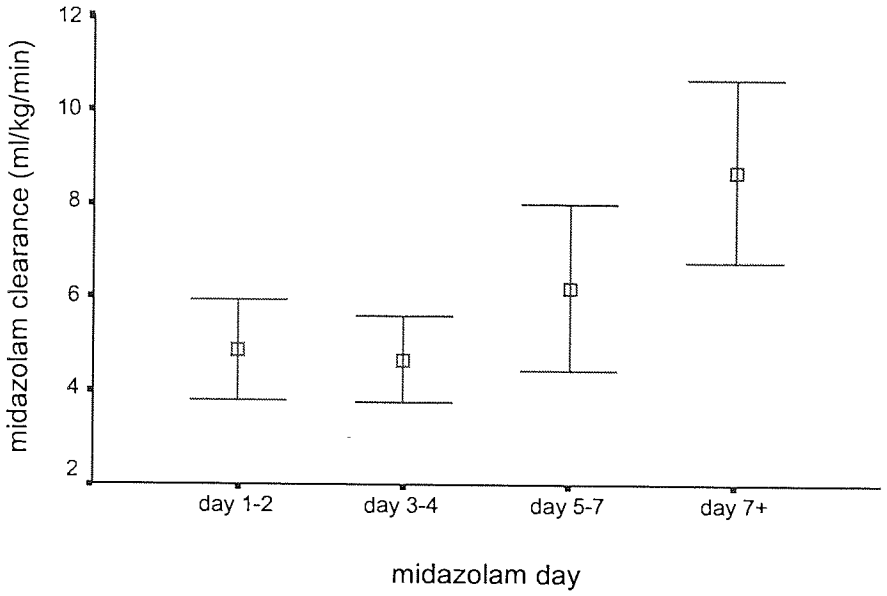
Midazolam clearance was calculated from all blood samples taken at steady state (n=224). The overall mean midazolam clearance calculated for all 52 patients recruited to the study was found to be 6.3ml/kg/min (± 0.36). Table 3.1 shows the mean midazolam clearance with duration of midazolam therapy. From the results it can be seen that there is an increase in midazolam clearance with time.

Table 3.1 Midazolam clearance (±s.e.mean) and duration of midazolam therapy

Midazolam day	Sample number (n=224)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	49	4.89 (±0.54)
3-4	62	4.67 (±0.40)
5-7	55	6.56 (±0.82)
+7	58	9.04 (±0.85)

Figure 3.1 shows the difference in mean midazolam clearance values during different days of midazolam therapy in all patients. A significant difference was seen in the midazolam clearance obtained during the first 48 hours of therapy compared to those seen after 7 days of continuous midazolam therapy (p= 0.001)

Figure 3.1 Midazolam clearance (±s.e.mean) and the corresponding length of time patients had received a continuous infusion of midazolam



3.2.2 The Relationship between patient age and midazolam clearance

Analysis of the data was undertaken as a function of patient age. The following age bands used during the analysis:

Neonates (age less than 1month)

Patients aged between 1 and 12 months

Patients aged between 1 and 3 years

Patients aged between 4 and 7 years

Patients greater than 7 years.

Midazolam clearance will be reported separately for each of these age groups of children.

Neonates

A total of 10 blood samples were taken at steady state from 6 neonatal patients. The overall mean midazolam clearance was calculated at 1.63ml/kg/min (±0.3). Clearance values ranged from 0.53-3.03ml/kg/min. There was no significant difference in the mean clearance values with duration of midazolam therapy. One of the patients had severe renal impairment. Excluding the samples taken from this patient (n=4) midazolam clearance calculated for the remaining patients was found to be 1.66ml/kg/min.

Patients aged between 1 and 12 months

A total of 78 blood samples were taken at steady state from 20 patients. From the results it was found that 2 midazolam plasma concentrations in this group were out outside the midazolam standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. Both of these samples were taken from 1 patient with liver impairment and are documented in Appendix 14. The overall mean midazolam clearance in patients aged 1 to 12 months was found to be 8.52ml/kg/min (± 0.72). In this group of patients, there were 2 children with severe liver impairment and 1 child with severe renal impairment. Excluding the samples from these patients (n=11), the mean midazolam clearance was found to be 9.03ml/kg/min.

A significant increase was found in midazolam clearance after day 5 of therapy (p=0.008). Table 3.2 shows the difference in midazolam clearance in this age range of patients over time.

Table 3.2 Mean midazolam clearance (±s.e.mean) and duration of midazolam therapy in patients aged between 1 and 12 months.

Midazolam day	Sample number (n=76)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	16	4.47 (±1.22)
3-4	19	4.87 (±0.63)
5-7	15	11.36 (±1.80)
7+	27	11.37 ± (1.23)

Patients aged between 1 and 3 years

A total of 51 blood samples were taken at steady state from 9 patients. All patients had normal renal and liver function. The mean midazolam clearance calculated in patients aged between 1 and 3 years was found to be 7.25ml/kg/min (± 0.59). Table 3.3 shows the mean midazolam clearance values calculated over time. The results indicate an increase in midazolam clearance with time.

Table 3.3 Mean midazolam clearance (±s.e.mean) with duration of midazolam therapy in patients aged between 1 and 3 years.

Midazolam days	Sample number (n=51)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	10	6.13 (±1.08)
3-4	18	6.19 (±0.78)
5-7	14	7.18 (±1.13)
7+	9	10.69 (±1.77)

Patients aged 4-7years

A total of 25 blood samples were taken at steady state from 5 patients between the ages of 4 and 7 years. However, it was found that 8 midazolam plasma concentrations taken in this group were outside the standard calibration range for midazolam (25-3000ng/ml) and were therefore excluded from the analysis. The mean midazolam clearance in this age group of patients was found to be 2.11/kg/min (±1.28). Table 3.4 shows the mean midazolam clearance values over time. In this group of patients 2 children has severe renal impairment. Excluding the samples from these patients (n=9) the mean midazolam clearance was found to be 4.85ml/kg/min.

It was found that a significant reduction in midazolam clearance occurred after day 5 of therapy (p=0.05). This reduction in midazolam clearance is in direct contrast to other age groups of children. Table 3.4 shows the mean midazolam clearance calculated over time.

Table 3.4 Mean midazolam clearance (±s.e.mean) and duration of therapy in patients aged between 4 and 7 years.

Midazolam day	Sample number (n=17)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	7	4.66 (±0.97)
3-4	2	3.72 (±2.44)
5-7	5	1.25 (±0.23)
7+	3	1.12 (±0.26)

Patients aged greater than 7 years

A total of 59 blood samples were taken at steady state from 10 patients aged greater than 7 years. A total of six midazolam plasma concentrations were found to be outside the standard calibration range for midazolam and were excluded form this analysis. The mean midazolam clearance in children aged above 7 years was found to be 5.34ml/kg/min (±0.57). In this group of patients, 2 children had severe liver impairment and 1 child had severe renal impairment. Excluding the samples from these patients from the analysis (n=14) the mean midazolam clearance was found to be 6.75ml/kg/min.

A significant increase in midazolam clearance was seen after day 7 of therapy (p=0.03). Table 3.5 shows the increase in midazolam clearance with time in patients aged above 7 years.

Table 3.5 Mean midazolam clearance (±s.e.mean) and duration of therapy in patients aged above 7 years.

Midazolam day	Sample number (n=53)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	12	4.8 (±0.74)
3-4	17	4.00 (±0.76)
5-7	11	7.02 (±1.51)
7+	13	8.71 (±1.39)

Summary of the relationship between midazolam clearance and patient age

Neonates were found to have the lowest midazolam clearance (1.63ml/kg/min) and patients aged between 1 month and 12 months were found to have the highest clearance (8.52ml/kg/min). A significant difference was found between the midazolam clearance calculated in neonates compared with that in children aged between 1 and 12 months ($p=0.001$) and also between neonates and children aged between 1 and 3 years ($p=0.001$).

Midazolam clearance was shown to gradually decrease in patients with normal renal and liver function after the age of 12 months to values of 4.85ml/kg/min and 6.75ml/kg/min in children aged between 4 and 7 years and those above 7 years of age respectively.

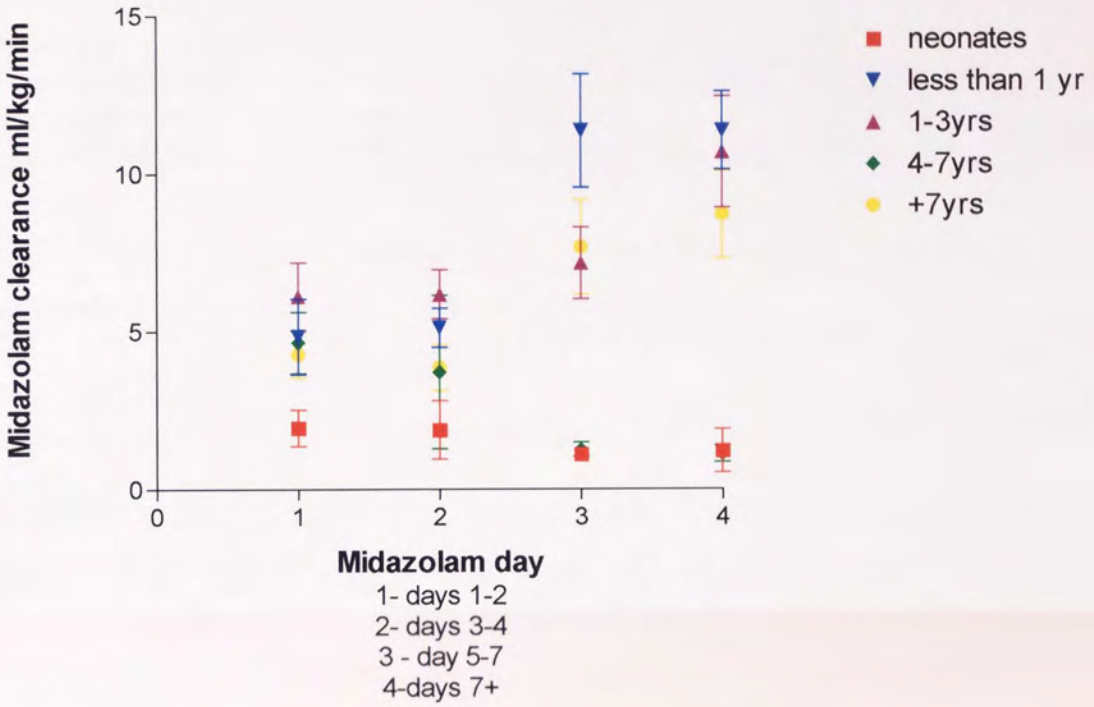
It can be seen from the results that renal and liver disease could affect midazolam clearance. Midazolam clearance was found to be lower in all age groups, if patients with liver and renal impairment were included in the analysis (table 3.6). The effect of liver and renal disease will be addressed later in the chapter and discussed in further detail.

Table 3.6 Midazolam clearance in different ages of children with and without renal and liver impairment

	All patients			Patients with normal renal/liver function		
	Patient number	Sample number	Clearance (ml/kg/min)	Patient number	Sample number	Clearance (ml/kg/min)
Neonates	6	10	1.63	5	6	1.66
Less than 1yr	20	78	8.52	17	67	9.03
1-3yrs	9	51	7.25	9	51	7.25
4-7yrs	5	25	2.11	3	8	4.85
Greater than 7 yrs	10	59	5.34	7	44	6.75

Figure 3.2 shows the differences in midazolam clearance values found in different ages of children over time. It can be seen that neonates have the lowest midazolam clearance throughout therapy and there is no evidence of increased midazolam clearance over time, as seen with other ages of children. Patients between the ages of 4 and 7 years are the only group of patients to show a reduction in midazolam clearance over time. The reasons for this are unclear but there were a limited number of patients in this group and two of these patients had severe renal impairment. All other patients over the age of 1 month show a significant increase in midazolam clearance that occurs after days 5 to 7 of therapy.

Figure 3.2 The relationship between midazolam clearance (±s.e.mean) and the length of time patients had received a continuous midazolam infusion as a function of patient age.



3.2.3 The relationship between midazolam clearance and different disease states

Analysis of the data was undertaken by investigating different disease states. The following conditions and disease states were investigated

Renal impairment	5 patients (13days to 18years)
Liver impairment	4 patients (7months to 14years)
Burns	1 patient (12years)
Cardiac disease	18 patients (0-12years)
Neurology problems	7 patients (1 to 8years)
Respiratory disorders	2 patients (2months, 2years)
Post-operative	11 patients (8days to 5years)
Downs syndrome	5 patients (2months to 12years)

Each of these conditions will be reported separately and then comparisons made between midazolam clearance in patients with different disease states.

Renal impairment and midazolam clearance

A total of 5 patients in the study aged 13 days, 2 months, 4 years, 5 years and 18 years required dialysis for severe renal impairment. A total of 34 blood samples were taken from these patients and midazolam clearance values calculated. The mean midazolam clearance was found to be 1.37ml/kg/min. No significant difference was found in midazolam clearance over time (table 3.7).

Table 3.7 Mean midazolam clearance (±s.e.mean) and length of time patients received a continuous midazolam infusion in patients with severe renal impairment.

Midazolam day	Sample number (n=34)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	13	1.46 (±0.27)
3-4	6	2.07 (±0.47)
5-7	8	1.08 (±0.16)
7+	7	0.95 (±0.28)

There were 8 outliers within this set of samples with a midazolam plasma concentration range between 3938ng/ml and 7643ng/ml. It is interesting to note that if these samples were included

in the analysis there was no significant difference in the findings and the mean midazolam clearance was calculated at 1.68ml/kg/min (±0.16).

Liver impairment and midazolam clearance

A total of 4 patients aged 7 months, 9 months, 9 years and 14 years were recruited to the study with severe liver impairment. Three patients had congenital liver abnormalities and one patient had liver impairment due to paracetamol toxicity. A total of 13 blood samples were taken from these patients and midazolam clearance values calculated. Two samples were taken from one patient after they had undergone a liver transplant and these samples were excluded from the analysis but are reported later to indicate clearance of midazolam before and after liver transplant.

The mean midazolam clearance found in patients with liver impairment was 0.74ml/kg/min (±0.13). No significant difference was seen in midazolam clearance in these patients over time. It was found that 4 of the blood samples taken in these patients were outside the standard calibration range for midazolam (25-3000ng/ml). The midazolam plasma concentrations of these samples ranged form 3957ng/ml to 9306ng/ml and have been included in the analysis.

Midazolam clearance before and after liver transplant

An increase in midazolam clearance was observed in the 9 month old patient who underwent a liver transplant after surgery. The results are shown in table 3.8 and table 3.9. Liver function tests before and after transplant are shown in table 3.10. The increase in midazolam clearance after liver transplant corresponds with the improvement in liver function tests after transplant.

Table 3.8 Midazolam clearance values in one patient with severe liver impairment before liver transplant

Sample	Midazolam clearance (ml/kg/min)
1	0.48
2	0.24

Table 3.9 Midazolam clearance values in one patient with severe liver impairment after liver transplant

Sample	Midazolam clearance (ml/kg/min)
1	5.3
2	18.9

Table 3.10 Liver function tests in one patient with severe liver impairment before and after liver transplant

	ALP(u/l)[1]	ALT(u/l)[2]	AST(u/l)[3]	Bilirubin(umol/l)
Before	368	111	545	717
Before	299	97	289	719
After	164	67	49	112
After	164	89	86	104

[1] - alkaline phosphatase
[2] - alanine aminotransferase
[3] - aspartate aminotransferase

Midazolam clearance and burns injury

A total of 10 blood samples were taken at steady state from a 12 year old male who suffered 70% burns. The mean midazolam clearance was found to be 1.78ml/kg/min (±0.45). However table 3.11 shows the increase in midazolam clearance that occurred in this patient between days 8 and 12 of midazolam therapy. Although midazolam plasma concentrations remained above 1000ng/ml during days 12 and 13 of midazolam therapy, the patient achieved a sedation score between 4 and 5 indicating a satisfactorily level of sedation. The present study has demonstrated that a midazolam plasma concentration above 1000ng/ml is in excess of that

required to provide an adequate level of sedation and the results from this patient suggest that the patient may have developed a degree of tolerance to midazolam and therefore required a higher plasma level to achieve a satisfactory level of sedation.

Table 3.11 Midazolam plasma concentration and the corresponding sedation score and midazolam clearance values in one patient with burn injury

Midazolam day	Midazolam plasma concentration (ng/ml)	Sedation score	Midazolam infusion rate (mcg/kg/min)	Midazolam clearance (ml/kg/min)
4	2069	9	2	0.97
4	2716	9	2	0.74
5	5494	10	2	0.36
6	4190	9	2	0.48
7	5556	9	4	0.71
8	4759	9	4.4	0.92
12	1463	Asleep	4.7	3.21
12	1213	5	4.7	3.87
13	1037	4	3.8	3.66
13	1319	4	3.8	2.88

Midazolam clearance and cardiac impairment

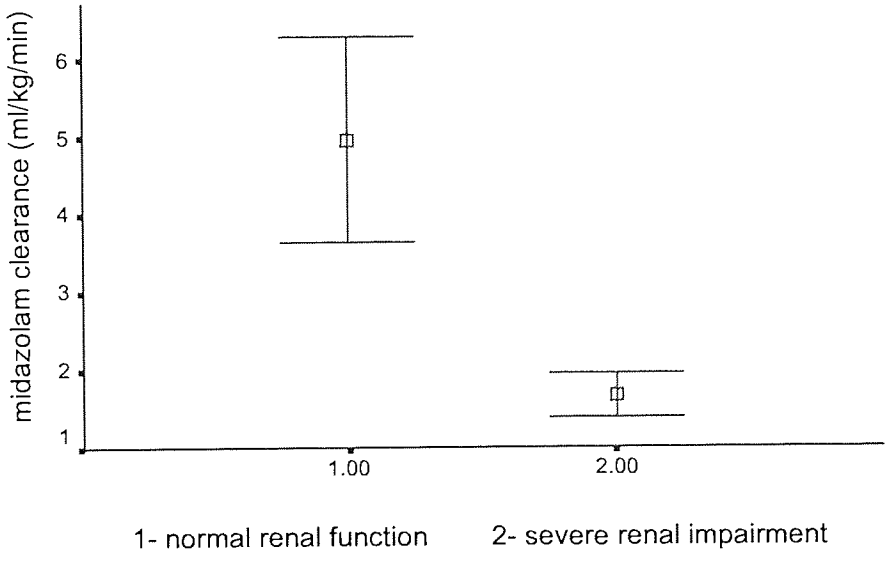
A total of 59 blood samples were taken at steady state from 23 cardiac patients. This group of patients consisted of 6 neonates, 8 children less than 1 year old, and 4 children between the ages of 2.5 years and 12 years all of whom had normal renal and liver function. The remaining 5 children all had severe renal impairment and their ages ranged from 13 days to 18 years. The mean midazolam clearance in all cardiac patients was found to be 3.74ml/kg/min (±0.46). Table 3.12 shows the midazolam clearance calculated over time in cardiac patients. No significant difference in midazolam clearance with time was found in these patients.

Table 3.12 Mean midazolam clearance (±s.e.mean) and length of time patients received a continuous midazolam infusion in patients with cardiac impairment.

Midazolam day	Sample number (n=59)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	17	3.41 (±0.59)
3-4	18	3.81 (±0.56)
5-7	13	3.87 (±1.49)
7+	11	4.19 (±2.21)

Four of the cardiac patients also had severe renal impairment. Cardiac patients with normal renal impairment were found to have a mean midazolam clearance of 4.97ml/kg/min (±0.65). Cardiac patients with severe renal impairment were found to have a mean midazolam clearance of 1.66ml/kg/min (±0.13). Figure 3.3 shows the difference observed between midazolam clearance found between cardiac patients with renal impairment and those without renal impairment (p=0.0001).

Figure 3.3 Midazolam clearance (±s.e.mean) observed in patients with cardiac impairment with and without renal impairment.



Midazolam clearance in Downs syndrome.

A total of 5 patients recruited to the study had Downs syndrome and were aged 2 months 4 months, 7 months, 9 months and 12 years. A total of 40 blood samples were taken from these patients and the mean midazolam clearance was found to be 7.21ml/kg/min (±0.70).

Table 3.13 shows the increase in midazolam clearance observed in these patients over time. The difference in the mean midazolam clearance calculated during the first 48 hours of treatment and after 7 days of treatment was highly significant (p=000.1).

Table 3.13 Mean midazolam clearance (±s.e.mean) and length of time patients received a continuous midazolam infusion in patients with Downs syndrome

Midazolam day	Sample number (n=40)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	6	2.77 (±0.48)
3-4	9	5.10 (±0.62)
5-7	6	7.87 (±2.09)
7+	19	9.40 (±1.01)

Midazolam clearance in neurology patients

A total of 57 blood samples were taken at steady state from 7 patients aged between 1 and 8 years who had suffered a head injury. All patients had normal liver and renal function. The mean midazolam clearance was found to be 7.46ml/kg/min (±0.59). Table 3.14 shows mean midazolam clearance values over time in neurology patients.

