Pharmacodynamics of intravenous and oral midazolam in preterm infants

Chapter 10

S.N. de Wildt, G.L. Kearns, S.D. Sie, W.C.J.Hop, J.N. van den Anker

Submitted

Summary

Introduction The aim of this study was to evaluate the pharmacodynamics and safety of oral and intravenous midazolam in preterm infants.

Methods Twenty-four preterm infants (gestational age: 26 to 34 weeks, postnatal age: 3 to 13 days) received a 30-minute intravenous infusion (n=20) and/or oral (n=11) bolus dose of midazolam (0.1mg/kg) in a random order. Pharmacodynamic measurements consisted of a COMFORT® score (a previously validated sedation scale for pediatric patients) at baseline and at 0.5, 1, 2, 4 and 6 hours postdose. Midazolam and 1-OH-midazolam concentrations were measured and vital signs were recorded at all pharmacodynamic measurement time points.

Results Overall, mean COMFORT scores decreased (=more sedated) significantly within 30 minutes after intravenous (p=0.002) and within one hour after oral midazolam administration (p=0.003). However, in 45% of patients the COMFORT scores decreased little or not at all after midazolam. The sedative response to midazolam did not differ after intravenous or oral midazolam administration. Blood pressure decreased significantly after intravenous (approximately 11%) but not after oral midazolam administration. No serious adverse events were reported.

Discussion In summary, midazolam administered as a 30-minute intravenous infusion or oral bolus dose appears to be effective and safe in a majority of preterm infants. However, a considerable proportion of neonates do not appear to respond to midazolam. The lack of response may be due to the fact that patients truly experienced therapeutic failure and/or consequent to the inability of the COMFORT score to adequately reflect sedation uniformly in sick preterm infants.

Introduction

In contrast to earlier beliefs, it is now acknowledged that preterm infants are not only able to experience stress in response to invasive and nursing procedures, but that their response to these stressful stimuli may also compromise their clinical condition (1). Therefore, the necessity for effective sedation in preterm infants is obvious. However, little is known regarding the benefits and/or risks of sedatives in preterm infants (2). One of the drugs used for sedation in preterm infants is the benzodiazepine midazolam (3). Midazolam appears to reversibly potentiate the effects of γ-amino butyric acid (GABA), an inhibitory neurotransmitter of the central nervous system. Through this effect midazolam exerts its sedative, anxiolytic, anticonvulsive, muscle relaxant and amnesic effects, as has been illustrated in adults and older children (4).

In a placebo-controlled trial designed to study the sedative effect of midazolam, continuous infusion of the drug induced effective sedation in preterm infants on mechanical ventilation. (5). In another placebo-controlled pilot study, designed to study the effect of sedation on neurological outcome in preterm infants, sedation scores (COMFORT scores) were significantly lower (more sedated) in patients who received continuous midazolam infusion as compared to those who received placebo (6) (7). Midazolam has also been used for premedication prior to intubation in newborn infants (8). However, little is known regarding either the extent or duration of the sedative effect from a single dose of oral or intravenous midazolam in preterm infants.

Adverse events of midazolam have occasionally been described in preterm infants including hypotension and brief periods of myoclonic activity (3). While hypotension has been observed after intravenous bolus injection of midazolam(2), administration of the drug as a 30-minute infusion or oral bolus dose conceivably may prevent hypotension associated with intravenous bolus dosing.

To evaluate the efficacy and safety of a single dose of midazolam given as a 30-minute infusion or as an oral bolus to preterm infants, we conducted a controlled clinical pharmacodynamic study that examined the plasma concentration vs. effect relationship.

Methods

Patient recruitment

This was a randomized, prospective pharmacodynamic investigation of intravenous and oral midazolam in preterm infants given for preprocedural sedation (e.g. endotracheal suction, elective nasopharyngeal intubation). The children were recruited from the Neonatal Intensive Care Unit of the Sophia Children's Hospital, Rotterdam. The institutional review board approved this research protocol. Written, informed consent was obtained from parents or legal guardians prior to subject enrollment.