Table 3.14 Mean midazolam clearance values (±s.e.mean) and length of time patients received a continuous midazolam infusion in neurology patients

Midazolam day	Sample number (n=57)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	15	6.38 (±0.72)
3-4	16	5.23 ± (0.65)
5-7	15	6.78 (±1.07)
7+	11	13.1 (±1.38)

The difference between midazolam clearance during the first 48 hours and after 7 days of treatment was found to be highly significant (p= 0.0001)

Post-operative patients

A total of 17 blood samples were taken at steady state from 2 post-operative patients with normal renal and liver function aged 3 months and 2 years. Although patient numbers are small in this group it is worth noting that the mean midazolam clearance found in these patients was 15.89ml/kg/min (±1.44), which is much higher than in other groups of patients. The midazolam clearance for each patient was 18.23ml/kg/min (3 month old) and 8.16ml/kg/min (2 year old). Again an increase in midazolam clearance with time was observed in these two patients (table 3.15). No blood samples were taken during the first 48 hours of midazolam therapy in these patients.

Table 3.15 Mean midazolam clearance (±s.e.mean) and length of time patients received a continuous midazolam infusion in post-operative patients.

Midazolam day	Sample no. (n=17)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
3-4	3	7.63 (±0.29)
5-7	8	15.70 (±1.91)
7+	6	20.26 (±1.21)

Midazolam clearance in respiratory patients

A total of 61 blood samples were taken at steady state from 11 patients aged between 8 days and 5 years who were admitted to PICU for respiratory failure. One patient in this group had severe renal impairment and the samples (n=9) from this patient were excluded from the analysis. The mean midazolam clearance found in this group of patients was 7.89ml/kg/min (±0.51). A significant increase in midazolam clearance was seen after 7 days of therapy (p=0.05) and the results are summarized in table 3.16. Three of the patients with respiratory failure were prescribed medication that could potentially interact with midazolam and included carbamazepine, sodium valproate and phenytoin. These samples (n=9) were removed

from the analysis and the subsequent mean midazolam clearance was found not to be significantly different (7.43ml/kg/min).

Table 3.16 Mean midazolam clearance (±s.e.mean) and length of time patients received a continuous midazolam infusion in patients with respiratory failure.

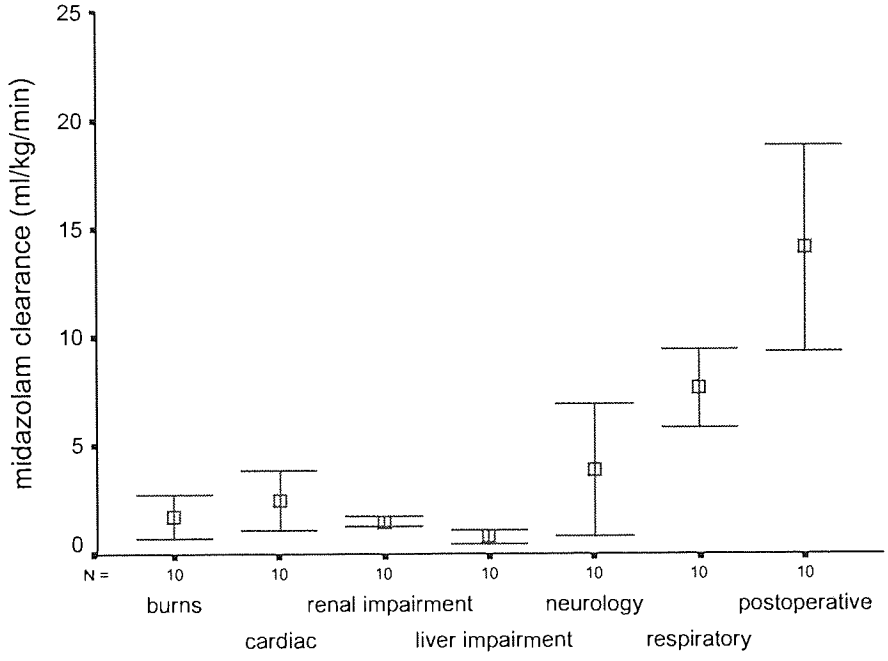
Days	Sample no. (n=56)	Mean midazolam clearance (ml/kg/min) (±s.e.mean)
1-2	8	5.85 (±1.37)
3-4	11	7.42 (±0.87)
5-7	10	8.48 (±1.23)
7+	27	8.25 (±0.81)

Summary of midazolam clearance and different disease states

It is clear from the results that disease state can play an important factor in the clearance of midazolam. Figure 3.4 summaries the midazolam clearance observed in different disease states in the patients recruited to the study. Patients with renal and liver impairment were found to have the lowest midazolam clearance values (1.37ml/kg/min and 0.74ml/kg/min respectively). Patients with respiratory failure and head injury were found to have a midazolam clearance of 7.89ml/kg/min and 7.46ml/kg/min respectively, which are significantly higher than those observed in patients with renal and liver impairment ($p=0.0001$); but lower than those documented in healthy children (9.11-13.3ml/kg/min). Midazolam clearance was found to be lower in patients with cardiac impairment (4.97ml/kg/min) compared to patients with respiratory failure and head injury. The one patient with burn injury was found to have a low midazolam clearance (1.78ml/kg/min) compared to patients with cardiac impairment, respiratory failure and head injury. Only two postoperative patients were recruited to the study, but one of these patients had a midazolam clearance of 18.23ml/kg/min, which is higher than that documented in healthy children (9.11-13.3ml/kg/min).

There was no evidence of increased midazolam clearance with time in patients with liver, renal and cardiac impairment and burns injury. However auto-induction of midazolam was shown in patients with respiratory failure and head injury

Figure 3.4 Midazolam clearance (±s.e.mean) as a function of disease state



3.2.4 The effect of changes in body temperature on midazolam clearance

Four patients were entered into a study to investigate the effect of cooling patients after sustaining a head injury. A total of 39 blood samples were taken at steady state from these patients which included 3 female patients and 1 male patient between the ages of 1 to 8 years. All patients had normal liver and renal function. Patients recruited to this study were randomised to be cooled for the first 24 hours after head injury or kept at normal body temperature. One of these patients was prescribed intravenous erythromycin during the study and as a result an interaction occurred between midazolam and erythromycin. This interaction is discussed later in the chapter.

Patient A (8 years)

A total of 9 blood samples were taken from patient A. 6 samples were taken whilst at a core temperature of between 32 and 34°C, and 3 samples were taken at a core temperature of 37°C. The mean midazolam clearance was found to be 8.17ml/kg/min (±1.08). No significant difference was found between midazolam clearance values taken at different body temperature.

Patient B (2.5years)

A total of 10 blood samples were taken from this patient. However, 6 of the blood samples were taken whilst the patient was receiving concomitant intravenous erythromycin. Subsequently an interaction occurred between midazolam and erythromycin and the results are discussed later. The remaining 4 samples were taken at a core temperature of 37°C.

Patient C (1 year)

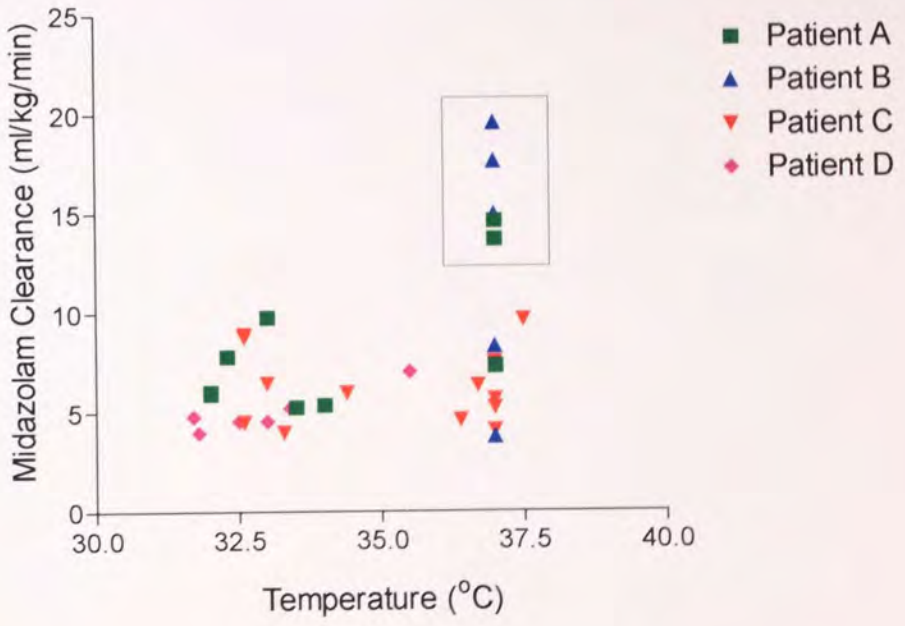
A total of 14 blood samples were taken from this patient. 6 samples were taken whilst at a core temperature of between 32.6 and 34.4°C, and 8 samples were taken at a core temperature of 37°C. The mean midazolam clearance was found to be 6.21ml/kg/min (±0.49). No significant difference was found between midazolam clearance values taken at different body temperature.

Patient D (8 years)

A total of 6 blood samples were taken from this patient. All 6 samples were taken whilst at a core temperature of between 31.7 and 35.0°C. The mean midazolam clearance was found to be 5.01ml/kg/min (±0.43). No significant difference was found between midazolam clearance values taken at different body temperature.

A summary of the results from these 4 patients can be seen in figure 3.5. The five samples highlighted in figure within the rectangle are all taken after day 5 of continuous midazolam therapy. It can be seen that these five midazolam clearance values are higher at temperatures of 37°C but may be as a result of increased midazolam clearance seen after days 5 to 7 of continuous midazolam therapy. It is clear from the remaining samples that there is no significant difference between midazolam clearance taken at different temperatures.

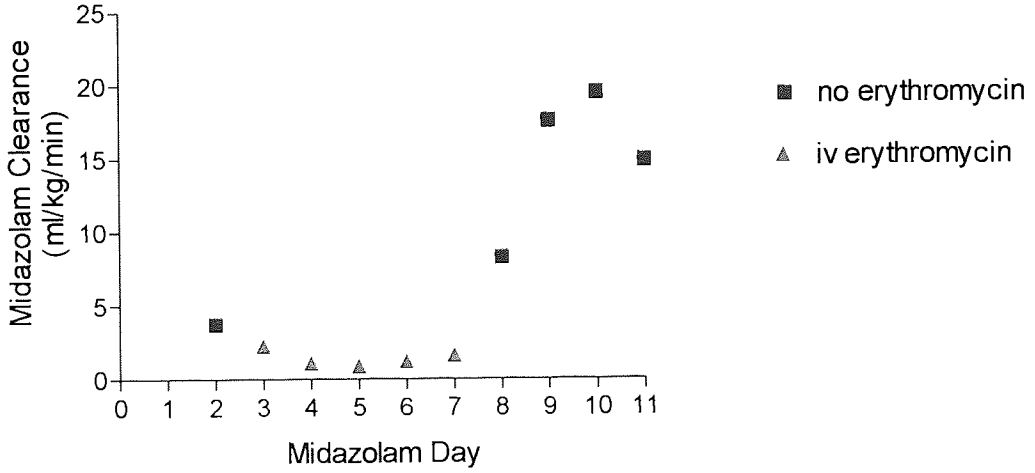
Figure 3.5 Midazolam clearance (ml/kg/min) in patients who received a continuous midazolam infusion and the effect of changes in core body temperature.



3.2.5 Midazolam clearance and the effect of erythromycin

Patient B was prescribed intravenous erythromycin 250mg four times daily for a period of 5 days whilst receiving a continuous midazolam infusion. Figure 3.6 shows the reduction in midazolam clearance observed whilst intravenous erythromycin was administered. The mean midazolam clearance was found to be significantly lower when receiving erythromycin, 1.20ml/kg/min (±0.15) compared to a midazolam clearance of 11.06ml/kg/min (±2.99) without concomitant erythromycin (p=0.01)

Figure 3.6 Midazolam clearance (ml/kg/min) in one patient who received a concomitant infusion of erythromycin



3.3 Discussion

The present study investigated the clearance of midazolam in critically ill children. The aim of the work was to investigate the relationship between age and midazolam clearance and also the relationship between different disease states and midazolam clearance.

Clearance of midazolam in healthy children has been found to be consistently higher than that found in adults ranging from 9.11ml/kg/min to 13.3ml/kg/min (Payne, Mattheyse et al. 1989; Rey, Delaunay et al. 1991) Midazolam clearance has been reported to range from 6 to 8ml/kg/min in young healthy adults and 4-5ml/kg/min in elderly adults (Greenblatt, Abernethy et al. 1984; Smith, Hazelwood et al. 1984). The elimination half-life of midazolam has also been reported to be shorter in healthy children (1.17hrs) compared to 1.5-2.5hours in young healthy adults and 5-6hours in elderly adults (Payne, Mattheyse et al. 1989).

In the present study midazolam clearance was calculated in a total of 224 arterial blood samples taken at steady state from 52 patients. The mean midazolam clearance was found to be 6.30ml/kg/min, which is lower than that reported in healthy children (9.11ml/kg/min to 13.3ml/kg/min). Only a limited number of studies have investigated any age related differences in midazolam clearance in critically ill children and most of these studies have been undertaken in neonates. It has been reported that the clearance of midazolam in critically ill neonates was 2ml/kg/min after a single iv bolus of midazolam of 0.2mg/kg (Jacqz-Aigrain, Wood et al. 1990). The corresponding elimination half-life was found to be 6.5hours. The pharmacokinetic parameters of midazolam have been studied in 15 critically ill neonates administered a midazolam infusion of 60mcg/kg/min (Jacqz-Aigrain 1992). Midazolam clearance was found to be 3.9ml/kg/min and the elimination half-life was 12hours. Midazolam clearance has also been reported to be 1.17ml/kg/min in neonates younger than 39weeks of gestation and 1.84ml/kg/min in neonates older than 39 weeks gestation (Burtin, Jacqz-Aigrain et al. 1994). This phenomenon was attributed to immature hepatic enzyme activity. In the neonates recruited to the present study the mean midazolam clearance was found to be 1.63ml/kg/min. These values are comparative to those found in previous studies where the clearance of midazolam was found to be in the range of 1.17-3.9ml/kg/min. As with other

studies undertaken in neonates an increase in midazolam clearance was not observed with continued midazolam administration and in the present study ranged from (0.53-3.03ml/kg/min).

Children between the ages of 1 month and 12 months were found to have the highest midazolam clearance (8.52ml/kg/min). Midazolam clearance was shown to decrease in patients after the age of 12 months to a value of 5.34ml/kg/min in children above 7 years of age.

In the present study there was evidence of increased midazolam clearance with duration of therapy in children above the age of 1 month. This phenomenon has been documented by Hartwig, Roth et al (1991) who found the clearance of midazolam in critically ill children aged between 26 days and 5 years to be 5.8ml/kg/min during the first 48hrs of therapy increasing to an average of 13.5ml/kg/min after 80hours therapy. In the present study children aged less than 1 year were found to have a mean clearance of 8.52ml/kg/min. However, during the first 48hours the clearance was found to be 4.47ml/kg/min and 4.87ml/kg/min during the following 48hours, increasing to 11.38ml/kg/min by day 7 of treatment. This finding is in keeping with a study undertaken by Hughes that found children under the age of 1 year to have a midazolam clearance of 3.1ml/kg/min during the first 72hours of treatment (Hughes, Gill et al. 1996). Children aged between 1-3 years were found to have a higher clearance (6.16ml/kg/min), during the first 4 days of treatment increasing to 10.66ml/kg/min after day 7 of treatment. The present study also found that children above the age of 7 years to have a mean midazolam clearance of 4.80ml/kg/min during the first 48hours of treatment increasing to 8.71ml/kg/min after day 7 of treatment. In direct contrast neonates recruited to the study showed no evidence of auto-induction. Children aged between 4 and 7 years were the only group to show a reduction in midazolam clearance with duration of therapy. The reasons for this are unclear but there were limited numbers of patients in this group and in addition to this, two of these patients had severe renal impairment, which could have influenced the results.

It was apparent from the analysis of the results that the clearance of midazolam could be affected by the presence of renal and liver impairment. After excluding patients with either

renal or liver impairment from the analysis midazolam clearance was found to be higher in all age groups. Therefore to study the influence of renal and liver disease on midazolam clearance further investigation into different disease states was undertaken.

Patients with liver and renal impairment were found to have the lowest mean midazolam clearance values (0.74ml /kg/min and 1.37ml/kg/min respectively).

Liver Impairment.

Midazolam undergoes hepatic microsomal oxidation. and is metabolized by the cytochrome P450 enzyme system that is part of an oxidation/reduction system located in the endoplasmic reticulum of hepatocytes. The clearance of midazolam is reduced in adults with various co-existing conditions such as hepatic disease and cardiac disease (Hamdy, Kennedy et al. 1986; Shelly, Dixon et al. 1989; Patel, Soni et al. 1990).

In total 4 patients were recruited to the study with liver disease who's ages ranged from 7 months to 14 years. 11 blood samples were taken at steady state from these patients and the mean midazolam clearance was found to be 0.74ml/kg/min. The midazolam infusion rate administered during the time of sampling ranged from 0.75-2.6mcg/kg/min. The clearance was found to be considerably lower in these patients compared to healthy children (9.11ml/kg/mins to 13.3ml/kg/min). Children recruited to the study with normal liver function including those with respiratory and neurological problems were found to have significantly higher midazolam clearance than those children with liver impairment. ($p=0.0001$).

One patient received a liver transplant during admission and samples were taken before and after the transplant. Before transplant clearance values were found to be, 0.48 and 0.24ml/kg/min. and after transplant clearance values increased to 5.3 and 18.9ml/kg/min. Midazolam plasma concentrations before transplant were 4550ng/ml and 9306ng/ml and after transplant were 751ng/ml and 106ng/ml. The midazolam infusion rate was comparable before and after transplant and ranged from 2-4mcg/kg/min. This is a considerable increase in the clearance of midazolam post transplant, which suggests enhanced metabolizing capacity of the

liver after transplant. This has been described in adults who have received a liver transplant (Shelly, Dixon et al. 1989) but not previously in children.

Renal impairment

Midazolam is metabolized by the liver and its major metabolites, 1-hydroxymidazolam and 4-hydroymidazolam are excreted renally. Therefore renal impairment theoretically should not affect the clearance of midazolam. However, it was found that the clearance in patients with severe renal impairment requiring dialysis was greatly reduced and mean midazolam clearance values were found to be 1.37ml/kg/min. Studies undertaken in adults have reported an extended half-life of midazolam in patients with severe renal impairment (13.3hours) compared with adults with normal renal impairment (7.6hours) (Driessen, Vree et al. 1991). Reasons for this remain unclear but are thought to be due to an increased volume of distribution in critically ill patients. There has been one report of renal disease affecting the elimination of midazolam in children but this patient also had severe liver impairment and therefore cannot be directly attributed solely to the effect of renal impairment (Lloyd-Thomas and Booker 1986). All four children with severe renal impairment in the present study had cardiac impairment which could also be a contributing factor to the lower clearance produced. The study compared the midazolam clearance in cardiac children with normal renal function and cardiac children requiring dialysis. Mean midazolam clearance was found to be significantly lower ($p=0.0001$) in the patients with renal impairment (1.72ml/kg/min) compared to those with normal renal function (4.9ml/kg/min).

Cardiac impairment

Adults recovering from cardiac surgery have been found to have a reduced clearance of midazolam (0.25L/min) and a prolonged elimination half-life (10.6hours) compared to healthy adults and patients who do not have cardiac problems (Maitre, Funk et al 1989). The reasons for this are unclear but are thought to be due to a reduced perfusion of the liver. Malacrida (1992) found that the elimination half-life of midazolam was prolonged in 8 critically ill adults

with cardiac impairment requiring midazolam for sedation during mechanical ventilation compared to healthy volunteers (5.4hrs compared to 2.3hrs). However, midazolam clearance was found not to be significantly different compared to healthy volunteers (6.3ml/kg/min compared to 4.9ml/kg/min) respectively. In the present study 23 children with cardiac disease were found to have a mean midazolam clearance of 3.74ml/kg/min. Four of these children had severe renal impairment. Cardiac children with normal renal function were found to have a clearance of 4.97ml/kg/min, which was lower than that documented in healthy children (9.11ml/kg/mins to 13.3ml/kg/min). Patients recruited to the study with normal cardiac function including patients with neurology and respiratory problems were found to have a significantly higher midazolam clearance ($p=0.0001$) than those patients with cardiac disease.

Neurology patients

In total 7 patients recruited to the study with head injury were found to have a mean midazolam clearance of 7.46ml/kg/min. All 7 patients had normal liver and renal function. The midazolam clearance in these patients was found to be significantly higher compared to patients with renal, liver and cardiac impairment ($p=0.001$). There is limited clinical data available investigating changes in pharmacokinetics in patients with head injury but some studies have demonstrated an increased clearance of some drugs including phenytoin and lorazepam (Boucher and Hanes 1998). The reasons for this are not entirely clear but one possibility is the interference of enzyme inducing agents used in head injury patients particularly phenytoin. All patients with head injury recruited to this study were prescribed intravenous phenytoin. Phenytoin is an enzyme-inducing agent that could potentially interact with midazolam and result in increased clearance. This concept will be investigated further in chapter four where the metabolism of midazolam to metabolites 1-hydroxymidazolam and 4-hydroxymidazolam will be undertaken.

Post-operative Patients

Although only two post-operative patients were recruited to the study it is interesting to look at their clearance values compared to other critically ill children. Patients admitted for simple uncomplicated planned surgery are generally otherwise well and healthy and therefore may produce clearance values similar to those seen in healthy children. The two children in the present study aged 3 months and 2 years were found to have a mean midazolam clearance of 18.23ml/kg/min and 8.16ml/kg/min respectively. Both patients had normal renal and liver function. The clearance value obtained for the patient aged 3 months (18.23ml/kg/min) is higher than that observed in healthy children (9.11-13.3ml/kg/min). Samples were taken over a period of 8 days after the patients had been receiving a continuous infusion of midazolam for 5 days. It is therefore possible that this patient experienced auto induction of midazolam and may explain the enhanced clearance. However firm conclusions cannot be draw from a single patient alone and further research is required to establish why some patients appear to have an enhanced metabolising capacity of midazolam despite their critical illness.

Respiratory failure

In total 11 patients were recruited to the study for respiratory failure and were found to have a mean midazolam clearance of 7.89ml/kg/min. One patient with severe renal impairment was omitted from this analysis and all other patients had normal renal and liver function. The mean midazolam clearance found in this group of patients was found to be significantly higher than patients with cardiac, renal and liver impairment ($p=0.0001$). However midazolam clearance is lower in patients with respiratory failure compared to healthy children.

Burns injury

One patient with severe burns was admitted to the study and was found to have a mean midazolam clearance of 1.78ml/kg/min that is much lower than that reported in healthy children (9.11-13.3ml/kg/min). This patient did not show any evidence of auto-induction, even after 13 days of continuous intravenous midazolam therapy. Burns injury can have a significant effect on the pharmacokinetics of drugs owing to changes in blood flow to tissues, changes in protein binding and hepatic metabolism of drugs (Bonate 1990). However few studies have been conducted investigating altered drug handling in children with burns injury. There is some evidence to suggest that the clearance of morphine is unaffected by burns injury whilst ketamine has shown an increased clearance (Cederholm, Bengtsson et al. 1990). The effect of burns injury on the clearance of benzodiazepines appears to be dependant on the drug (Jaehde and Sorgel 1995). Clearance of diazepam has been shown to be unaffected in patients with severe burns. In contrast clearance of lorazepam was increased in burns patients. Some studies have suggested that owing to the limited amount of data available regarding the effects of burns injury on the metabolism of drugs that therapeutic drug monitoring should be undertaken with certain drugs for example antibiotics to establish drug levels and therefore adequacy of dosage (Weinbren 1999). This maybe relevant to other drugs but it is clear that further work is required in this area to establish the effect that burns injury has on the pharmacokinetics of midazolam.

Downs syndrome

Five patients with Downs syndrome were recruited to the study. Three of these patients were admitted for cardiac surgery. Downs syndrome is a common congenital abnormality associated with a number of disorders including cardiac defects and respiratory problems (Mitchell, Howard et al. 1995). Mean clearance for these children was found to be 7.21ml/kg/min, which is comparable to other clearances, found in critically ill children. Clearance during the first 48hours was 2.77ml/kg/min increasing to 9.4ml/kg/min by day 7. Clearance values were compared in the three cardiac children with Downs syndrome, to cardiac children of the same age without Downs syndrome. Mean clearance values were found to be 6.06ml/kg/min and 4.28ml/kg/min respectively. It has been documented that children with Downs syndrome require substantially higher doses of morphine compared to other

children, to achieve the same concentration of analgesia (Gakhal, Scott et al. 1998). It has also been noticed that children with Downs syndrome are often difficult to sedate adequately and require a lot more sedation in comparison to other children of the same age. Although numbers in this study are small and no definite conclusions can be drawn, the results suggest patients with Downs syndrome who have cardiac impairment have a higher midazolam clearance than those patients without Downs syndrome who have cardiac disease. It may be that these children possess the ability to metabolise certain drugs differently than other children and therefore achieve a higher clearance rate. Further work is required in this area to clarify this situation.

Changes in core body temperature on midazolam clearance

Changes in midazolam clearance and body temperature were investigated in the study. Patients who had sustained a head injury were recruited to an independent study to investigate the effect that cooling the body for the first 24hours after injury, had on patient outcome. As part of this study temperature change on midazolam clearance was investigated. Mild hypothermia has been shown to reduce the clearance of some drugs including vecuronium, rocuronium atracurium (Caldwell, Heier et al. 2000; Beaufort, prost et al. 2001; Playfor, Thomas et al. 2000). Few other studies have looked at the effect of hypothermia on other drugs, but animal studies have suggested that the clearance of benzodiazepines is only marginally reduced by mild hypothermia (Mortensen and Dale 1995). Four patients were recruited to this study and blood samples were taken during changes in body temperature. However it was found that no difference in midazolam clearance was evident at different body temperature.

Interaction between midazolam and erythromycin

One patient was found to have a reduced midazolam clearance whilst receiving intravenous erythromycin. The interaction between erythromycin and midazolam has been documented (Yeates, Laufen et al 1997). The extent of the interaction is not clearly documented but is thought to be quite considerable. The present study found that the reduction in midazolam clearance was just less than 10 fold. Therefore this led to a dramatic increase in midazolam plasma concentrations. Moreover, the interaction occurred within 24hours of commencing

intravenous erythromycin, suggesting that the interaction has a rapid onset time. Medical and nursing staff as well as pharmacists need to be aware of the extent of this interaction and the rapidity of onset, particularly if prescribing to patients who already have a reduced midazolam clearance such as those with renal, liver and cardiac impairment.

Summary

The clearance of midazolam was found to be 6.3ml/kg/min in critically ill children, which is lower than that documented in healthy children (9.11-13.3.ml/kg/min). Midazolam clearance was also found to be dependent on age. Neonates were found to have the lowest midazolam clearance (1.63ml/kg/min) whilst children aged less than one year had the highest midazolam clearance (8.52ml/kg/min). Midazolam clearance was found to decrease after the age of 12 months to a mean value of 5.24ml/kg/min in children over 7 years of age.

Auto-induction of midazolam was shown to be evident with continued intravenous administration of midazolam in children over the age of 1 month and occurred between days 5 and 7 of therapy. The consequences of auto-induction are important and can lead to patients becoming tolerant to midazolam and requiring higher plasma concentrations to achieve a desired effect.

Disease state was also found to affect midazolam clearance. Patients with renal and liver disease were found to have the lowest midazolam clearance (1.37 and 0.74ml/kg/min respectively). It is imperative from these findings that extreme care must be taken when prescribing midazolam for these patients. Although only one patient with burn injury was recruited to the study, midazolam clearance was also found to be low (1.78ml/kg/min). Further work is required to be undertaken in patients with burn injury to establish the effect this has on the pharmacokinetics of midazolam. Patients with cardiac impairment were found to have a reduced midazolam clearance compared to healthy children and may also be at risk of accumulation and therefore caution is required when midazolam is prescribed. Patients with respiratory failure and head injury were found to have a significantly higher midazolam clearance compared to those with renal, liver and cardiac disease.

Summary of major findings

- Midazolam clearance is reduced in critically ill children compared to that reported in healthy children.
- Midazolam clearance is significantly reduced in neonates compared to other ages of children.

- Midazolam clearance is significantly reduced in patients with renal and liver impairment.
- Auto-induction of midazolam occurred after 5 to 7 days of continuous midazolam therapy.

It is now important to try and establish why some of these differences are occurring. The following chapter investigates the metabolism of midazolam and looks at the production of the metabolites of midazolam.

CHAPTER 4

THE INVESTIGATION OF THE METABOLITES OF MIDAZOLAM - 1-HYDROXYMIDAZOLAM AND 4-HYDROXYMIDAZOLAM - IN CRITICALLY ILL CHILDREN

CONTENTS

4.1 Introduction

The major metabolic pathway for midazolam involves hydroxylation to form 1-hydroxymidazolam, which undergoes rapid conjugation with glucuronic acid (Allonen, Ziegler et al. 1981). Approximately 60 to 80% of the administered dose is excreted as conjugated 1-hydroxymidazolam (Heizmann, Eckert et al. 1983). The 1-hydroxymidazolam metabolite is pharmacologically active in animals but markedly less than the parent drug and the glucuronide conjugate is inactive (Heizmann, Eckert et al. 1983). The extent to which 1-hydroxymidazolam is thought to contribute to the sedative effect of midazolam in adults is controversial. Some reports indicate minimal pharmacological effect whilst others state that it can contribute significantly to sedative effects. Two other metabolites, 4-hydroxymidazolam and 1,4-hydroxymidazolam, are excreted in insignificant amounts as conjugates in the urine (3% and 1% of the dose respectively (Heizmann, Eckert et al. 1983) and these are thought to have minimal pharmacological effect.

There is very little work done on the production of 1-hydroxymidazolam and 4-hydroxymidazolam in critically ill children. The present study investigates the production of the metabolites in this patient group and the effect that age and disease states have on each of these metabolites.

4.2 Results

The effect of age on metabolite production was investigated by subdividing patient age into the following groups:

Neonates (patients aged less than 1 month)
Patients aged less than 1 year
Patients aged between 1 and 3 years
Patients aged between 4 and 7 years
Patients aged greater than 7 years.

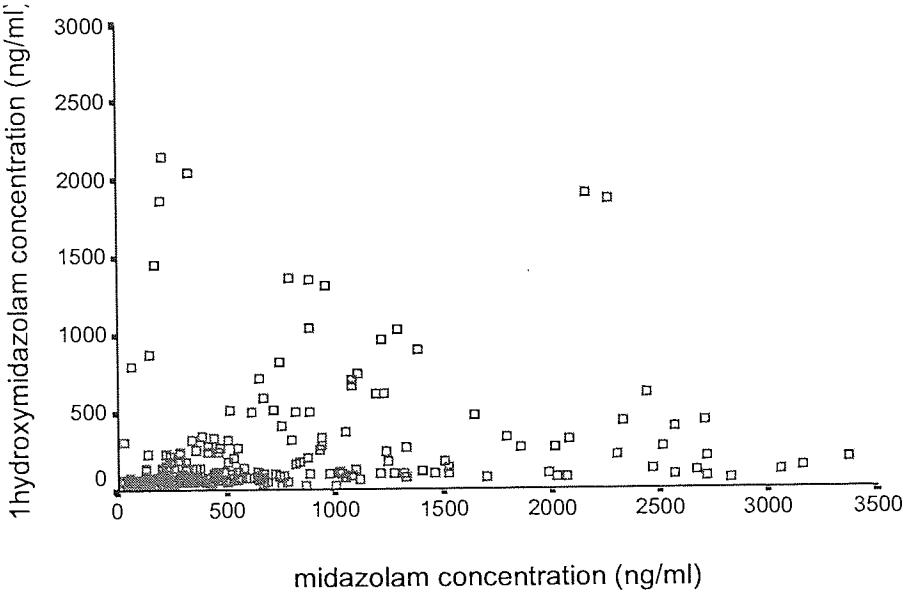
The metabolite ratio was calculated by the following formula:

$$\text{Metabolite ratio} = \frac{\text{metabolite plasma concentration}}{\text{midazolam plasma concentration}}$$

4.2.1 The relationship between midazolam plasma concentration and 1-hydroxymidazolam production.

A total of 303 blood samples were taken from 52 critically ill children. In order to investigate the production of 1-hydroxymidazolam (1-OH) in critically ill children, a total of 241 samples were used, in which both the midazolam plasma concentration and 1-OH plasma concentration were found to be above 25ng/ml (the limit of detection used during analysis). A further 17 samples were excluded from the analysis as they were found to be above the standard calibration range for midazolam and 1-OH (3000ng/ml) and can be found in Appendix 14. Figure 4.1 shows the relationship between midazolam plasma concentration in critically ill children and the production of 1-OH. Only a weak correlation was found using the Pearson coefficient (0.178 p=0.08).

Figure 4.1 Midazolam plasma concentration (ng/ml) and the corresponding 1-hydroxymidazolam plasma concentration (ng/ml) in critically ill children



4.2.2 Calculation of 1-hydroxymidazolam midazolam plasma ratio

The mean 1-OH midazolam plasma ratio was calculated and was found to be 0.68 (±0.15) (n=224). With inclusion of the outliers, the mean 1-OH midazolam plasma ratio was found to be 0.64 (±0.10) (n=241). A summary of these results can be found in table 4.1.

4.2.3 Numbers of patients producing minimal quantities of 1-hydroxymidazolam

Out of the 303 blood samples initially taken from 52 patients, 45 blood samples were found to contain 1-OH in concentrations below the limit of detection of 25ng/ml (16.5%). A summary of these results can be found in table 4.2

4.2.4 1-hydroxymidazolam production and patient age

The production of 1-OH was investigated as a function of patient age. The results suggest that all ages of children are capable of manufacturing the 1-OH metabolite. However, a correlation between patient age and extent of production of 1-OH was not found. The results for each age group of children are reported initially and summarized in tables 4.1 and 4.2.

Neonates.

A total of 18 blood samples were taken from 8 neonatal patients including two premature neonates, which were found to have a concentration of 1-OH greater than 25ng/ml. The mean 1-OH plasma concentration was found to be 137ng/ml and the 1-OH midazolam plasma ratio was found to be 0.292 (table 4.1).

Patients aged between 1 and 12 months

A total of 72 blood samples were taken from 20 patients aged between 1 and 12 months, which were found to have a concentration of 1-OH greater than 25ng/ml. Two of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. The mean 1-OH plasma concentration was found to be 69ng/ml and the 1-OH midazolam plasma ratio was found to be 0.372 (table 4.1). In this age group, one patient had severe renal impairment and two patients had severe liver impairment. With exclusion of the samples taken from these patients (n=10) the 1-OH midazolam plasma ratio was found to be 0.374

Patients aged between 1 and 3 years

A total of 55 blood samples were taken from 9 patients aged between 1 and 3 years, which were found to have a concentration of 1 OH greater than 25ng/ml. The mean 1-OH plasma concentration was found to be 458ng/ml and the 1-OH midazolam plasma ratio was found to be 1.62 (table 4.1).

Patients aged between 4 and 7 years

A total of 27 blood samples were taken from 5 patients aged between 4 and 7 years, which were found to have a concentration of 1 OH greater than 25ng/ml. Seven of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. The mean 1-OH plasma concentration was found to be 80ng/ml and the 1-OH midazolam plasma ratio was found to be 0.117 (table 4.1). In this age group, two patients had severe renal impairment. With exclusion of the samples taken from these patients (n=16) the 1-OH midazolam plasma ratio was found to be 0.167.

Patients aged greater than 7 years

A total of 69 blood samples were taken from 10 patients aged greater than 7 years, which were found to have a concentration of 1-OH greater than 25ng/ml. Seven of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. The mean 1-OH plasma concentration was found to be 369ng/ml and the1-OH midazolam plasma ratio was found to be 0.479 (table 4.1). In this age group, two patients had severe liver impairment and one patient had severe renal impairment. With exclusion of the samples taken from these patients (n=16) the 1-OH midazolam plasma ratio was found to be 0.555.

Table 4.1 1-hydroxymidazolam plasma concentrations (±s.e.mean) and 1-hydroxymidazolam midazolam plasma ratio (±s.e.mean) as a function of age.

Age band	Sample number	1-OH concentration (ng/ml) (±s.e.mean)	1-OH midazolam ratio (±s.e.mean)
All patients	224	271 (30.1)	0.680 (0.15)
Neonates	18	137 (24.47)	0.292 (0.057)
1-12 months	69	69 (3.8)	0.372 (0.042)
1-3 yrs	55	458 (71.1)	1.62 (0.396)
4-7 yrs	20	80 (8.45)	0.117 (0.023)
+7 yrs	62	369 (6.87)	0.479 (0.047)

Table 4.2 summarises the number of samples taken from patients in which production of 1-OH was found to be below 25ng/ml and therefore insignificant. It can be seen that all age groups of children, including neonates have the capacity to produce 1-OH.

Table 4.2 Numbers of samples taken from patients in which 1-hydroxymidazolam was found to be minimal and the corresponding midazolam plasma concentration range.

Age band (total no of samples)	Sample number	% no. samples	Midazolam concentration range (ng/ml)
All patients (273)	45	16.5	26-5221
Neonates (22)	4	18.2	50-552
1-12 months (106)	37	34.9	26-1398
1-3 yrs (58)	3	5.2	30-342
4-7 yrs (24)	4	4.2	581-5221
+7 yrs (63)	1	1.6	1454

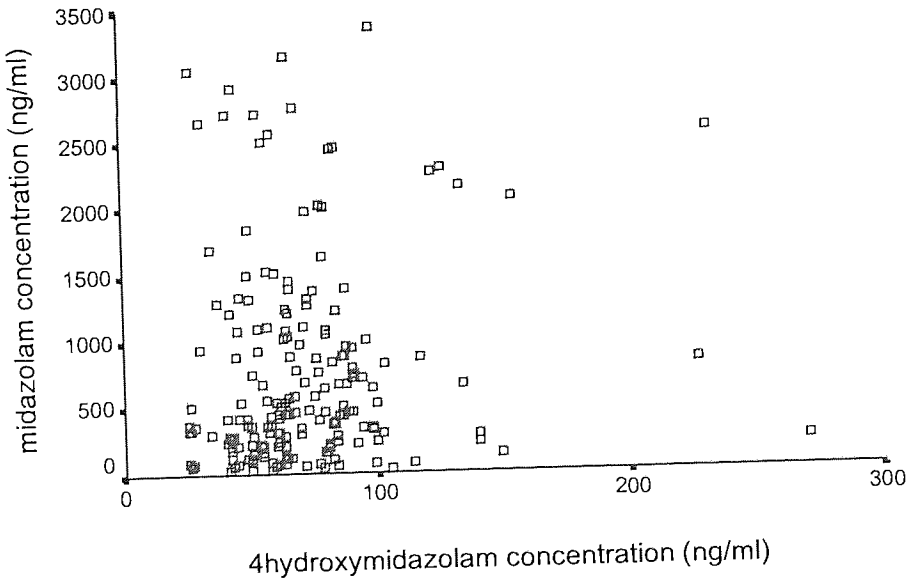
Summary of 1-hydroxymidazolam midazolam plasma ratio and patient age

The results suggest that all patients irrespective of age are capable of manufacturing the 1-OH metabolite. It appears from the results that children aged between 1 and 3 years produce the highest 1-OH midazolam plasma ratio. However this result is probably due to concomitant drug therapy and not as a consequence of age. Within this age group it was found that four patients were prescribed potentially enzyme-inducing agents including phenytoin and carbamazepine and this is the probable reason for the higher metabolite ratio seen in this age group. This point will be discussed in further detail later in the chapter.

4.2.5 The relationship between midazolam plasma concentration and 4-hydroxymidazolam production.

A total of 303 blood samples were taken from 52 critically ill children. In order to investigate the production of 4-OH in critically ill children, a total of 199 samples were used, in which both the midazolam plasma concentration and 4-OH plasma concentration were found to be above 25ng/ml (the limit of detection used during analysis). A further 10 samples were excluded from the analysis as they were found to be above the standard calibration range for midazolam and 4-OH (3000ng/ml) and can be found in Appendix 14. Figure 4.2 shows the relationship between midazolam plasma concentration in critically ill children and the production of 4-hydroxymidazolam. No correlation was found between the midazolam plasma concentration and the 4-hydroxymidazolam plasma concentration

Figure 4.2 Midazolam plasma concentration (ng/ml) and the corresponding 4-hydroxymidazolam plasma concentration (ng/ml) in critically ill children



4.2.6 Calculation of 4-hydroxymidazolam midazolam plasma ratio

The mean 4-OH midazolam plasma ratio was calculated and was found to be 0.298 (±0.034) (n=188). With inclusion of the outliers, the mean 4-OH midazolam plasma ratio was found to be 0.283 (±0.033) (n=199).

4.2.7 Numbers of patients producing minimal quantities of 4-hydroxymidazolam

Out of the 303 blood samples initially taken from 52 patients, 87 blood samples were found to contain 4-OH in concentrations below the limit of detection of 25ng/ml (31.2%).

4.2.8 4-hydroxymidazolam production and patient age

The production of 4-OH was investigated as a function of patient age. The results suggest that all ages of children are capable of manufacturing the 4-OH metabolite but to a much lesser extent compared to the 1-OH metabolite. A correlation between patient age and extent of production of 4-OH was not found. The results from each age group of children are reported initially and summarized in tables 4.3 and 4.4

Neonates

A total of 13 blood samples were taken from 8 neonatal patients, which were found to have a concentration of 4-OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 97ng/ml and the 4-OH midazolam plasma ratio was found to be 0.145 (table 4.3).

Patients aged between 1 and 12 months

A total of 75 blood samples were taken from 20 patients aged between 1 and 12 months, which were found to have a concentration of 4-OH greater than 25ng/ml. Two of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. The mean 4-OH plasma concentration was found to be 70ng/ml and the 4-OH midazolam plasma ratio was found to be 0.460 (table 4.3). In this age group, two patients had severe liver impairment and one patient had severe renal impairment. With exclusion of the samples taken from these patients (n=8) the 4-OH midazolam plasma ratio was found to be 0.454.