Patients were included if they had a gestational age between 26 and 34 weeks, needed midazolam for preprocedural sedation and had an indwelling arterial catheter, previously placed for purposes associated with medical care. Patients were excluded if: (1) they received concomitant or recent (i.e. 12 hours prior to dosing) morphine, dobutamine or dopamine; (2) were exposed to any sedating agents within a 12-hour period prior to study drug administration or (3) had significant underlying hemodynamic, renal, hepatic or neurological dysfunction.

Concomitant, recent (i.e. 24 hours prior to dosing) or chronic treatment with medications known or suspected to alter the pharmacokinetics of midazolam was prohibited. Since midazolam is a substrate for cytochrome P450 3A enzymes, potential study objects were specifically assessed for exposure to drugs known to induce, inhibit or serve as substrates for CYP3A4 (e.g. erythromycin, phenobarbital, rifampin, dexamethasone, fentanyl, cisapride) (9).

The concomitant use of sedative/anxiolytic drugs that could potentially affect the pharmacodynamics of midazolam was also prohibited during the 6-hour postdose period.

Study design and treatment groups

Patients were randomly assigned to initially receive midazolam as a 30-minute intravenous infusion or an oral bolus, followed in cross-over fashion by midazolam administration via the alternate route. To ensure complete washout of the first dose of midazolam, the minimum interval between doses was 72 hours. A nurse not involved in the investigation or clinical care of the study subject installed the treatment according to a computer generated randomization list. Both the patient's nurse and the investigator (S.N.W.) were blinded to the drug formulation given.

Dosing

Midazolam (Dormicum® injection, Roche Laboratories, The Netherlands) was administered as a single 0.1 mg/kg dose in a 5% glucose solution (0.03 mg/ml) infused by syringe pump over 30 min through microbore tubing into a peripheral vein or into a central catheter. Oral (PO) midazolam was administered via the gastric tube using a syringe at a concentration of 0.5 mg/ml diluted with glucose 5% to a final volume of 0.5 ml. Next, the gastric tube was flushed with 0.5 ml glucose 5% to ensure complete drug delivery.

Plasma sampling and drug concentration analysis

Serial arterial blood samples (0.2 ml) were obtained at baseline and at 0.5, 1, 2, 4, and 6 hours from the time of dosing. Plasma was separated from whole blood by centrifugation (1000 X g for 10 minutes) and then stored at –80°C until analysis. Plasma samples were analyzed for midazolam and 1-OH-midazolam by gas chromatography with mass spectrometric detection (Hewlett Packard 6890, Agilent Technologies Inc, Palo Alto, CA). The column used was a J&W Scientific DB-17 EVDX [0.2 micron, 25 meters (J&W Scientific, Folsom, CA)]. Diazepam (Elkins Sinn, Cherry Hill, NJ), 5 µl of 500 ng/ml solution, was added to each sample as internal standard and solid phase extraction was performed using a Varian Bond Elut Column (Varian Inc, Palo Alto, CA). The inter-day and intra-day coefficients of variation at the low standard concentration (2ng/ml) were less than 10% for both midazolam and 1-OH midazolam. The lower limit of quantitation was 1 ng/ml for midazolam and 0.5 ng/ml for 1-OH-midazolam using a 0.2 ml sample volume.

Pharmacodynamic measurements

Sedation level was quantitated prior to dosing and at 0.5, 1, 2, 4 and 6 hours after midazolam administration. Sedation levels were determined with the COMFORT score, a previously validated sedation scale that rates eight behavioral or physiologic dimensions of distress (*Table 1.*) (10). Each dimension is scored on a subscale from 1 to 5. Each observation consisted of a 2-min period of intensive evaluation of the patient. After each observation,

Table 1 *(adapted with permission from van Dijk et al. (11)*

Scale item	Score
Alertness	
Deeply asleep	1
Lightly asleep	2
Drowsy	3
Fully awake and alert	4
Hyperalert	5
Calmness	
Calm	1
Slightly anxious	2
Anxious	3
Very anxious	4
Panic	5
Respiratory response	
No coughing and no spontaneous respiration	1
Spontaneous respiration with little or no response to ventilation	2
Occasional cough or resistance to ventilator	3
Actively breathes against ventilator or coughs regularly	4
Fights ventilator; coughing or choking	5
Crying	
Quiet breathing, no crying	1
Sobbing or gasping	2
Moaning	3
Crying	4
Screaming	5
Physical movement	
No movement	1
Occasional, slight movement	2
Frequent, slight movements	3
Vigorous movement limited to extremities	4
Vigorous movements including torso and head	5
Muscle tone	
Muscles totally relaxed; no muscle tone	1
Reduced muscle tone	2
Normal muscle tone	3
Increased muscle tone and flexion of fingers and toes	4
Extreme muscle rigidity and flexion of fingers and toes	5
Facial tension	1
Facial muscles totally relaxed	2
Facial muscle tone normal; no facial muscle tension evident	3
Tension evident in some facial muscles	4
Tension evident throughout facial muscles	5
Facial muscles contorted and grimacing	
Blood pressure	1
Blood pressure below baseline	2
Blood pressure consistent at baseline	3
Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation)	4
Frequent elevations of 15% or more above baseline (> 3 during 2 minutes observation)	5
Sustained elevations of 15% or more	
Heart rate	
Heart rate below baseline	1
Heart rate consistent at baseline	2
Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation)	3
Frequent elevations of 15% or more above baseline (> 3 during 2 minutes observation)	4
Sustained elevations of 15% or more	5

the COMFORT scores were totaled by a single trained observer (minimal 8, maximal 40). The COMFORT score at 0.5 h after midazolam administration was determined immediately prior to the stressful procedure, which was carried out at 32 minutes after midazolam dosing. We assumed that the effect of the procedure on sedation levels did not carry over to the next pharmacodynamic observation point (i.e., 1 hour after dosing).

Safety

Observation of each patient for adverse events was performed at each of the pharmacodynamic assessment points. An adverse event was defined as a clinically significant change from the baseline (pretreatment) condition for any of the following: pulse rate, systolic and diastolic blood pressure by manometry and oxygen saturation of hemoglobin by pulse oximetry. Respiratory depression was defined as $SpO_2 < 85\%$ for greater than 10 consecutive seconds.

Adverse event severity was categorized as: (1) mild, (2) moderate or (3) severe. The relationship of an adverse event to midazolam dosing was adjudicated by the investigator as 'not related', 'remotely related', 'possibly related' or 'probably related'. Serious adverse events were defined as those that were lethal or life threatening, and were immediately reported to the institutional review board.

Data analysis

Sedation

COMFORT scores were categorized as *oversedated* (8-16), *awake/calm* (17-26) or *agitated* (>26) as previously validated in pediatric intensive care patients (10). Sedation scores from patients who had a baseline and at least one posttreatment assessment were included in the analysis. Patients were considered unevaluable if a sedation score was not obtained at a specified observation point. The proportion of patients in each sedation category and for each midazolam formulation group was determined at all pharmacodynamic measurement time points.

The change in COMFORT score from baseline was determined at all individual time points. The effect of formulation at each pharmacodynamic time-point on change in COMFORT score from baseline was also determined. Next, changes in COMFORT score were used to calculate area under the effect curve (AUEC) from baseline to 6 hours postdose, after which the overall effect of formulation was determined

We defined patients with a COMFORT AUEC of –5 or greater as "non-responders" given that the mean decrease in COMFORT score was less than 1 per time point. Patients with a COMFORT AUEC lower than –5 were classified as "responders". Patients whose COMFORT AUEC was higher than -5, but who had a decrease in COMFORT score of more than 2 points at one time point, were also defined as responders.