Patients aged between 1 and 3 years

A total of 42 blood samples were taken from 9 patients aged between 1 and 3 years, which were found to have a concentration of 4 OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 71ng/ml and the 4-OH midazolam plasma ratio was found to be 0.169 (table 4.3).

Patients aged between 4 and 7 years

A total of 23 blood samples were taken from 5 patients aged between 4 and 7 years, which were found to have a concentration of 4 OH greater than 25ng/ml. Three of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. The mean 4-OH plasma concentration was found to be 66ng/ml and the 4-OH midazolam plasma ratio was calculated and the mean was found to be 0.078 (table 4.3). In this age group, two patients had severe renal impairment. With exclusion of the samples taken from these patients (n=13) the 4-OH midazolam plasma ratio was found to be 0.122.

Patients aged greater than 7 years

A total of 43 blood samples were taken from 10 patients aged between greater than 7 years, which were found to have a concentration of 4-OH greater than 25ng/ml. Six of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and were excluded from this analysis. The mean 4-OH plasma concentration was found to be 69ng/ml and the 4-OH midazolam plasma ratio was found to be 0.196 (table 4.3). In this age group, two patients had severe liver impairment and one patient had severe renal impairment. With exclusion of the samples taken from these patients (n=5) the 4-OH midazolam plasma ratio was found to be 0.188.

Table 4.3 4-hydroxymidazolam plasma concentration (±s.e.mean) and 4-hydroxymidazolam midazolam plasma ratio (±s.e.mean) as a function of age

Age band	Sample number	4-OH concentration (ng/ml) (±s.e.mean)	4-OH midazolam plasma ratio (±s.e.mean)
All patients	185	72 (6.4)	0.298 (0.034)
Neonates	13	97 (14.2)	0.145 (0.024)
1-12 months	73	70 (4.0)	0.460 (0.073)
1-3 yrs	42	71 (3.42)	0.169 (0.019)
4-7 yrs	20	66 (3.5)	0.078 (0.013)
+7 yrs	37	69 (6.1)	0.196 (0.049)

Table 4.4 shows a summary of the numbers of patients in which production of 4-OH was found to be minimal and therefore insignificant. The number of samples for which 4-OH production was minimal was 31.2%.

Table 4.4 Numbers of samples taken from patients in which 1-hydroxymidazolam was found to be minimal and the corresponding midazolam plasma concentrations

Age band (total number)	Sample number	% of Patients	Midazolam concentration range (ng/ml)
All patients (275)	87	31.2	30-6302
Neonates (18)	6	33.3	46-3012
1-12 months (107)	34	31.8	28-866
1-3 yrs (58)	12	20.7	30-801
4-7 yrs (28)	8	28.6	126-6302
+7 yrs (64)	27	42.1	95-4215

Summary of 4-hydroxymidazolam midazolam plasma ratio and patient age

The results suggest that all patients were capable of manufacturing the 4-OH metabolite irrespective of age. However, plasma concentrations of 4-OH were lower than those seen for 1-OH. In addition a greater number of samples were found to have minimal quantities of 4-OH (31.2%) compared to 1-OH (16.5%) (table 4.4).

4.2.9 The effect of different disease states on the production of 1-hydroxymidazolam

Liver impairment

A total of 19 blood samples were taken from 4 patients with severe liver impairment, which were found to have a concentration of 1-OH greater than 25ng/ml. The ages of the patients in this group were 7 months, 9 months, 9 years and 14 years. Four of the samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and have been included in this analysis. The mean 1-OH plasma concentration was found to be 243ng/ml and the 1-OH midazolam plasma ratio was found to be 0.210 (table 4.5). The relationship between the plasma concentration of 1-OH and midazolam was investigated in all four liver patients (figure 4.3). However, this relationship was only found to be statistically significant if the 3 patients with congenital liver abnormalities were analysed alone (figure 4.4). The relationship between the plasma concentrations of 1-OH and midazolam was found to be highly significant (r^2 = 0.902 and the slope of the line = 0.0875±0.0074)

Figure 4.3 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in patients with liver impairment

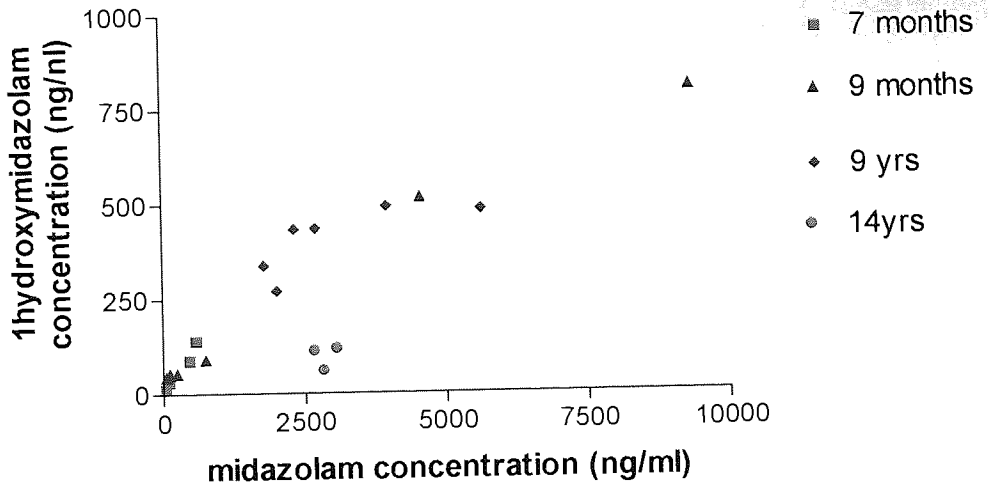
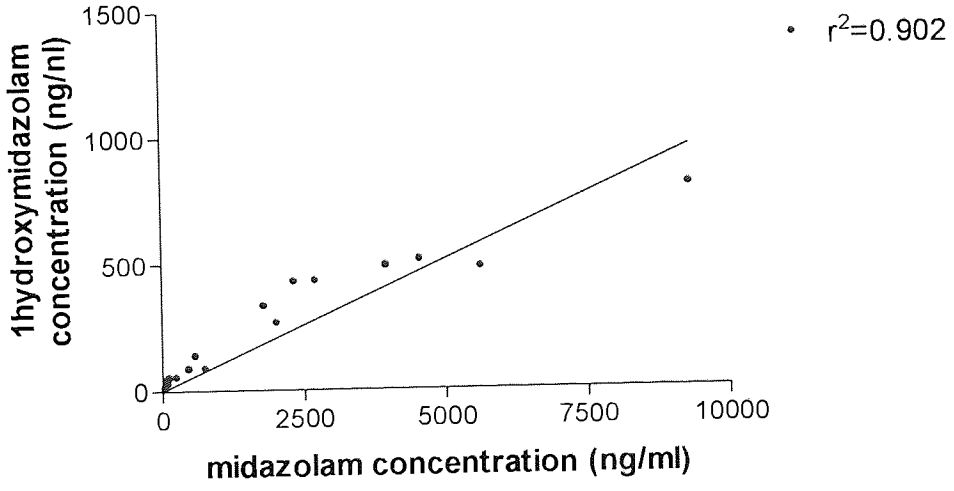


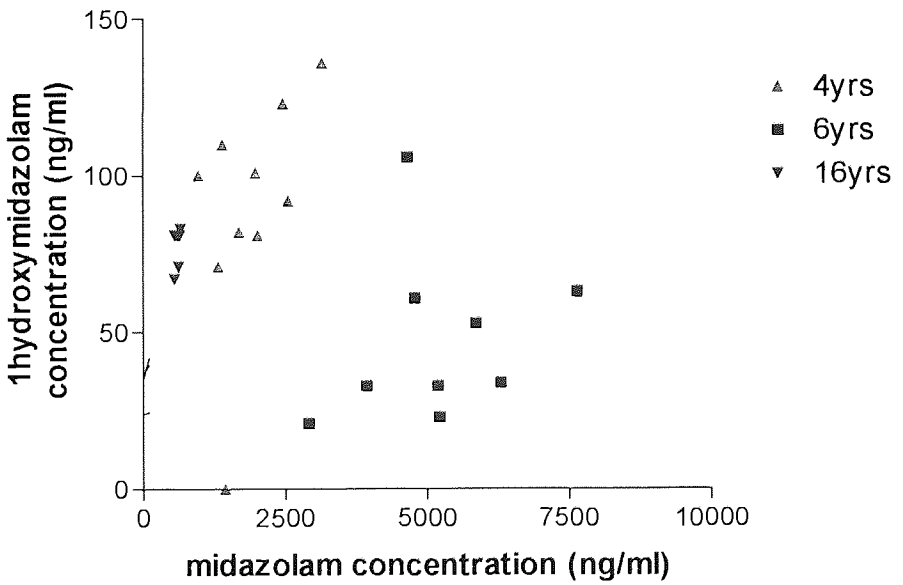
Figure 4.4 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in three patients with congenital liver impairment



Renal impairment

A total of 25 blood samples were taken from 5 patients with severe renal impairment, which were found to have a concentration of 1-OH greater than 25ng/ml. The ages of the patients included in this group were 13 days, 2 months, 4 years, 5 years and 18 years. Eight of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and have been included in this analysis. The mean 1-OH plasma concentration was found to be 73ng/ml and the 1-OH midazolam plasma ratio was found to be 0.059 (table 4.5). No correlation was found between the plasma concentrations of 1-hydroxymidazolam and midazolam (figure 4.5).

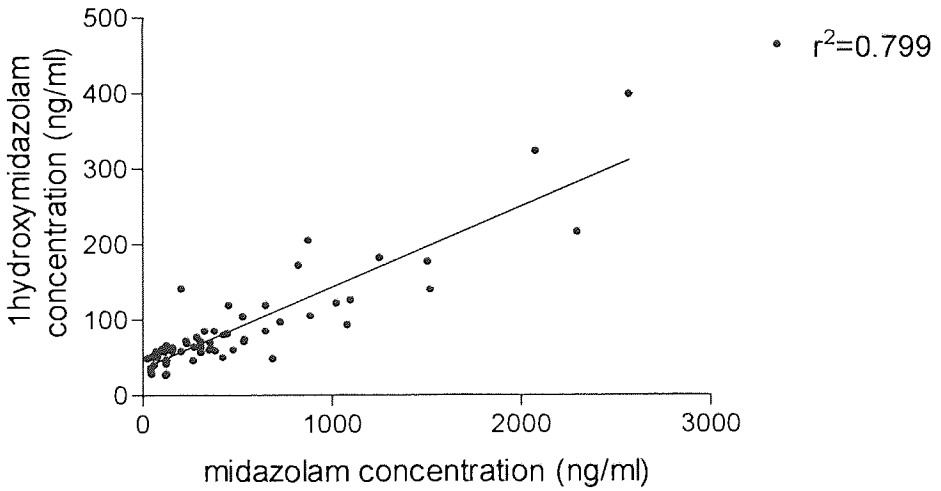
Figure 4.5 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in patients with renal impairment.



Cardiac impairment

A total of 63 blood samples were taken from 18 patients with cardiac impairment and normal renal function, which were found to have a concentration of 1-OH greater than 25ng/ml. The ages in this group of patients ranged from 13 days to 12 years. The mean 1-OH plasma concentration was found to be 89ng/ml and the 1-OH midazolam plasma ratio was found to be 0.362 (table 4.5). A significant correlation was found between the plasma concentrations of 1-hydroxymidazolam and midazolam in patients with cardiac impairment and normal renal function (Figure 4.6). ($r^2 = 0.799$ and the slope of the line = 0.107±0.0069)

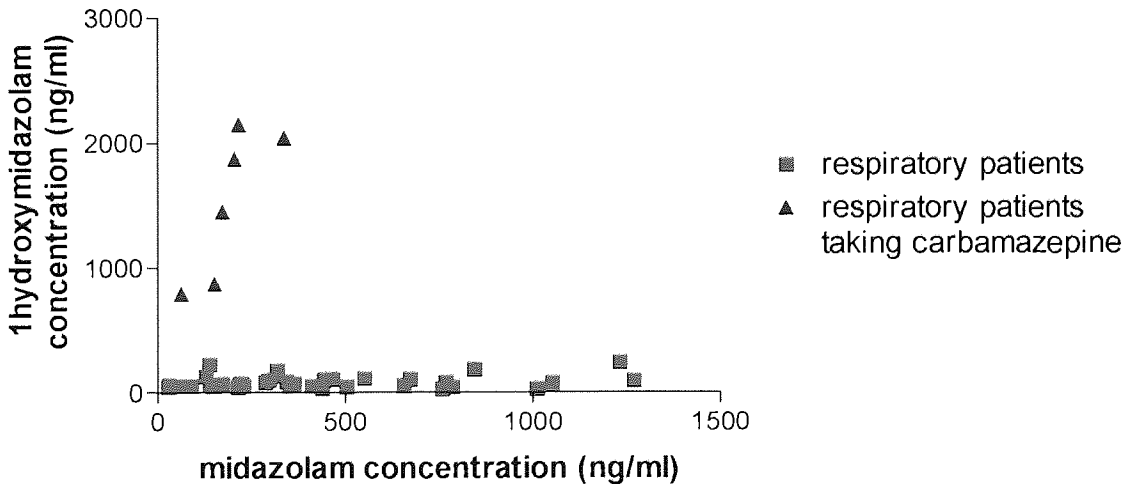
Figure 4.6 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in patients with cardiac impairment and normal renal function



Respiratory failure

A total of 52 blood samples were taken from 10 patients with respiratory failure, which were found to have a concentration of 1-OH greater than 25ng/ml. The ages of patients included in this group ranged from 8 days to 5 years. The mean 1-OH plasma concentration was found to be 280ng/ml and the 1-OH midazolam plasma ratio was found to be 1.49 (table 4.5). One of the patients in this group was taking carbamazepine for epilepsy. Figure 4.7 shows the production of 1-OH in this patient compared to the other patients in this group.

Figure 4.7 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in patients with respiratory failure.



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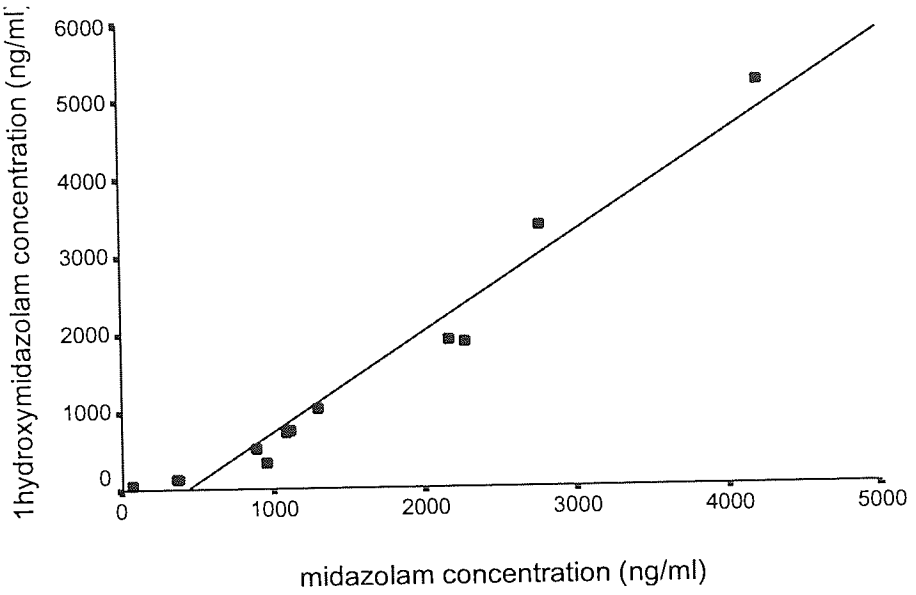
Post-operative patients

A total of 7 blood samples were taken from 2 post-operative patients, which were found to have a concentration of 1-OH greater than 25ng/ml. The two patients were aged 3 months and 2 years. The mean 1-OH plasma concentration was found to be 132ng/ml and the 1-OH midazolam plasma ratio was found to be 0.337 (table 4.5).

Neurology patients

A total of 63 blood samples were taken from 7 neurology patients, which were found to have a concentration of 1-OH greater than 25ng/ml. The ages of patients included in this group ranged from 1 to 8 years. One of these samples was found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and has been included in this analysis. The mean 1-OH plasma concentration was found to be 604ng/ml and the 1-OH midazolam plasma ratio was found to be 0.858 (table 4.5). Figure 4.8 shows the plasma concentrations of 1-OH and midazolam taken from one neurology patient. It can be seen that there is a significant correlation between the plasma concentration of 1-OH and midazolam.

Figure 4.8 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in one neurology patient.



The relationship between the plasma concentrations of 1-hydroxymidazolam and midazolam were investigated in all neurology patients and the results are shown in figure 4.9. It can be seen that the relationship between plasma concentrations in all neurology patients is no longer evident. However it was found that patients 2 and 3 were receiving potential enzyme-inhibiting agents (erythromycin and sodium valproate). Excluding these two patients from the analysis a significant correlation between the plasma concentrations of 1-hydroxymidazolam and midazolam in the remaining neurology patients can be seen (r^2=0.923 and a slope of 1.13±0.057) (figure 4.10)

Figure 4.9 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in all neurology patients.

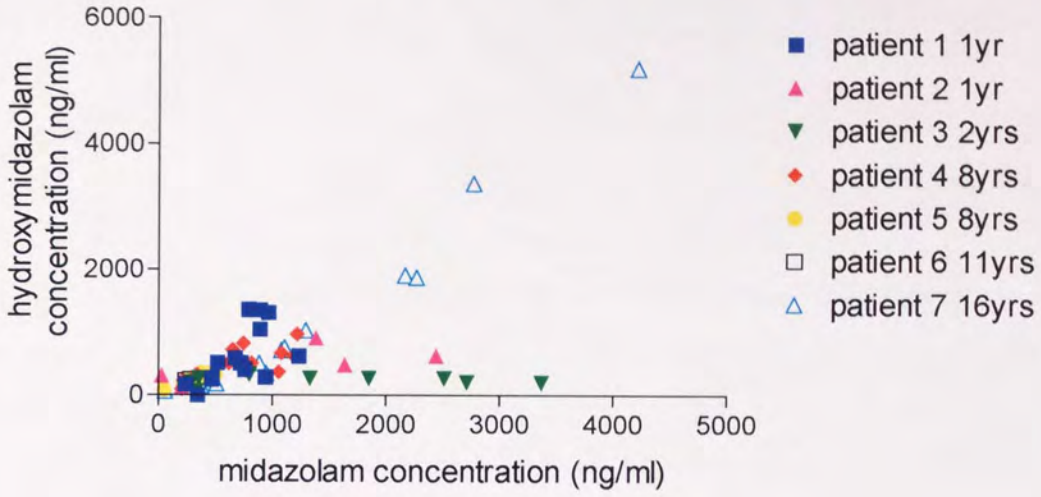
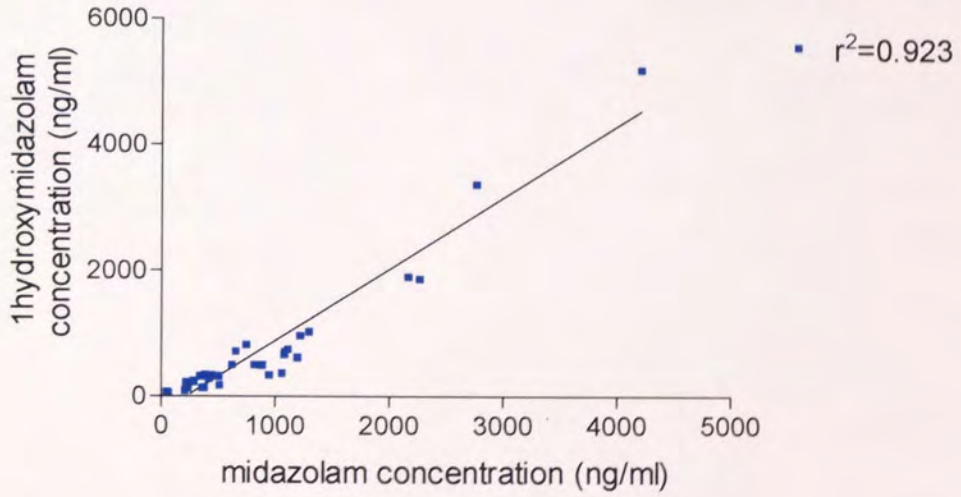


Figure 4.10 The relationship between midazolam plasma concentrations (ng/ml) and 1-hydroxymidazolam plasma concentrations (ng/ml) in neurology patients (excluding patients receiving enzyme-inhibitors).



Burns injury

A total of 10 blood samples were taken from 1 burns patients aged 12 years, which were found to have a concentration of 1-OH greater than 25ng/ml. Four of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and have been included in this analysis. The mean 1-OH plasma concentration was found to be 107ng/ml and the 1-OH midazolam plasma ratio was found to be 0.049 (table 4.5).

Summary of the effects of disease state on 1-hydroxymidazolam

Table 4.5 shows the production of 1-OH in different disease states. The highest mean plasma concentrations of 1-OH are seen in neurology patients (604ng/ml). The highest mean 1-OH midazolam plasma ratios are seen in respiratory patients (1.296) and neurology patients (0.858). The lowest 1-OH midazolam plasma ratios are seen in patients with severe renal impairment (0.086) and burns injury (0.0495).

Table 4.5 1-hydroxymidazolam plasma concentration (±s.e.mean) and 1-OH midazolam plasma ratio (±s.e.mean) as a function of disease state

Disease state	Sample no	1-OH concentration (ng/ml) (±s.e.mean)	1-OH midazolam plasma ratio (±s.e.mean)
Liver	19	243 (51.44)	0.21 (0.0427)
Renal	16	73 (6.06)	0.059 (0.0097)
Cardiac(NR[1])	54	89 (8.3)	0.362 (0.039)
Respiratory	52	280 (80.0)	1.49 (0.44)
Post-op	7	132 (40.57)	0.337 (0.059)
Neurology	63	604 (100.9)	0.858 (0.162)
Burns	10	107 (7.62)	0.049 (0.009)

[1]Cardiac NR – cardiac patients with normal renal function

Table 4.6 Numbers of samples taken from patients in which 1-hydroxymidazolam production was minimal as a function of disease state

Disease state	Sample number	% of Patients	Midazolam concentration range (ng/ml)
Liver	21	9.5	43,1454
Renal	35	28.5	250-7643
Cardiac(NR[1])	70	10.0	28-2557
Respiratory	66	21.2	30-1398
Post-op	18	61.1	50-110
Neurology	64	1.5	342
Burns	10	0	

[1]Cardiac NR – cardiac patients with normal renal function

4.2.10 The effect of different disease states on the production of 4-hydroxymidazolam

Liver impairment

A total of 11 blood samples were taken from 4 patients with severe liver impairment, which were found to have a concentration of 4-OH greater than 25ng/ml. Four of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and have been included in this analysis. The mean 4-OH plasma concentration was found to be 85ng/ml and the 4-OH midazolam plasma ratio was calculated and the mean was found to be 0.294 (table 4.7).

Renal impairment

A total of 13 blood samples were taken from 5 patients with severe renal impairment, which were found to have a concentration of 4-OH greater than 25ng/ml. Three of these samples were found to have a midazolam plasma concentration above that of the standard calibration curve range (25-3000ng/ml) and have been included in this analysis. The mean 4-OH plasma concentration was found to be 58ng/ml and the 4-OH midazolam plasma ratio was found to be 0.028 (table 4.7).

Cardiac impairment

A total of 54 blood samples were taken from 18 patients with cardiac impairment and normal renal function, which were found to have a concentration of 4-OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 67ng/ml and the 4-OH midazolam plasma ratio was found to be 0.307 (table 4.7).

Respiratory failure

A total of 50 blood samples were taken from 10 patients with respiratory failure, which were found to have a concentration of 4-OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 76ng/ml and the 4-OH midazolam plasma ratio was found to be 0.274 (table 4.7).

Post-operative patients

A total of 7 blood samples were taken from 2 post-operative patients, which were found to have a concentration of 4-OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 69ng/ml and the 4-OH midazolam plasma ratio was found to be 0.859 (table 4.7).

Neurology patients

A total of 47 blood samples were taken from 7 neurology patients, which were found to have a concentration of 4-OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 75ng/ml and the 4-OH midazolam plasma ratio was calculated and the mean was found to be 0.161 (table 4.7).

Burns injury

A total of 9 blood samples were taken from 1 burns patient, which were found to have a concentration of 4-OH greater than 25ng/ml. The mean 4-OH plasma concentration was found to be 77ng/ml and the 4-OH midazolam plasma ratio was found to be 0.035 (table 4.7).

Table 4.7 shows the production of 4-OH in different disease states. The results indicate that the plasma concentrations of 4-OH are lower in all disease states compared to plasma concentrations of 1-OH and midazolam. The lowest 4-OH midazolam plasma ratios occurred in patients with severe renal impairment (0.028) and burns injury (0.035).

Table 4.7 4-hydroxymidazolam plasma concentrations (±s.e.mean) and 4-OH midazolam plasma ratio as a function of disease states

Disease state	Sample no	Mean 4-OH conc (ng/ml)	4-OH midazolam plasma ratio
Liver	11	85 (11.0)	0.294 (0.168)
Renal	13	58 (4.2)	0.028 (0.005)
Cardiac(NR[2])	54	67 (48.75)	0.307 (0.104)
Respiratory	50	76 (5.52)	0.274 (0.048)
Post-op	7	69 (7.55)	0.859 (0.146)
Neurology	47	75 (4.95)	0.161 (0.034)
Burns	9	77 (5.7)	0.035 (0.006)

[2]Cardiac NR – cardiac patients with normal renal function

Table 4.8 Numbers of samples taken from patients in which 4-hydroxymidazolam production was minimal as a function of disease state

Disease state	Sample number	% of Patients	Midazolam concentration range (ng/ml)
Liver	19	42.1	59-3056
Renal	35	62.8	250-6302
Cardiac(NR[1])	70	22.9	43-2557
Respiratory	64	21.9	64-767
Post-op	16	56.3	50-552
Neurology	63	25.4	205-4215
Burns	10	10.0	2069

[1]Cardiac NR – cardiac patients with normal renal function

4.3 Discussion

Midazolam is metabolized in the liver to two main metabolites 1-OH and 4-OH. The purpose of this part of the study was to investigate the production of these metabolites in critically ill children with respect to different ages and disease states. Significant concentrations of 1-OH have been found in critically ill adults. The half-life was found to be longer than in healthy patients and it was therefore thought to potentially contribute significantly to the pharmacodynamic effects of midazolam in these patients (Boulieu, Lehmann et al. 1998). Much less work has been undertaken to investigate the 4-OH metabolite but its contribution to the sedative effect of midazolam is thought to be much less significant.

The plasma concentrations of 1-OH and 4-OH obtained in this study ranged from 0-5189ng/ml and 0-271ng/ml respectively. It can be seen that there is a large range in the plasma concentrations of 1-OH compared to 4-OH. The 1-OH midazolam plasma ratio was calculated in all patients and the mean was found to be 0.641. 1-OH midazolam plasma ratios reported in adults have ranged from 0.03 to 15.6. In the present study, no correlation was found between plasma concentration of midazolam and that of the 1-OH metabolite when the results for all patients were analyzed together.

1-hydroxymidazolam production and patient age

The production of 1-OH was considered as a function of patient age. The results suggest that all patients irrespective of age were capable of producing the 1-OH metabolite. However, no correlation was observed between patient age and the 1-OH midazolam plasma ratios. The results do show however, that children aged between 1-3 years and those greater than 7 years achieved the highest plasma concentration of 1-OH compared to other children. Children aged between 1 and 3 years achieved a mean plasma concentration of 1-OH of 458ng/ml (44-2152ng/ml). Children greater than 7 years of age achieved a mean plasma level of 369ng/ml (31-5189ng/ml). These two groups of children also achieved the highest 1-OH midazolam plasma ratios, indicating that they may have an enhanced metabolism of midazolam, producing greater quantities of the 1-OH metabolite compared to other ages of children. At closer inspection of the results it was observed that within the age group of 1-3 years, four patients were responsible for achieving the highest plasma concentrations of 1-OH (407-

2152ng/ml). Of these four patients, three were admitted to PICU for head injuries and 1 with respiratory failure. Within the group of children aged above 7 years, two patients were responsible for achieving the highest plasma concentrations of 1-OH (505-5189ng/ml). Both of the children were admitted to PICU with head injury. All head injury patients in the study were prescribed prophylactic intravenous phenytoin against fitting after head trauma. Phenytoin is a known enzyme-inducing agent and it has been documented that it can enhance the metabolism of midazolam. The patient with respiratory failure achieving high plasma concentrations of 1-OH (793-2152ng/ml) compared to other children in the same age group suffered with epilepsy that was controlled with carbamazepine. Carbamazepine is a known enzyme-inducing agent and it is possible that an interaction took place in this patient causing an enhanced metabolism of midazolam and therefore higher plasma concentrations of 1-OH.

4-hydroxymidazolam production and patient age

From the results it can be seen that all ages of patients including neonates were capable of producing the 4-OH metabolite. However, no correlation was found between patient age and the 4-OH midazolam plasma ratio. The mean plasma concentration of 4-OH was found to be 72ng/ml. It is interesting to note that the range of plasma concentrations achieved for 4-OH (69-97ng/ml) were lower compared to the plasma concentrations achieved for 1-OH (69-458ng/ml). Plasma concentrations of 4-OH below 25ng/ml were present in 31.2% of blood samples, which is slightly higher than that seen for the 1-OH metabolite (16.5%).

1-hydroxymidazolam production and disease state

Analysis of the data was undertaken by considering different disease states. The highest 1-OH midazolam plasma ratios were observed in patients with respiratory failure (1.49) and neurology patients (0.858). One of the respiratory patients suffered with epilepsy and was controlled on carbamazepine. This patient achieved the highest plasma concentrations of 1-OH ranging from 793-2152ng/ml. Excluding the samples from this patient from the analysis the mean plasma concentration of 1-OH for the remaining respiratory patients was found to be 87.5ng/ml and the mean midazolam 1-OH plasma ratio to be 0.40. From these results it is likely that carbamazepine, which is a known enzyme-inducing agent has caused an interaction with midazolam producing an enhanced metabolism of midazolam leading to increased

amounts of 1-OH in this patient. The neurology patients recruited to the study all suffered head injuries. All of these patients received phenytoin intravenously for prophylaxis of fitting after head trauma. Phenytoin can also induce liver enzymes and therefore can potentially interact with drugs metabolised in the liver. Again it is likely that an interaction occurred in these patients between phenytoin and midazolam to produce and enhanced metabolism of midazolam causing higher concentrations of 1-OH to be produced compared to other patients not prescribed enzyme-inducing agents.

The lowest 1-OH midazolam plasma ratios were seen in patients with renal impairment (0.086) and burns injury (0.049) compared to other disease states. No correlation was evident between the plasma concentration of midazolam and the plasma concentration of 1-OH for either of these disease states.

The reasons for these differences between disease states are difficult to explain. There is no published work on the altered pharmacokinetics of midazolam in burns patients in either adults or children. It has been shown that diazepam clearance is reduced in patients with burns injury and accumulation can occur. However lorazepam has been shown to have an increased clearance and a shortened half-life in burns patients (Martyn, Greenblatt et al. 1987). It is well established that burns injury can affect the pharmacokinetics and pharmacodynamics of a range of drugs due to altered protein binding and alterations in plasma volume. However, further work is needed to establish the effect that a burns injury has on the pharmacokinetics of midazolam. In this patient accumulation of midazolam was evident and the production of metabolites lacking.

The lack of production of 1-OH in patients with renal impairment is difficult to explain, as this should theoretically not interfere with the manufacture of midazolam metabolites. Previous studies have shown that elimination of the conjugated metabolite is reduced and the half-life prolonged in renal impairment (Buer, Ritz et al 1995; Boulieu, Lehmann et al.1998). A recent study has investigated the role of P450 4A5 in the metabolism of midazolam and has found that this enzyme may contribute significantly in the metabolism of midazolam (Wandel, Bocker et al 1994). The other two enzymes P450 3A3 and 3A4 also are involved in the

metabolism of midazolam but these are found predominately in the liver. P450 3A5 is found predominately in the kidney. This may explain the lack of metabolite production in renal impairment if this enzyme plays a significant role in midazolam metabolism. Further work is required in this area to clarify this issue.

Patients with liver impairment achieved a mean plasma concentration of 1-OH of 243ng/ml (32-803ng/ml) and a ratio of 0.21. It is interesting to note that the 1-OH midazolam plasma ratio observed in patients with severe liver impairment is higher than that observed in patients with severe renal impairment. The reasons for this are unclear but the results suggest that even when the liver is severely damaged there is still a capacity to metabolise midazolam and produce metabolites.

There was found to be no significant difference in the 1-OH midazolam plasma ratios between patients with liver impairment, cardiac impairment, neurology patients, post-operative patients and those with respiratory failure (excluding the patient taking carbamazepine). However, it was observed that for some of these disease states a significant correlation was evident between the plasma concentration of midazolam and the plasma concentration of 1-OH. Significant correlations existed between the plasma concentrations of midazolam and 1-OH in patients with congenital liver abnormalities; patients with cardiac impairment and neurology patients. The results indicate that although a direct correlation existed in these specific disease states the extent at which the metabolite was produced was slightly different in each group. This was indicated by the slope of the gradient in each case, which was found to be 0.0875 in liver patients, 0.107 in cardiac patients and 1.13 for neurology patients. These results suggest that neurology patients produced higher quantities of 1-OH metabolite and patients with liver impairment in comparison produced lower quantities of the 1-OH metabolite. No correlation between the plasma concentration of midazolam and 1-OH was found in patients with respiratory failure, patients with renal impairment, post-operative patients and burns injury.

4-hydroxymidazolam production and disease state

Plasma ratios were calculated for 4-OH and ranged from 0.0346-0.307. The lowest ratio was seen in patients with renal impairment (0.028) and the patient with burns injury (0.0346). The production of 4-OH was evident in all patients but to a much smaller degree than 1-OH. The 4-OH plasma concentration ranged from 67-85ng/ml over all disease states, which was much lower by comparison to the 1-OH metabolite plasma concentration. No correlation was established between different disease states and the production of 4-OH.

Summary

The results from the study suggest that all critically ill children irrespective of age are capable of producing the 1-OH and the 4-OH metabolite. However, no correlation was evident between the plasma concentration of midazolam and the plasma concentration of 1-OH when analyzed for all patients. The 1-OH midazolam plasma ratio was calculated for all patients and found to be 0.641 but no trend was established with age. Disease state however appears to have a significant effect on the production of the 1-OH metabolite compared with the age of the child. It was found that patients with renal impairment and burns injury produced the lowest quantities of 1-OH. Whereas patients with head injury produced significantly higher quantities of 1-OH metabolite. The results suggest the reasons for this could be due to the presence of concomitant medication including enzyme-inducing agents such as phenytoin and carbamazepine. The results also suggest that for certain disease states including liver impairment, cardiac impairment and patients with head injury a significant correlation exists between the plasma concentration of midazolam and 1-OH.

It was found that all critically ill children in the study were capable of producing the 4-OH metabolite but in lower concentrations compared to the 1-OH metabolite. No correlation was established between the plasma concentration of midazolam and 4-OH for either age or disease state.

Summary of major findings

- All patients irrespective of age were found to be capable of manufacturing 1-hydroxymidazolam and 4-hydroxymidazolam.
- No correlation was found between the production of 1-hydroxymidazolam and 4-hydroxymidazolam and patient age.
- Disease state was found to be a more important factor than patient age in the production of 1-hydroxymidazolam and 4-hydroxymidazolam.
- A significant correlation was found between the 1-hydroxymidazolam plasma concentration and midazolam plasma concentration in patients with liver impairment, cardiac impairment and patients with head injury.

The lack of work undertaken in the production of metabolites in critically ill adults or children makes comparative work difficult. It is evident that all ages of children including neonates have the capacity to produce both metabolites although younger children produce the 1-OH metabolite at a reduced extent. It is interesting to note that disease state has a significant impact on the production of 1-OH metabolite and this must be taken into consideration when prescribing midazolam in children. It is evident that much more work is required to be done in this area to clarify a number of points and it may be necessary to undertake multi centre studies to obtain sufficient numbers to draw any valid conclusions.

DISCUSSION

Discussion

It is a government recommendation that, wherever possible, critically ill children should be cared for in paediatric intensive care units with specialist paediatric nursing and medical staff. Children have different needs compared to adults and it has been shown that their treatment is improved when cared for in specialist areas by specialist staff. Children should not be seen as small adults and this is particularly true where the administration of medicines is concerned. Children handle and metabolise drugs in some cases very differently to adults therefore the scaling down of doses in relation to weight is inappropriate. In addition children of different ages can metabolise drugs differently to other children. Neonates are particularly vulnerable to the effects of drugs owing to immature renal and hepatic systems (Jacqz-Aigrain 1996). In contrast children between the ages of 1 and 3 years have been shown to metabolise certain drugs more quickly than older children. Therefore it is important not to treat all children the same but to consider all variables, age being an important factor. Many research studies consider only healthy children. Again this can lead to difficulties when treating children with a particular disease state. It has been shown that patients with renal, liver and cardiac impairment are particularly sensitive to the effects of some drugs.

There are fewer studies carried out in children compared to adults investigating differences in drug handling. Undertaking research studies in children is far more difficult than in adults and involves many ethical dilemmas. To undertake research studies in healthy children is fraught with problems compared to adults and there has to be substantial evidence for the reason to undertake studies in healthy children. Consent is a major issue and there has been much debate with regard to when a child is considered capable of giving consent to be recruited to a research study (Paul 1997). Undertaking studies in children who are critically ill also poses considerable problems. It is necessary to study the literature and show that there is a definite need to undertake the study before ethical approval can be granted. If the study is to include blood analysis this again causes issues with regard to the amount of blood that can be taken from a patient and this will of course depend on the age and weight of the child. It has become necessary to develop assays that are both sensitive and selective to allow analysis on small volumes of blood.

This study was undertaken to investigate the pharmacokinetics and pharmacodynamics of midazolam in critically ill children, which is the most commonly used sedative in paediatric intensive care in the UK. Sedation is an important part of treatment for a critically ill child receiving mechanical ventilation (Bavdekar, Mahajan et al. 1999; Polaner 2001). Although PICUs are specifically designed for children the environment remains an extremely stressful one and all attempts should be made to reduce anxiety. Sedation is therefore administrated to reduce anxiety states and to provide amnesia. Providing effective sedation in critically ill children remains a very challenging problem (Bhatt-Mehta and Rosen 1998). It is widely recognized that the administration of sedation in children is poorly handled and often leads to children being under sedated or over sedated. Under sedation leads to increased anxiety levels and children become aware of their surroundings. In addition under sedation can lead to inadvertent pulling out of lines, canulae and on occasions the ET tube. Over sedation is also problematic as children are slow to wake from the effects of sedation, this can lead to an increase in side effects from the drug and in some cases delayed extubation and delayed discharge from intensive care. Neither of these situations is ideal and improvement is required to administer sedation more effectively and safely to critically ill children.

There are a number of reasons why these problems have arisen. And this study attempted to address some of these issues. Children have been shown to metabolise and handle drugs differently to adults. Moreover, studies have shown that children of different ages metabolise drugs differently. Therefore this study investigated the pharmacokinetics of midazolam across a wide age range of children. Disease state can also affect drug handling and few studies have addressed the issue of altered drug handling of midazolam in different disease states in children. Midazolam is not licensed for use as a sedative in critically ill children and this has led to a gap in the knowledge of specific dosing requirements in this group of patients. Consequently midazolam is prescribed in critically ill children based mainly on past experience and dosing used in adults, rather than evidence based research undertaken in children. The aim of the present study was to improve the knowledge of the metabolism of midazolam in critically ill children of different ages and different disease states.

A key issue of the present study was to investigate measures of sedation as a basis for studying the effects of midazolam. Assessment of sedation in critically ill children is poorly undertaken. Sedation assessment is subjective in nature and often little credibility is associated with a sedation score. There are a number of sedation scales available in the literature but few have been fully validated and few have been used in critically ill children. Without sedation assessment, administration of sedation becomes very difficult to undertake effectively. Sedation assessment in adults using a validated scoring system has been shown to reduce the extent of over sedation (Detriche, Berre et al. 1999). Therefore before embarking on the pharmacokinetic analysis of midazolam in critically ill children it was first necessary to develop a validated method of sedation assessment. The present study investigated two different types of observational sedation assessment scales. Each scale was assessed for reproducibility and practicality and as a result one of the sedation assessment scales was ultimately employed in the remainder of the study and was also incorporated into the regular sedation policy at Birmingham Children's Hospital PICU.

Sedation Assessment

There are a number of sedation assessment scales available in the literature. Many have been specifically designed for adults and use communication and speech as part of the assessment (Ramsay, Savege et al. 1974, Chernik, Gillings et al.1990). These scales are inappropriate for the preverbal children. Other sedation scales have been designed for use in extubated children during recovery from sedation (Macnab, Levine et al. 1991). Few sedation scales have been specifically designed for use in children who are intubated. There are a number of different designs of sedation scale. Some are very simple in design and require a single assessment of the patient. Other sedation scales are more complex in design and breakdown the assessment into stages. A major criticism of many sedation scales are that they are too subjective in design and are therefore perceived as being inaccurate and of little use. Attempts have been made to correlate objective parameters with level of sedation such as heart rate, blood pressure and oxygen requirements. However, the problems with many of these factors when assessing critically ill patients is that patients are often being treated with cardiovascular drugs such as ionotropes. As such heart rate and blood pressure are being controlled to a certain extent pharmacologically and will interfere with an assessment.

This study investigated two different types of observational sedation assessment scales. The two sedation scales were very different in design one being a simple 5-point scale design and the other more complicated in design. Each sedation scale was validated for reproducibility over a 12-week period. The practicality of each sedation scale was assessed by involving the nursing staff and asking their opinions via questionnaire and face-to-face interviews. There are no papers reported of a comparative study of sedation scales of this type. The results from the study suggest that the reproducibility of each sedation scale was good irrespective of design. The results from the questionnaire and interviews however were very interesting in that the nursing staff clearly preferred sedation scale 2 compared to scale 1. This was a very surprising result, as the nursing staff found scale 1 easier and less time consuming to use compared to scale 2. However, the perception of the nursing staff was that scale 2 gave a more accurate measure of sedation assessment.

An important part of the sedation assessment part of the study was the development of sedation scale 2. The objectives set in the method, for the development of the scale were useful in focusing on what was required from an assessment scale. The objectives set included, making the scale appropriate for use in critically ill children of all ages. This was achieved by excluding any components that were reliant on verbal communication. Children are continually developing physically and psychologically and therefore it is difficult to develop a sedation assessment scale that can be used in all ages of children. This has been demonstrated with regard to pain assessment in children (Lawrence, Alcock et al. 1993). Pain assessment scales have been developed and validated for use in different ages of children. For example pictorial pain scales have been developed for the very young whereas for older children words are used to described the degree of pain children are experiencing. In the present study both scales were assessed for reproducibility with regard to age. Both scales demonstrated that reproducibility was good across different ages of children including neonates. During the development of scale 2 it was also decided to try and include parameters that had previously been associated with sedation assessment. Parameters that were included were facial expression, body movement and position, presence of patient agitation and respiratory effort. All these parameters were considered by the nursing staff as appropriate and useful when

considering sedation assessment. Other parameters considered by the nursing staff as useful when undertaking sedation assessment included heart rate and blood pressure. These were not included in the sedation assessment scale as these parameters can be considerably affected by other medication particularly inotropes, which are used extensively in critical care. The sedation scale was developed so that the assessment of the patient could be broken down and theoretically made more objective rather than merely making a single assessment of the patient. One of the conclusions that can be drawn from this study is the need not just to consider reproducibility of sedation scales but also practicality. Previous studies have criticised some sedation scales for being too cumbersome and time consuming to use and although they perhaps are shown to provide good reproducibility between staff, they are impractical to use in a busy intensive care unit. This point was evident from the results of the nursing staff questionnaire where it was clear that although sedation scale 2 was more complicated in design it was felt that it gave a more accurate assessment of sedation and anxiety than scale 1. In addition, even though it looked more complex than scale 1 it was found to be both practical and easy to use.

This study also attempted to investigate the reproducibility of both scales for children with different disease states. However, the only group of patients that contained sufficient numbers to draw any conclusions from, were patients with cardiac impairment. Numbers in other disease groups were too small. However in the cardiac group there was again good reproducibility for both scales. Patients with neurological problems including head injury patients and patients with learning difficulties can be particularly difficult with regard to sedation assessment (Mirski, Muffelman et al. 1995). These patients were also highlighted in the study by some of the nursing staff as posing particular problems with regard to effective sedation administration and assessment. These patients require further research with regard to sedation assessment and it may be necessary to develop a sedation assessment scale specifically for these patients. The Paediatric Glasgow Coma Scale was developed specifically to assess level of consciousness in children with head injury and therefore there may be a case to develop a specific sedation assessment scale for these patients as well (Tatman, Warren et al.1997).

Another patient that poses a difficult problem with regard to sedation assessment is the paralyzed patient. This group of patients were also highlighted in the study by some of the nursing staff as patients whose assessment of level of sedation was difficult to carry out accurately. Clearly it is inappropriate to use either of the scales in the present study for these patients and therefore that was the reason for excluding them from the sedation assessment study. However, it is apparent from the pharmacokinetic study that these patients are at great risk of over sedation and one of the reasons for this is that effective sedation assessment using the developed methods is impossible. One method to assess sedation in these patients is to stop sedation for a period of time each day and allow sedation to wear off - once sedation has worn off and therefore the risk of accumulation is reduced, level of sedation can be assessed. The problem with this is that patients are continually having therapy discontinued and resumed and this can cause disruption to a patient's treatment if they wake quickly and become aware of their surrounding. There is a great need for further research to be undertaken in the paralyzed patient and new methods need to be developed to be able to assess the level of sedation in these patients accurately and effectively to avoid the risk of side effects developing.

From the results of this part of the study sedation scale 2 was found to be not only reproducible but also easy and practical to use. It was considered to give an accurate measure of the level of sedation and anxiety in critically ill children and was therefore incorporated into PICU policy and used routinely at Birmingham Children's Hospital as part of the sedation protocol. It was imperative to conduct this part of the study first in order to use the validated sedation assessment scale in the pharmacokinetic study.

Pharmacokinetics of midazolam in critically ill children

This part of the study aimed to investigate any altered pharmacokinetic and pharmacodynamic handling of midazolam in critically ill children. An important aspect of the pharmacokinetic study was the development and validation of the midazolam assay. The assay was required to be not only robust but also selective and sensitive. Other previously documented midazolam assays have used large volumes of plasma in excess of 1ml, which is inappropriate when dealing with children, particularly small children (Eeckoudt, Desager et al.1998). In addition patients in intensive care frequently have blood taken for routine monitoring including gas

analysis, biochemistry and monitoring of drug levels. Therefore when undertaking research in critically ill children careful consideration must not only be given to the quantity of blood taken but more importantly that the study is necessary. The present study found that the limits of detection for the assay of midazolam and its metabolites were 25ng/ml. Previously documented midazolam assays have been able to detect levels of midazolam in the region of 2ng/ml (Kanazawa, Nishimura et al.1995). It was felt that for the purposes of this study it was unnecessary to try to reproduce detection levels at such low concentrations of midazolam and its metabolites. The reasons for this were that the main aims of the study included the investigation of the correlation between midazolam plasma concentration and level of sedation; and clearance of midazolam by considering steady state midazolam plasma concentrations. Therefore both of these situations were expected to consider midazolam plasma concentrations in excess of 25ng/ml. However, an alteration that would be considered if the project were to be repeated would be in relation to the standard calibration curves for midazolam and it metabolites. The standard calibration curves ranged from 25ng/ml to 3000ng/ml. It was unexpected to find midazolam plasma concentrations in excess of 3000ng/ml however, this was seen in a number of samples. In addition the standard calibration curves for the metabolites could be reduced, as the concentrations found for both metabolites did not exceed 2000ng/ml.

Although studies have been conducted investigating the use of midazolam in intensive care there is still a great need for further research to be conducted particularly in the field of paediatrics where information is lacking (Ostermann, Keenan et al. 2000). The parameters that were specifically investigated included plasma concentration of midazolam and the relationship between plasma concentration and level of sedation; clearance of midazolam and the metabolites 1-OH and 4-OH were also investigated.

In previous studies it has been difficult to establish any correlation with midazolam plasma concentration and level of sedation (Oldenhof, de Jong et al.1988). There is considerable patient inter-variability of midazolam plasma concentration and many studies have found that no correlation between effect and concentration can be elucidated. However, from this study it

has been clearly demonstrated that midazolam plasma levels can be correlated with level of sedation. A satisfactory level of sedation was observed in critically ill children with a mean midazolam plasma concentration of 223ng/ml. This finding was supported in the study by the observation that patients who were assessed as sleeping also achieved a plasma concentration similar to that associated with satisfactory sedation. Patients who are assessed as sleeping are clearly not distressed and can be considered as satisfactorily sedated. One of the reasons why this study has clearly shown a correlation between sedative effect and plasma concentration of midazolam could be due to the fact that a validated sedation assessment scale was used, compared to previous studies where this has not been the case. It has been highlighted that pharmacokinetic studies investigating the correlation between plasma concentration of midazolam and sedative effect that do not use a fully validated sedation assessment method are open to criticism (Ostermann, Keenan et al. 2000).

Other important finding from this study was the lack of a strong correlation between midazolam dose and midazolam plasma concentration, suggesting that dose adjustment cannot be accurately done to achieve desired plasma concentration and therefore a desired level of sedation. This has strong clinical implications as it is widely accepted that titration of effect can be achieved by increasing or decreasing the dose of a medication. The findings from this study suggest that this may not be the case in critically ill children. The reasons for this are unclear but may be due to the fact that there are a number of factors which are evident in critically ill children including disease state that affect the handling of midazolam compared to healthy patients. It is imperative therefore that medical staff prescribing and adjusting the dose of midazolam in this patient group are made aware of this fact and that clinical assessment of the level of sedation is required to aid dose adjustment.

The present study found a wide range in the plasma concentrations of midazolam that have been reported previously in other studies (Hughes, Gill et al.1996). In order to investigate the reasons for this occurring it was necessary to investigate the clearance of midazolam to identify those children that were accumulating midazolam and consequently achieving high plasma concentrations. Clearance was calculated in the study by using steady state plasma concentrations. An assumption made in the present study was that steady state had been

achieved after 6 hours of continuous midazolam infusion in the absence of any bolus doses. It was decided to investigate clearance of midazolam rather than half-life owing to constraints on the volume of blood that could be taken from each individual child. The results of the study found that the clearance of midazolam in critically ill children was lower than that previously documented in healthy children. Midazolam clearance was also found to alter with age. Neonates were found to have the lowest clearance compared to other ages of children. Although the numbers of neonates recruited to the study were small, previous studies investigating midazolam clearance have found similar values, clarifying reduced clearance of midazolam in this age group compared to older children. The highest rate of midazolam clearance was seen in patients aged between 1 month and 3 years. This phenomenon has been described for other drugs including morphine where children aged between 1 and 3 years appear to have an increased clearance of some drugs (Olkkola, Hamunen et al. 1995). Midazolam clearance was found to gradually decrease after the age of 12 months in critically ill children to values reported in the literature for adults (4-8ml/kg/min).

The results of the study suggested evidence of auto-induction of midazolam. A significant increase in the clearance of midazolam was evident after five to seven days of continuous midazolam therapy. However, not all patients exhibited this phenomenon. Neonates did not show any indication of increased clearance with time. In addition children aged 4 to 7 years demonstrated a reduced midazolam clearance with time. It is unclear why this occurred in this age group, but was probably unrelated to age but rather the disease states that were present within this group of children. Within the group of patients aged 4 to 7 years two patients suffered severe renal impairment. If age related differences are to be investigated further then greater patient numbers are required in this age group to draw valid conclusions. The results from the present study suggest that most patients show evidence of auto-induction of midazolam after 5 to 7 days of continuous therapy as previously stated. This in part may explain the wide range in midazolam plasma concentrations observed in this study to achieve a satisfactory level of sedation. Patients who have received midazolam continuously for more than 5 days may be at risk of auto-induction and therefore show a degree of tolerance to midazolam and subsequently require higher plasma concentrations of midazolam to achieve a satisfactory level of sedation. Further studies are required to clarify the long-term effects of

midazolam on level of sedation and to establish the consequences of auto-induction of midazolam in critically ill patients.

A significant difference in midazolam clearance was seen in different disease states. Lower midazolam clearance values were observed in patients with liver, renal and cardiac impairment and patients with burn injury compared to other children in the study. The lowest midazolam clearance was seen in patients suffering with severe liver impairment. These patients are at great risk of accumulating midazolam and achieving high plasma concentrations of midazolam, as was evident in the present study where patients with severe liver impairment attained the highest midazolam plasma concentrations compared to other children. The liver is the major elimination route for midazolam and therefore it is not surprising that clearance was dramatically reduced in these patients. However, an interesting finding in this study was in patients with severe renal impairment that also showed a significant reduction in midazolam clearance. Previous studies investigating the clearance of midazolam in renal impairment are conflicting. Some studies have reported that critically ill adults with severe renal impairment accumulate midazolam but the reasons for this remain unclear (Driessen Vree et al.1991). Midazolam is thought to be predominantly metabolised by the P450 cytochrome enzyme system which includes the 3A3, 3A4 and 3A5 enzymes. The role that the P450 3A5 plays in the metabolism of midazolam has not as yet been fully clarified but the results from a recent study suggest that it may contribute significantly to the metabolism of midazolam (Wandel, Bocker et al. 1994). This enzyme is found predominantly in the kidney and therefore in part may explain the apparent reduced metabolism of midazolam in renal impairment. However, further research is required to clarify this. Children with cardiac impairment demonstrated a reduced midazolam clearance compared to other children in the study. A reduced midazolam clearance has been previously reported in critically ill adults. Reasons for this remain unclear but are thought to be due to deceased hepatic and renal blood flow leading to reduced midazolam metabolism. It was found that patients with normal renal and liver function including, post-operative patients, neurology patients and patients with respiratory failure had a midazolam clearance similar to that documented in healthy children. It is interesting to note that one patient recruited to the study with severe burns injury showed a significant reduction in midazolam clearance. Although no clear conclusions can be drawn from a single patient it is

clear that these patients may be at great risk of accumulating midazolam and achieving high plasma concentrations. Further work is required to be undertaken in patients with burns to establish the effect on the pharmacokinetics of midazolam.

A total of 5 patients were recruited to the study with Downs syndrome. Little work has been undertaken with regard to drug metabolism within this small group of children. However, it has been documented that patients with Downs syndrome may have an increased metabolism of morphine and therefore could require higher doses to obtain a desired effect compared to patients without the syndrome (Gakhal, Scott et al. 1998). The nursing staff during the study also highlighted this group of patients as posing a difficult problem with regard to achieving effective sedation. The midazolam clearance was found to be similar in Downs syndrome children compared to other children with normal renal and liver function. However when clearance values were compared in cardiac patients with and without Downs syndrome differences were observed. Cardiac patients with Downs syndrome were found to have a higher midazolam clearance than those without the syndrome. Numbers in this study are small and therefore no clear conclusion can be drawn from this work. However observations have been made that children with Downs syndrome are often difficult to sedate effectively compared to other children. Further work is required to establish any differences in drug metabolism in children with Downs syndrome. It maybe necessary to conduct multi centre studies with such groups of children to achieve adequate numbers from which to draw any valid conclusions.

The effect of changes in body temperature on the clearance of midazolam was investigated in head injury patients. However, no significant differences were found in clearance in patients during cooling compared to clearance values calculated whilst patients were at core temperature. This is interesting as a reduction in midazolam metabolism might be expected at lower body temperatures Changes in drug metabolism at lower body temperatures have been demonstrated with other drugs including neuromuscular blocking agents. Numbers were small in this study and it may be that further work is required to clarify this finding.

An interaction between midazolam and erythromycin was observed in the study. This interaction has been documented previously and is thought to be potentially severe although the exact extent of the interaction is unknown. In the present study a 10 fold decrease in the clearance of midazolam was observed and occurred within a 24 hour period of starting erythromycin. Previous reports have suggested that this interaction may take longer than 24 hours to occur however this was not evident in the present study. Nursing and medical staff as well as pharmacists need to be aware of the serious nature of this interaction and the onset with which it can occur.

Midazolam is metabolised to two major metabolites 1-OH and 4-OH by the liver. It is thought that a significant amount of sedative effect is obtained from the 1-OH metabolite but very little from 4-hydroxymidazolam. Very little work has been undertaken to investigate these metabolites in adults, let alone in children. Plasma concentrations of 1-OH and 4-OH were found to be much lower compared to plasma concentrations of midazolam. In order to investigate the production of each metabolite in critically ill children the metabolite midazolam plasma ratio was calculated. It was found that all critically ill children including neonates were capable of producing both metabolites. However, a correlation was only demonstrated between 1-OH plasma concentration and midazolam concentration when certain disease states were considered in isolation. This was in contrast to the 4-OH metabolite where no correlation was found between 4-OH plasma concentration and midazolam concentration. The reasons for this remain unclear but 4-OH is thought to have a very short half-life and may disappear from the plasma very quickly making accurate analysis difficult. Further studies to investigate the production of metabolites in this group of children may be undertaken looking at glucuronidation. Both metabolites are water-soluble and renally excreted therefore investigation of the presence of the metabolites in the urine rather than blood products maybe more appropriate.

Although no trend in 1-OH production was evident in relation to the age of the patient, the presence of certain disease states was found to be a significant factor. Patients with severe renal impairment and burns injury were found to produce the smallest quantities of 1-OH whereas patients with head injury and respiratory failure were found to produce the highest

quantities of 1-OH. These finding are very closely related to midazolam clearance where patients with renal impairment and burns injury produced the lowest midazolam clearance and patients with head injury produced the highest clearance values. Enzyme-inducing agents including phenytoin and carbamazepine prescribed in the head injury patients and one of the respiratory patients were thought to be responsible for the increased metabolism of midazolam and consequently the higher concentrations of 1-OH observed. Although the interaction between midazolam and orally administered phenytoin has been reported there are no papers reporting the significance of the interaction between midazolam and intravenous phenytoin in critically ill head injury patients. Phenytoin is a commonly prescribed agent in critically ill patients who have sustained a head injury and medical and nursing staff need to be made aware of the consequences of the interaction and the potential for increased clearance of midazolam and therefore a reduced sedative effect. A significant correlation was observed between plasma concentrations of midazolam and plasma concentrations of 1-OH in patients with congenital liver impairment, patients with cardiac impairment and neurology patients. The results suggest that these patients are capable of producing the metabolite but at different rates.

One of the major problems when undertaking clinical research studies is the complexity of the environment and the patients that are involved. This situation is made more complex when dealing with children. Although 52 children were recruited to this study the amount of parameters that had to be taken into consideration were considerable. Age is an important factor to consider, as it has been demonstrated that children are constantly changing physiologically and emotionally. This study not only needed to consider that physiological factors such as an immature renal and liver system could affect pharmacokinetic handling of drugs but also had to take into consideration emotional maturity when considering sedation assessment. This study investigated critically ill children and therefore disease state was also an important consideration. Some children recruited to the study may have had more than one disease state to consider, which is very often the case in critically ill patients, making analysis very difficult. Other complicating factors in such a study include the potentially vast and varied numbers of other medication that can be commonly administered in critically ill patients. It was necessary to ensure that commonly prescribed medication did not interfere

with the midazolam assay. In addition it was necessary to document all medication that patients received whilst recruited to the study. The importance of this was highlighted when the results of some of the findings suggested the possibility of drug interactions with midazolam in particular the effects of enzyme-inducing agents such as phenytoin and carbamazepine and also enzyme-inhibitors such as erythromycin and sodium valproate. New techniques are continually being developed in the care of the critically ill. An example of this was the investigation into the effects of cooling patients during the first 24 hours of a head injury. The effect of cooling patients on the metabolism of drugs is largely unknown and therefore this is yet another complicating factor in the analysis of this study.

It can be seen that to clarify a number of findings in this study larger patient numbers are required. However, as demonstrated by this study recruitment of critically ill children to research studies is very difficult and fraught with problems. Consent is a major issue and as was demonstrated in the study approaching parents and relatives to obtain consent during the first 24 hours of a child being admitted to intensive care was extremely difficult. Recruiting critically ill children to research studies will remain a difficult problem and consequently collaboration between PICUs may be required to achieve sufficient numbers to clarify findings.

Recommendations

- All critically ill children should have regular assessments of their sedation and anxiety levels using a sedation assessment scale specifically designed for use in paediatric intensive care.

- Patients at risk of accumulating midazolam and achieving high plasma concentrations include; neonates, patients with severe liver and renal impairment and patients with burns injury. Therapeutic drug monitoring of midazolam should be considered in all these groups of patients.

- Patients receiving neuromuscular blocking agents are at risk of achieving high plasma concentration of midazolam owing to a lack of a reliable method with which to assess level of sedation. Therapeutic drug monitoring should also be considered in these patients.

- Care should be taken in patients prescribed continuous intravenous midazolam for more than 5 days owing to the potential of auto-induction occurring and therefore the development of tolerance.

- The development of national guidelines are required for the use of sedatives in critically ill children similar to the clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult produced by the Task Force of the American College of Critical Care Medicine (Jacobi, Gilles 2002).

Conclusions

Administration of medicines to children is fraught with difficulties. This situation has arisen owing to an array of problems including insufficient knowledge of drug handling in children, lack of licensed drugs available for use in children and insufficient evidence based research in the field of paediatric pharmacology. It is clear from this study that there is still a great deal to be learnt about commonly prescribed drugs in the critically ill child. Sedation is a vital part of treatment in the child cared for in intensive care. Midazolam is a commonly prescribed agent and has been used for many years. However administration of this agent is still poorly undertaken in critically ill children and results in children often receiving too much or too little.

The major findings of the study are detailed below:

- A sedation assessment scale specifically designed for use in critically ill children was developed and fully validated.

- A significant correlation was established between midazolam plasma concentration and level of sedation in critically ill children.
- A poor correlation was only evident between midazolam plasma concentration and dose of midazolam.
- A poor correlation was only evident between dose of midazolam and level of sedation.
- Clearance of midazolam was reduced in critically ill children compared to that reported in healthy children.
- Clearance of midazolam was significantly reduced in patients with severe renal and liver impairment; patients with cardiac impairment and patients with burn injury.
- Auto-induction of midazolam was evident after 5 to 7 days of continuous midazolam therapy.
- Patients receiving neuromuscular blocking agents were found to be at great risk of achieving high plasma concentrations of midazolam.
- Patients of all ages were found to be capable of producing 1-hydroxymidazolam and 4-hydroxymidazolam.
- Disease state was found to be a more important factor than age in the production of 1-hydroxymidazolam and a correlation between plasma concentrations of midazolam and 1-hydroxymidazolam were established for patients with liver impairment, cardiac impairment and head injury patients.
- An interaction between midazolam and phenytoin was highlighted and thought to cause an enhanced metabolism of midazolam.

The work has highlighted the need to assess level of sedation effectively and has resulted in a validated sedation assessment scoring system that is suitable to be used in the critically ill child. The assessment scale has been validated to ensure reproducibility and consistency over time. It is suitable to be used in all ages of children including preverbal children and children who are ventilated. It was imperative to obtain the opinion of the nursing staff in the final

choice of sedation assessment method to ensure ownership by the staff and inclusion of the sedation scale in the departmental sedation policy.

Once the sedation assessment part of the study was complete, it was then possible to proceed to the pharmacokinetic part of the study. It is clear from the results of the pharmacokinetic study that age is an important factor and must be taken into consideration when undertaking any research in children. Age related differences in midazolam plasma concentration, clearance and the production of metabolites where all evident in the results of the study. It is also clear from the results that disease state plays an important role in the pharmacokinetics of midazolam. It was found that midazolam plasma concentration, clearance and production of metabolites were all dependant on the disease state. Neonates were found to be at risk of accumulating midazolam. This has been documented in other studies but it is clear that some of neonates require very low levels of midazolam to achieve a satisfactory level of sedation. When prescribing midazolam it is imperative to consider a number of patient factors particularly age as well as disease state. Patients at greatest risk of accumulating midazolam include those with severe liver impairment and renal impairment and to some extent cardiac impairment. Therefore care must be taken when prescribing midazolam in these particular patients. Further work is required to be undertaken in patients with burns injury as the results suggest these patients are at particular risk of accumulation of midazolam and may require substantially reduced dosing.

Undertaking research in critically ill children is fraught with difficulties. There are ethical issues as well as consenting difficulties to overcome. When undertaking any research investigating drug concentration blood sampling is inevitable. There will be restrictions on the amount of blood that can be taken from individual children and this will depend on the age of the child. Therefore techniques must be developed to reduce the amount of blood taken where necessary. The midazolam assay in this project was selective and sensitive enough to handle small blood volumes but was a difficult problem to overcome. Consenting issues were also difficult particularly within the environment of PICU. It became evident very early on in this study that approaching parents in the first 24 hours of PICU admission was a difficult time to obtain consent. Therefore review of the study protocol was made and parents were approached

after the first 24 hours of admission to PICU. When undertaking such research is important to develop a robust protocol but it is also important to be aware that revisions may be necessary.

These problems should not deter researchers from undertaking research in children as there is a great need for further work to be done not only with midazolam but also other agents. It is only by undertaking quality research that the safe and effective administration of medicines to children will be improved upon.

APPENDICIES

Appendix 1- Sedation Assessment Scale 1

Sedation Score				
1	2	3	4	5
Wide awake	Awake but sleepy	Asleep but moves spontaneously	Asleep, but responds to stimulation	Hard to rouse

Appendix 2 - Sedation assessment scale 2

SCORING			
	0	1	2
Facial expression	Anxious/anguished Silent cry Frown Crumples face =0	Quietly alert Relaxed =1	Asleep =2
Eyes	Eyes narrowed Eye squeeze =0	Open but relaxed =1	Closed =2
Body/arm/ leg movement	Uncoordinated Flexed/extended Jerky/startled =0	Relaxed movements Purposeful movement =1	No movement =2
Agitation	Major agitation Cannot be comforted Crying/silent cry =0	No agitation or Can be comforted =1	No movement =2
Respiration	Fighting ventilator or Asynchrony with ventilator =0	Making some respiratory effort/simv or extubated =1	No respiratory effort over ventilator =2

A sedation score will range from 0-10

- A baseline sedation score can be calculated when the child is not being handled.
  Highlight this by (B) in the documentation.

- A responsiveness sedation score can be calculated when the child is being handled or undergoing physiotherapy/suctioning.
  Highlight this by (R) in the documentation.

- **If the patient is asleep highlight this by (A) in the documentation.**

- If the patient is paralysed this sedation score cannot be used.
  Highlight this by (P) in the documentation.

The following is a guide to using the sedation score

Type of sedation Score	Score and Action required
Baseline	A score between 4 and 8 - no action required A score between 0 and 3 or 9 and 10 - review sedation
Responsiveness	A score between 3 and 7 - no action required A score between 1 and 2 or 8 and 10 - review sedation

Appendix 3 - Parent information leaflet for sedation assessment study.

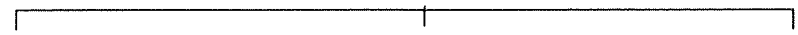
Sedation Assessment in Children in Intensive Care

Information Sheet for Parents or Guardian

Introduction.
Sick children who require Intensive Care usually need medication to keep them calm and prevent them from becoming distressed or uncomfortable. Although children receive the highest possible standard of nursing and medical care, it is sometimes difficult to achieve the right amount of sedation. Too much or too little sedation can occur. Over sedation can delay discharge from Intensive Care Units and make children too sleepy. Under sedation may allow distress or pain.

We want you to know about a study that aims to assess sedation in children cared for in Intensive Care.

The Project.
One of the ways to help us assess if we are giving enough sedation, is to simply observe the child and assess for comfort.
This can be done using a scale for example from 0 to 10 as shown below.



0 10

very uncomfortable (under sedated)

deeply asleep (over sedated)

However this is often quite difficult to do, as there are few scales available that have been properly tested and studied in practice.
We are looking at two types of sedation scales in this project. To investigate how good each of these scales are, two nursing or medical staff will make an assessment of sedation at the same time. Therefore you may see two members of staff writing down their assessments.

The study involves no discomfort to your child since it only involves observing your child.

We hope to develop a sedation assessment scale, which is both accurate and easy to use, and one that will therefore help children in Intensive Care.
If you would like to see either of the sedation scales being used in this study, please do not hesitate to ask myself, Karen Whitfield or the nurse looking after your child.

Karen Whitfield – Research Pharmacist 0121 359 3611 ext. 5237

Poster information for parents for sedation assessment study.

Parent/Carer Information

Jan.2000

Sedation Assessment Project

Sedation - What is it and why is it necessary?

Intensive care can be a very stressful place at times and sick children often need medication to help them relax and stop them getting distressed and upset.

Achieving the right level of sedation in a child is very important, to ensure that they do not receive too much and become too drowsy or too little and become uncomfortable. Getting the right level is often difficult as every child is different.

We would like to tell you about this study that aims to improve the way we assess sedation in these children

The Project

This project is looking at the best method of sedation assessment.

One way of assessing a child to see if the correct amount of sedation is being given, is to simply observe the child and assess for comfort.

This method uses sedation assessment scales.

In this project we are looking at two different types of sedation assessment scales. Both scales are observational and therefore the study involves no additional discomfort to a child

What should you expect?

If your child is receiving sedation you may see two members of staff assessing your child for sedation at the same time.

Please do not worry. It is necessary for the project that two people make an assessment at the same time. This project involves no additional discomfort to your child.

The aim of the project

To develop a sedation assessment scale that is both accurate and easy to use, improving the care given to children in Intensive Care

Further Information

For further information about sedation scales being used in the study please contact myself Karen Whitfield or ask the nurse looking after your child

Thank you for taking the time to read this poster

Karen Whitfield - Research Pharmacist, Aston University 0121 359 3611 ext.5237

Appendix 4
Written information to PICU regarding sedation assessment project

Dept. Pharmacy
Aston University
Aston Triangle
Birmingham

0121 359 3611 ext. 5237

24th February 2000

To all PICU Staff,

Re: Sedation Assessment

I will be introducing the second sedation assessment scale onto the Paediatric Intensive Care Unit on Monday 28th February 2000. I will be assessing this sedation scale for a period of 4 to 6 weeks.

I would like you to be aware that this assessment scale ranges from 0–10 unlike the previous scale, which ranged from 1-5.

I hope this will not cause any confusion or disruption to you.
If you have any questions please do not hesitate to contact me.

With thanks

Karen Whitfield.

Appendix 5

Sedation Assessment Questionnaire

I would be very grateful if you could complete the following questionnaire about the two types of sedation assessment scoring systems that have been used on the Intensive Care Unit over the last 3 months. The questionnaire will take you no longer than 15-20 minutes to answer and will provide valuable information on your thoughts about the usefulness and practicality of both sedation assessment tools.

Please return completed forms to Karen Whitfield in the envelope provided and place in my tray on the reception desk in PICU.

If you could complete the questionnaire by **Wednesday 19th April 2000** I would be very grateful.

Thank you

Karen Whitfield
Aston University

0121 359 3611 ext. 5237.

Sedation Assessment Questionnaire

The questionnaire is divided into 3 sections

A) refers to questions about sedation tool no.1
B) refers to questions about sedation tool no.2
C) refers to general questions about sedation in PICU.

Section A - Sedation Tool No.1

Sedation Score				
1	2	3	4	5
Wide awake	Awake but sleepy	Asleep but moves spontaneously	Asleep but responds to stimulation	Hard to rouse

Q1 Have you used the **sedation assessment tool No.1** (see above) during the last 3 months? *(Please circle your answer)*

a)Yes b)No

Q2 During the last 3 months how many times have you used sedation assessment tool **No.1**? In total this can include during the same shift or in the same patient. *(Please circle your answer)*

a) Less than 5 times
b) 5-10 times
c) 11-20 times
d) more than 20 times

Q3 On average how long does it take you to make an assessment using sedation tool **No.1**? *(Please circle your answer)*

a) less than 1 minute
b) 1-3 minutes
c) 4-5 minutes
d) more than 5 minutes

Q4 Would you use sedation tool **No.1** in a patient receiving neuromuscular blocking agents? *(please circle your answer)*

a)Yes b)No

Q5 Would you use sedation tool **No.1** in a child receiving ventilation but no sedation? *(please circle your answer)*

a)Yes b)No

Q6 Do you think the wording used in sedation tool **No.1** is appropriate? *(please circle your answer)*

a) Wide awake	yes	no
b) Awake but sleepy	yes	no
c) Asleep but moves spontaneously	yes	no
d) Asleep but responds to stimulation	yes	no
e) Hard to rouse	yes	no

Q6a If you have answered 'no' to any of the categories please suggest an alternative or say why you think it inappropriate, below.

Statement	Please suggest your alternatives or comments by the appropriate letter.
a	
b	
c	
d	
e	

Q7. Using the scale below indicate how subjective/objective you think sedation tool **No.1** is by circling a number.

0	1	2	3	4	5	6	7	8	9	10
very subjective										**very objective**

Q8. Here are some questions about sedation assessment tool **No.1.**
To what extent do you **agree**?

Please circle the most appropriate letter where;
a - very much
b - fairly
c - somewhat
d - not very
e - not at all.

A	The sedation assessment tool is very easy to use.	a	b	c	d	e
B	The sedation assessment tool allows accurate measurement of depth of sedation	a	b	c	d	e
C	The sedation assessment tool is very easy to understand	a	b	c	d	e
D	The sedation assessment tool is very useful	a	b	c	d	e
E	The sedation assessment tool is appropriate for patients receiving mechanical ventilation	a	b	c	d	e
F	The sedation assessment tool is appropriate for extubated or self ventilating patients	a	b	c	d	e
G	The sedation assessment tool is appropriate for patients receiving CPAP	a	b	c	d	e
H	The sedation assessment tool is very time consuming to use	a	b	c	d	e
I	The wording used is the assessment tool is very ambiguous	a	b	c	d	e
J	The assessment tool is suitable for patients receiving neuromuscular blocking agents	a	b	c	d	e
K	The assessment tool can be used by all grades of nursing staff	a	b	c	d	e
L	The assessment tool is very subjective	a	b	c	d	e

Q9. From the list below choose the phrase or word that you think best describes or correlates with the numbers in the sedation assessment tool. You may choose more than one statement for a particular number if you wish. Please answer by placing the letter(s) in the box under the sedation assessment numbers below.

Sedation Score				
1	2	3	4	5
Wide awake	Awake but sleepy	Asleep but moves spontaneously	Asleep but responds to stimulation	Hard to rouse

A - under sedated
B - over sedated
C - satisfactorily sedated
D – asleep
E – anxious
F - distressed
G - deeply asleep
H - comfortable

1	2	3	4	5

Q10. Would you make any modifications to sedation tool **No.1?**

Yes No

Q10a If you have answered yes to Q10 please list the modifications you would make if any in the space provided below.

_____

_____

_____

_____

_____

Section B - Sedation Tool No.2

Sedation Tool **No.2** (see opposite)

Q11. Have you used **sedation assessment tool No.2** (see opposite) during the last 3 months? *(Please circle your answer)*

a)Yes b)No

Q12 During the last 3 months how many times have you used sedation assessment tool **No.2**? I total this can include during the same shift or in the same patient.*(Please circle your answer)*

a) Less than 5 times

b) 5-10 times

c) 11-20 times

d) more than 20 times

Q13 On average how long does it take you to make an assessment using sedation tool **No.2**? *(Please circle your answer)*

a) less than 1 minute

b) 1-3 minutes

c) 4-5 minutes

d) more than 5 minutes

Q14 Would you use sedation tool **No.2** in a patient receiving neuromuscular blocking agents? *(please circle your answer)*

a)Yes b)No

Q15 Would you use sedation tool **No.2** in a child receiving ventilation but no sedation? *(please circle your answer)*

a)Yes b)No

Q16 Do you think the wording used in sedation tool **No.2** is appropriate? *(please circle your answer)*

a)Yes b)No

Q16a If you have answered 'no' please suggest an alternative or say why you think it inappropriate, below by writing directly onto the version below.

Sedation Score for Non-Paralysed Children

SCORING			
	0	1	2
Facial expression	Anxious/anguished Silent cry Frown Crumples face =0	Quietly alert Relaxed =1	Asleep =2
Eyes	Eyes narrowed Eye squeeze =0	Open but relaxed =1	Closed =2
Body/arm/ leg movement	Uncoordinated Flexed/extended Jerky/startled =0	Relaxed movements Purposeful movement =1	No movement =2
Agitation	Major agitation Cannot be comforted Crying/silent cry =0	No agitation or Can be comforted =1	No movement =2
Respiration	Fighting ventilator or asynchrony with ventilator =0	Making some respiratory effort/simv or extubated =1	No respiratory effort over ventilator =2

A sedation score will range from 0-10

- A baseline sedation score can be calculated when the child is not being handled.
  Highlight this by (B) in the documentation.
- A responsiveness sedation score can be calculated when the child is being handled or undergoing physiotherapy/suctioning.
  Highlight this by (R) in the documentation.
- **If the patient is asleep highlight this by (A) in the documentation**
- If the patient is paralysed this sedation score cannot be used.
  Highlight this by (P) is the documentation.

The following is a guide to using the sedation score

Type of sedation Score	Score and Action required
Baseline	A score of 4,5,6,7 or 8 - no action required A score of 1,2,3,9 or 10 - review sedation
Responsiveness	A score of 3,4,5,6 or 7 - no action required A score of 1,2,8,9 or10 - review sedation

Q17 Using the scale below indicate how subjective/objective you think sedation tool **No.2** is by circling a number.

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Very subjective										**very objective**

Q18. Here are some questions about sedation assessment tool **No.2.**
To what extent do you **agree**?

Please circle the most appropriate letter where ;
a - very much
b - fairly
c - somewhat
d - not very
e - not at all.

A	The sedation assessment tool is very easy to use.	a	b	c	d	e
B	The sedation assessment tool allows accurate measurement of depth of sedation	a	b	c	d	e
C	The sedation assessment tool is very easy to understand	a	b	c	d	e
D	The sedation assessment tool is very useful	a	b	c	d	e
E	The sedation assessment tool is appropriate for patients receiving mechanical ventilation	a	b	c	d	e
F	The sedation assessment tool is appropriate for extubated or self ventilating patients	a	b	c	d	e
G	The sedation assessment tool is appropriate for patients receiving CPAP	a	b	c	d	e
H	The sedation assessment tool is very time consuming to use	a	b	c	d	e
I	The wording used is the assessment tool is very ambiguous	a	b	c	d	e
J	The assessment tool is suitable for patients receiving neuromuscular blocking agents	a	b	c	d	e
K	The assessment tool can be used by all grades of nursing staff	a	b	c	d	e
L	The assessment tool is very subjective	a	b	c	d	e
M	Documenting a baseline sedation score is useful	a	b	c	d	e
N	Documenting a responsiveness score is useful	a	b	c	d	e
O	The guidelines for the need to review sedation are accurate	a	b	c	d	e
P	The wording of the guidelines to review sedation are clear	a	b	c	d	e
Q	The guidelines to review sedation are useful	a	b	c	d	e

Q19. From the list below, choose the phrase or word that you think best describes or correlates with the numbers in the sedation assessment tool. You may choose more than one statement for a particular number if you wish. Please answer by placing the letter(s) in the box under the sedation assessment numbers below.

A - under sedated
B - over sedated
C - satisfactorily sedated
D – asleep
E – anxious
F - distressed
G - deeply asleep
H – comfortable

0	1	2	3	4	5	6	7	8	9	10

Q20 Please list any modifications you would make if any, to assessment tool **No.2** in the space provided below if you have not previously mentioned them in this questionnaire.

_____
_____
_____
_____
_____

Q20a) A low sedation score (i.e. zero) should reflect:
(please circle your answer)

a) either under sedation or over sedation as long as it is specified on the scoring system
b) under sedation
c) over sedation

Q20b) A high sedation score (i.e. 10) should reflect:
(please circle your answer)

a) either under sedation or over sedation as long as it is specified on the scoring system

b) over sedation

c) under sedation

Section C – General Questions

Q21 Which sedation assessment tool would you prefer to use in Paediatric Intensive Care *(please circle your answer)*

a) Tool **No.1**
b) Tool **No.2**
c) Another sedation tool - please state which one _____
d) No sedation tool

Q22. Have you ever used any other sedation assessment tool?
(please circle your answer)

a)Yes b)No

Q22a) If you have answered yes please specify

_____
_____
_____

Q23. How would you rate the usefulness of considering the following in sedation assessment where:
(please circle your answer)

a - very much
b - fairly
c - somewhat
d - not very
e - not at all.

Facial expression	a	b	c	d	e
Eyes	a	b	c	d	e
Body movement	a	b	c	d	e
Respiration	a	b	c	d	e
Heart rate	a	b	c	d	e
Blood pressure	a	b	c	d	e
Oxygen requirement	a	b	c	d	e

Q24. If there are any other factors you would consider during sedation assessment please state below.

Q25 How many years have you worked in Paediatric Intensive Care *(please circle your answer)*

a) less than 1 year
b) 1-4 years
c) 5-10 years
d) more than 10 years

Q26 Please circle your age band

a) <20 years
b) 20-29 years
c) 30-39 years
d) 40-49 years
e) 50-60 years
f) > 60 years

Q27. Please use the space below to make any general comments about, for example:

Sedation
Sedation assessment
Work you would like to see undertaken with regard to sedation

Or if there is anything else you would like to add please do so in the space below.

Thank you for your co-operation.

Karen Whitfield
14th March 2000.

Appendix 6

Nursing staff interviews
Sedation Assessment

1. Do you think sedation assessment on PICU is relevant for:

• Ventilated children	Yes	No
• Recently extubated children	Yes	No
• Self ventilating children	Yes	No
• Paralysed children	Yes	No
• None of the above.	Yes	No

Different assessment criteria?

2. Should level of sedation and pain control be assessed:
- In isolation using different assessment tools
- Together using different assessment tools
- Together using the same assessment tool

3.Do you think, in general, there is a tendency to over-sedate or under-sedate children

In which children and why

4. In your experience are there particular children in whom a safe level of sedation is difficult to achieve:

- certain age groups
- certain disease states

5.Do you have a preference of sedation assessment tool used at BCH
- Tool 1
- Tool 2

5a.Is this due to:

- Clarity
- Accuracy
- Ease of use
- More comprehensive
- Easy to understand
- Quick to use

6.Do you think training in sedation assessment is necessary

Yes No

6a. Should this be in the form of:

Lectures
Small tutorials
One to one
Simply as part of hand over

6. What influence do parents/carers have in the effective sedation of their children:

- Parental influence invaluable
- Are informed parents more helpful, calmer etc.
  Should parents be more involved informed.

7. What work, if any, would you like to see done in the area of sedation assessment.

Appendix 7
Written information to PICU staff regarding midazolam pharmacokinetic study

0121 359 3611 ext.2359

20th September 2000

To all PICU medical and nursing staff

Re: Sedative Pharmacokinetic Study.

I would like to inform you of the Sedative Pharmacokinetic Study which will be starting on Monday 2nd October 2000 This research, which has been granted full ethical approval, will involve the recruitment of certain PICU patients receiving midazolam as part of their treatment.

The study is being coordinated by myself, Karen Whitfield with the support of Dr Charles Ralston.

Patients will be recruited to the study after consultation with the medical and nursing staff in charge of the unit at the time and after obtaining consent from parents/carers.

The aim of the study is to investigate the pharmacokinetics of midazolam in critically ill children. Therefore a series of blood samples will be taken from each patient recruited to the study. A full set of instructions will be available at the bedside of each patient involved in the study clearly stating when blood samples are to be taken and any documentation that is required to be recorded.

A protocol of the study will be made available in the sedation folder to be found in the study area on PICU.

I will be involved at the start of each patient recruited to the study and therefore will be available to answer any questions that may arise.

If there are any problems or issues regarding this study please do not hesitate to contact Dr Ralston or myself.

Thank you for your continued support.

Karen Whitfield.

Appendix 8
Consent Form

Study Title: Sedation Assessment in Children.....

Please ask the patient's parent/legal guardian to complete the following:

	Please cross out as necessary
Have you read the Patient Information Sheet?	Yes / No
Have you had an opportunity to ask questions and discuss this study?	Yes / No
Have you received satisfactory answers to all your questions?	Yes / No
Have you received enough information about the study?	Yes / No

To whom have you spoken? .....

Do you understand that you are free to withdraw your child from the study:

- At any time?
- Without having to give a reason for withdrawing?
- And without affecting your future medical care? Yes / No

Do you agree for your child to take part in this study? Yes / No

Signed ..... Date.....

(Name in block letters) .....

Signed (Researchers): ..... Date.....

Appendix 9
Parent/Carer information sheet for the midazolam pharmacokinetic study

Sedation Study in Children

Information Sheet for the Parent or Guardian

Introduction

Sick children who require Intensive Care usually require drugs to sedate them to prevent them from becoming distressed or uncomfortable. Although children cared for on Intensive Care Units receive the highest possible standard of nursing and medical care, it is often difficult to control the right amount of sedation to ensure that a child is not over or under sedated. Over sedation can delay discharge from Intensive Care and the drugs used can have side effects. Under sedation may result in distress or pain.

We would like to invite you to help us improve our knowledge about the way in which children handle sedative agents, by taking part in this study.

What will I have to do if I take part?

Whilst in the Paediatric Intensive Care Unit, your child will be given a sedative medication as part of their routine treatment. Administration of sedation like this is quite normal and is given to reduce the stress and discomfort during their time in intensive care. Whilst your child is receiving sedation we would like to take a blood sample to measure the level of drug in the body. 2mls of blood will be taken during the first 24 hours and then 1ml of blood taken each day after that.

What are the possible risks of taking part?

There are no risks attached to taking these blood samples. Your child will not suffer any discomfort as a result of withdrawing a blood sample, as they will already have a cannulae in place from which to draw other routine blood samples, which are necessary during their stay in the intensive care unit.

Are there any possible benefits?
Although there will be no direct benefit to your child, it is hoped that by understanding more clearly how children respond to sedative agents, administration of sedation in these ill children can be improved. As a result the degree of anxiety and distress sometimes experienced by children when they are ill can be reduced.

Who else is taking part?
All children receiving sedative medication in intensive care will be invited to take part in this study.

Do I have to take part?
No, taking part is voluntary. If you would prefer not to take part you do not have to give a reason. Your doctor will not be upset and your treatment will not be affected. If you take part but later change your mind you can withdraw without affecting your treatment.

What happens to the information?
The blood samples taken will provide a lot of information about how sick children handle sedative medication. The results will be looked at regularly by a team of experts. This study will continue over a period of time, up to 3 years. Once all the information has been collected it is hoped that the results will help other medical people looking after sick children. In this way we hope to improve the way we look after children in intensive care.

What do I do now?
The research pharmacist organising the study will answer any questions and you can let her know if you are interested in taking part.

Thank you very much for considering taking part in our research.

Karen Whitfield, Research Pharmacist

0121 359 3511 ext. 5237
07719 711058

Appendix 10

Child Consent Form for Sedative Study

Title:

Project to look at medicine you have been given during your stay in the Children's Intensive Care Unit.

Please ask the child, who is expected to receive treatment in intensive care after elective admission to to complete the following with the assistance of a parent or guardian.:

	Please cross out as necessary
Have you read the Children's Information Sheet?	Yes / No
Have you any questions about the project?	Yes / No
Have all your questions been answered?	Yes / No
Do you want to know anything else about the project?	Yes / No

Who have you spoken to about the project? .....

Do you understand that you do not have to take part in the project if you do not want to Yes/No

Do you want to take part in the project? Yes / No

Signed ..... Date .....

(Name in block letters) .....

Signed (Researchers): ..... Date .....

Appendix 11

Children's Information Sheet

Project to look at sedative medication children receive whilst staying in Intensive Care.

Introduction

Children who stay in intensive care often receive medication to help them sleep. This medication is called a sedative. Sometimes it is difficult to give the right amount of sedative, as every child is different. Too much or too little sedative can be given. This can make you too sleepy or too awake. This project will help us understand how much sedative each child needs.

What will I have to do if I take part?

During your stay in the Children's Intensive Care Unit you will be given a sedative as part of your treatment. This is quite normal and will help you sleep. When you are having your sedative we would like to take a few blood samples to measure how much sedative is in your body. You will not feel anybody taking the blood samples and it will not hurt at all. We would like to take 5 small blood samples when you first have your sedative and 5 small blood samples when the doctors stop your sedative.

Do I have to take part?

No.

Taking part in this project is up to you. You do not have to take part if you do not want to. Your doctor will not be upset and your treatment will not be altered.

What do I have to do now?

The person doing the study is called Karen Whitfield and she will answer any questions you may have. Then she will ask you if you would like to take part in the project.

Karen Whitfield, Research pharmacist
0121 359 3611 ext.5237.

Appendix 12 Results from the self-completion sedation assessment questionnaire

The questionnaire is divided into 3 sections
A) refers to questions about sedation tool no.1
B) refers to questions about sedation tool no.2
C) refers to general questions about sedation in PICU.

Section A - Sedation Tool No.1

Sedation Score				
1	2	3	4	5
Wide awake	Awake but sleepy	Asleep but moves spontaneously	Asleep but responds to stimulation	Hard to rouse

Q1 Have you used the **sedation assessment tool No.1** (see above) during the last 3 months? *(Please circle your answer)*

a)Yes b)No

Q1	Response
yes	48
no	6

Q2 During the last 3 months how many times have you used sedation assessment tool **No.1**? In total this can include during the same shift or in the same patient. *(Please circle your answer)*

a) Less than 5 times
b) 5-10 times
c) 11-20 times
d) more than 20 times

Q2	Response
a	14
b	18
c	3
d	14
Non responder	5

Q3 On average how long does it take you to make an assessment using sedation tool **No.1**? *(Please circle your answer)*

e) less than 1 minute
f) 1-3 minutes
g) 4-5 minutes
h) more than 5 minutes

Q3	Response
Less than 5 times	40
5-10 times	10
11-20 times	0
More than 20 times	0
Non responder	4

Q4 Would you use sedation tool **No.1** in a patient receiving neuromuscular blocking agents? *(please circle your answer)*

a)Yes b)No

Q4	Response
Yes	8
No	44
Non responders	2

Q5 Would you use sedation tool **No.1** in a child receiving ventilation but no sedation? *(please circle your answer)*

a)Yes b)No

Q5	Response
Yes	40
No	11
Non responders	3

Q6 Do you think the wording used in sedation tool **No.1** is appropriate? *(please circle your answer)*

a) Wide awake	yes	no
b) Awake but sleepy	yes	no
c) Asleep but moves spontaneously	yes	no
d) Asleep but responds to stimulation	yes	no
e) Hard to rouse	yes	no

Q6	appropriate	Not appropriate	No response
Wide awake	47	5	2
Awake but sleepy	49	3	2
Asleep but moves spontaneously	49	3	3
Asleep but responds to stimulation	46	5	3
Hard to rouse	46	6	2

Q6a If you have answered 'no' to any of the categories please suggest an alternative or say why you think it inappropriate, below.

Comments made by nursing staff about the wording used in scale 1 are as follows:

- 'First category should be separated into awake and orientated, and awake and confused or uncomfortable'
- 'First category does not take into consideration agitated or upset'
- 'A patient can be awake and agitated or awake and settled'
- 'This scale suggests you should stimulate the child in order to complete assessment'
- 'Wording is too subjective'

Q7. Using the scale below indicate how subjective/objective you think sedation tool **No.1** is by circling a number.

0 1 2 3 4 5 6 7 8 9 10

very objective **very subjective**

0	1	2	3	4	5	6	7	8	9	10	No response
0	1	6	7	6	5	9	8	7	2	0	0

Q8. Here are some questions about sedation assessment tool **No.1.** To what extent do you **agree**?

Please circle the most appropriate letter where;
a - very much
b - fairly
c - somewhat
d - not very
e - not at all.

	Q8	a	b	c	d	e
A	The sedation assessment tool is very easy to use.	38	12	0	0	0
B	The sedation assessment tool allows accurate measurement of depth of sedation	2	16	22	8	3
C	The sedation assessment tool is very easy to understand	32	12	7	0	0
D	The sedation assessment tool is very useful	11	17	19	4	0
E	The sedation assessment tool is appropriate for patients receiving mechanical ventilation	12	20	14	4	1
F	The sedation assessment tool is appropriate for extubated or self ventilating patients	19	22	7	3	0
G	The sedation assessment tool is appropriate for patients receiving CPAP	16	20	11	2	0
H	The sedation assessment tool is very time consuming to use	1	2	1	21	26
I	The wording used is the assessment tool is very ambiguous	4	1	11	18	17
J	The assessment tool is suitable for patients receiving neuromuscular blocking agents	2	1	4	9	35
K	The assessment tool can be used by all grades of nursing staff	45	4	2	0	0
L	The assessment tool is very subjective	6	15	17	10	1

Q9. From the list below choose the phrase or word that you think best describes or correlates with the numbers in the sedation assessment tool. You may choose more than one statement for a particular number if you wish. Please answer by placing the letter(s) in the box under the sedation assessment numbers below.

Sedation Score				
1	2	3	4	5
Wide awake	Awake but sleepy	Asleep but moves spontaneously	Asleep but responds to stimulation	Hard to rouse

A - under sedated
B - over sedated
C - satisfactorily sedated
D – asleep
E – anxious
F - distressed
G - deeply asleep
H - comfortable

Q9	Wide awake	Awake but sleepy	Asleep but moves spontaneously	Asleep but responds to stimulation	Hard to rouse
Under sedated	29	8	4	4	1
Over sedated	0	0	0	9	44
Satisfactorily sedated	6	28	38	27	2
Asleep	1	6	30	17	0
Anxious	29	8	4	1	0
Distressed	28	8	3	0	0
Deeply asleep	0	0	1	29	22
Comfortable	27	31	28	23	3

Q10. Would you make any modifications to sedation tool **No.1?**

a)Yes b)No

Q10	Response
Yes	21
No	22
Non responders	4

Q10a If you have answered yes to Q10 please list the modifications you would make if any in the space provided below.

- 'There is no category for distressed or anxious patient'

Section B - Sedation Tool No.2 (see opposite)

Q11. Have you used **sedation assessment tool No.2** during the last 3 months? *(Please circle your answer)*

a)Yes b)No

Q11	Response
yes	51
no	2

Q12 During the last 3 months how many times have you used sedation assessment tool **No.2**? In total this can include during the same shift or in the same patient.*(Please circle your answer)*

a) Less than 5 times

b) 5-10 times

c) 11-20 times

i) more than 20 times

Q12	Response
a	9
b	16
c	13
d	12
Non responder	3

Q13 On average how long does it take you to make an assessment using sedation tool **No.2**? *(Please circle your answer)*

a) less than 1 minute
b) 1-3 minutes
c) 4-5 minutes
d) more than 5 minutes

Q13	Response
Less than 5 times	10
5-10 times	38
11-20 times	3
More than 20 times	0
Non responder	3

Q14 Would you use sedation tool **No.2** in a patient receiving neuromuscular blocking agents? *(please circle your answer)*

a)Yes b)No

Q14	Response
Yes	16
No	37
Non responders	1

Q15 Would you use sedation tool **No.2** in a child receiving ventilation but no sedation? *(please circle your answer)*

a)Yes b)No

Q15	Response
Yes	46
No	7
Non responders	1

Q16 Do you think the wording used in sedation tool **No.2** is appropriate? *(please circle your answer)*

a)Yes b)No

Q16	Response
Yes	38
No	6
Non responders	3

Q16a If you have answered 'no' please suggest an alternative or say why you think it inappropriate, by writing directly onto the version opposite.

- 'A patient can score 0 due to pain rather than under sedation'
- 'Guidelines should go from 0-10'

Q17 Using the scale below indicate how subjective/objective you think sedation tool **No.2** is by circling a number.

0 1 2 3 4 5 6 7 8 9 10
very subjective very objective

0	1	2	3	4	5	6	7	8	9	10	No response
1	0	3	4	10	6	1	7	14	3	1	1

Q18. Here are some questions about sedation assessment tool **No.2.** To what extent do you **agree**?

Please circle the most appropriate letter where ;
a - very much
b - fairly
c - somewhat
d - not very
e - not at all.

	Q18	a	b	c	d	e
A	The sedation assessment tool is very easy to use.	15	27	9	6	0
B	The sedation assessment tool allows accurate measurement of depth of sedation	14	21	8	4	0
C	The sedation assessment tool is very easy to understand	16	21	10	4	0
D	The sedation assessment tool is very useful	25	17	8	5	0
E	The sedation assessment tool is appropriate for patients receiving mechanical ventilation	26	18	7	1	0
F	The sedation assessment tool is appropriate for extubated or self ventilating patients	23	17	7	4	0
G	The sedation assessment tool is appropriate for patients receiving CPAP	23	17	10	2	0
H	The sedation assessment tool is time consuming to use	4	12	14	11	11
I	The wording used is the assessment tool is very ambiguous	0	9	9	21	13
J	The assessment tool is suitable for patients receiving neuromuscular blocking agents	9	5	4	9	25
K	The assessment tool can be used by all grades of staff	34	13	5	0	0
L	The assessment tool is very subjective	5	11	15	18	1
M	Documenting a baseline score is useful	25	18	8	0	0
N	Documenting a responsiveness score is useful	21	18	11	0	0
O	The guidelines for the need to review sedation are accurate	8	26	12	4	1
P	The wording of the guidelines to review sedation are clear	12	22	10	7	0
Q	The guidelines to review sedation are useful	14	19	16	1	1

Q19. From the list below, choose the phrase or word that you think best describes or correlates with the numbers in the sedation assessment tool. You may choose more than one statement for a particular number if you wish. Please answer by placing the letter(s) in the box under the sedation assessment numbers below.

A - under sedated
B - over sedated
C - satisfactorily sedated
D – asleep
E – anxious
F - distressed
G - deeply asleep
H – comfortable

	0	1	2	3	4	5	6	7	8	9	10
Under sedated	25	25	24	18	6	0	0	0	5	0	0
Over sedated	0	0	0	0	0	0	1	2	8	27	37
Satisfactorily sedated	0	1	0	5	19	25	26	25	19	7	4
Asleep	1	1	1	1	13	12	12	11	7	4	4
Anxious	20	23	18	18	7	0	1	0	0	0	0
Distressed	35	23	17	10	2	1	0	1	0	0	0
Deeply asleep	0	0	0	0	1	3	9	5	16	17	12
Comfortable	2	4	5	7	18	26	18	22	11	3	2

Q20 Please list any modifications you would make if any, to assessment tool **No.2** in the space provided below if you have not previously mentioned them in this questionnaire.

- 'Try to make it look less complicated'
- 'In the respiration assessment – include making some respiratory effort'

Q20a) A low sedation score (i.e. zero) should reflect:
(please circle your answer)

d) either under sedation or over sedation as long as it is specified on the scoring system
e) under sedation
f) over sedation

Q20A	Response
Either under sedation or over sedation as long as it is specified on the scoring system	9
Under sedation	36
Over sedation	1

Q20b) A high sedation score (i.e. 10) should reflect:
(please circle your answer)

a) either under sedation or over sedation as long as it is specified on the scoring system
b) over sedation
g) under sedation

Q20b	Response
Either under sedation or over sedation as long as it is specified on the scoring system	10
over sedation	36
under sedation	0

Section C – General Questions

Q21 Which sedation assessment tool would you prefer to use in Paediatric Intensive Care *(please circle your answer)*

a) Tool **No.1**
b) Tool **No.2**
c) Another sedation tool - please state which one _____
d) No sedation tool

Q21	Response
Tool 1	15
Tool 2	38
Another sedation tool	
No sedation tool	
Non responders	1

Q22. Have you ever used any other sedation assessment tool?
(please circle your answer)

a)Yes b)No

Q22	Response
Yes	5
No	39
Non responders	3

Q22a) If you have answered yes please specify

- Great Ormond Street
- Portsmouth
- Flacc pain score
- Sedation scores in adults

Q23. How would you rate the usefulness of considering the following in sedation assessment where:
(please circle your answer)

a - very
b - fairly
c - somewhat
d - not very
e - not at all.

	a	b	c	d	E
Facial expression	35	13	3	0	0
Eyes	26	20	3	1	1
Body movement	34	11	5	0	0
Respiration	25	17	7	0	0
Heart rate	29	17	5	0	0
Blood pressure	22	22	6	0	0
Oxygen requirement	12	18	9	4	6

Q24. If there are any other factors you would consider during sedation assessment please state below.

- 'Prior knowledge about patient from parents'
- 'Dose of sedation – high low dosage'
- 'Underlying condition – eg head injury, post ictal state'

Q25 How many years have you worked in Paediatric Intensive Care (please circle your answer)

a) less than 1 year
b) 1-4 years
c) 5-10 years
d) more than 10 years

Q25	Response
Less than 1 year	10
1-4yrs	21
5-10yrs	11
More than 10yrs	5

Q26 Please circle your age band

a) <20 years
b) 20-29 years
c) 30-39 years
d) 40-49 years
e) 50-60 years
f) > 60 years

Q26	Response
<20yrs	0
20-29yrs	22
30-39yrs	19
40-49yrs	5
50-60yrs	0
>60yrs	0

Q27. Please use the space below to make any general comments about, for example:

Sedation
Sedation assessment
Work you would like to see undertaken with regard to sedation

Or if there is anything else you would like to add please do so in the space below.

- 'Sedation scale 2 more applicable and would give a more truthful reading of how sedated a patients is'
- 'Sedation scales should be simple, easy and quick to use'
- 'Research needed into paralysed patients'
- 'Useful to include baseline and responsiveness scores'
- 'Action in scale 2 needs to be in bold i.e. more clear'
- 'Found tool 2 difficult to use at first but after clarifying found it easier and comprehensive than scale 1'
- 'Prefer tool 2 self-explanatory and easy to use although to use- allows a better assessment than scale 1'
- 'I feel scale 2 would work but it is time consuming at the moment because it is new. It is more accurate assessment of sedation'

Thank you for your co-operation.
Karen Whitfield
14th March 2000.

Appendix 13
Nursing staff interviews
Sedation Assessment

2. Do you think sedation assessment on PICU is relevant for:

- Ventilated children Yes No
- Recently extubated children Yes No
- Self ventilating children Yes No
- Paralysed children Yes No
- None of the above. Yes No

	yes	no
Ventilated children	31	0
Recently extubated children	28	3
Self ventilating children	28	3
Paralysed children	30	1
None of the above	0	0

2. Should level of sedation and pain control be assessed:

- In isolation using different assessment tools
- Together using different assessment tools
- Together using the same assessment tool

In isolation using different assessment tools	27
Together using different assessment tools	0
Together using the same assessment tool	1
No comment	3

3.Do you think, in general, there is a tendency to over-sedate or under-sedate children

Over sedate	6
Under sedate	9
neither	16

4. In your experience are there particular children in whom a safe level of sedation is difficult to achieve:

- certain age groups
- certain disease states

Downs syndrome	4
Neonates	5
Over 15yrs	3
1-3yrs	4
Neurological patients	1

5 Do you have a preference of sedation assessment scales used at BCH

- Scale 1
- Scale 2

Scale 1	9
Scale 2	20
No preference	2

5a.Is this due to:

- Clarity
- Accuracy
- Ease of use
- More comprehensive
- Easy to understand
- Quick to use

	Scale 1	Scale 2
Clarity		10
Accuracy		7
Ease of use	4	
More comprehensive		1
Easy to understand		2
Quick to use	5	
Other		

6.Do you think training in sedation assessment is necessary

Yes No

Yes	27
No	1
No comment	3

6a. Should this be in the form of:

Lectures
Small tutorials
One to one
Simply as part of hand over

Lectures	2
Small tutorials	17
One to one	4
Simply as part of hand over	
Other	
No comment	8

7. What influence do parents/carers have in the effective sedation of their children:

- Parental influence valuable
- Are informed parents more helpful, calmer etc.
  Should parents be more involved informed.

Parental involvement can be helpful – 6
Should encourage parents to be more involved with care of child - 2

8. What work, if any, would you like to see done in the area of sedation assessment.

More research required in the sedation assessment of paralysed patients – 6
More research required in the sedation assessment of neurological patients – 2

Appendix 14

Midazolam plasma concentrations found to be outside the standard calibration curve for midazolam (25-3000ng/ml)

Patient Age	Sedation Score	Midazolam Plasma Concentration (ng/ml)	Disease State
9 months	P	9306	Liver
9 months	P	4550	Liver
5 years	9	5865	Renal
5 years	9	7643	Renal
5 years	9	4788	Renal
5 years	P	5193	Renal
5 years	P	3938	Renal
5 years	P	5221	Renal
5 years	P	4658	Renal
5 years	P	6302	Renal
16 years	10	4215	Head injury
12 years	10	5494	Burns
12 years	9	4190	Burns
12 years	9	5556	Burns
12 years	9	4759	Burns
9 years	P	3957	Liver
9 years	p	5628	Liver
2 years 6 months	P	3371	Head injury

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