Pharmacokinetic-pharmacodynamic relationship

The relationship between concentrations of midazolam and/or 1-OH-midazolam and COMFORT scores or changes in COMFORT score from baseline (i.e. all paired values at baseline and 5 postdose intervals) were determined. The analysis was performed with overall data and data grouped per pharmacodynamic time-point.

Hemodynamic parameters

Changes in hemodynamic parameters (heart rate, systolic and diastolic blood pressure) from baseline were also determined and used to calculate respective area under the effect curves (AUEC) from baseline to 6 hours postdose. As with the COMFORT scores, formulation and post-dose time-point related differences were determined.

Statistical methods

The effect of formulation or time-point on the pharmacodynamic parameters (COMFORT, change in COMFORT, heart rate, diastolic and systolic blood pressure) was determined using a mixed model ANOVA allowing for inter- and intra-patient differences [SAS PROC MIXED software (version 6.12, SAS institute, Inc, Cary, N.C)]. The relationship between COMFORT scores or changes in COMFORT score and midazolam, 1-OH-midazolam, and the sum of 1-OH-midazolam plus midazolam plasma concentrations was also determined using mixed model ANOVA.

Data are expressed as means ± SEM. However, if a given parameter was not normally distributed medians (range) are used. AUECs and AUC were calculated by the linear trapezoidal rule. All other statistical analyses were obtained using SPSS software (version 9.0.0, SPSS Inc., Chicago, Ill). The level of significance accepted for all statistical analysis was p=0.05.

Results

Patients

24 preterm infants were enrolled of whom seven patients received both intravenous and oral midazolam, 13 patients received only intravenous midazolam and four only oral. Demographic characteristics for all patients are summarized in Table 2.

All patients received medications prior to study enrollment, as well as during the study period, including antibiotics (100 %), surfactant (65% in the IV midazolam group, 46% in the PO midazolam group), caffeine (60% in the IV midazolam group, 73% in the PO midazolam group), indomethacin (45% in the IV midazolam group, 55% in the PO midazolam group), morphine at least 12 hours before study drug administration (43% in the IV midazolam group, 27% in the PO midazolam group) and furosemide (5% of patients in the IV midazolam group).

Sedation

Before study drug administration, 5% of patients in the IV group was agitated, 60 % was awake/calm and 35% was oversedated, according to the COMFORT score. In the oral group, none of the patients was agitated, 82% was awake/calm and 18% was oversedated. The mean COMFORT score before midazolam administration was higher in the oral group than in the intravenous group, but this difference was not statistically significant (20.5 ± 3.8 SD vs. 18.8 ± 3.6 SD, p=0.28). After drug administration the proportion of patients that was oversedated was 76 % at one hour after start of the intravenous infusion and 64 % at two hours after oral dosing (*Figure 1*).

Figure 2 illustrates a significant reduction in COMFORT score starting at the end of the 30-minute infusion of midazolam. The nadir was reached one hour after start

of the infusion [-3.7 ± 1.1 (p = 0.002)]. After oral administration, the COMFORT score also decreased significantly and reached a nadir one hour after dosing [-3.7 ± 1.2 (p=0.003)]. However, in individual patients, the time-point at which the maximum change in COMFORT score was observed varied widely between 0.5 and 6 hours postdose. When the COMFORT score was integrated over time ($AUEC_{COMFORT}$), the total sedative effect of midazolam was not different between the two treatment groups (p=0.74).

Table II *Demographic and physical characteristics of patients who participated in the investigation*

	Intravenous midazolam	**Oral midazolam**
Parameters		
Patients (n)	20	11
Sex (M/F)	7/13	8/7
Gestational age (weeks)	29.0 ± 2.2# (26.3 - 33.6)*	27.6 ± 1.3 (26 - 30.7)
Postnatal age (days)	6.0 ± 2.7 (3 - 11)	6.5 ± 3.1 (3 - 13)
Birth weight (g)	1081 ± 245 (745 - 1630)	1037 ± 241 (745 - 1630)
Study weight (g)	1094 ± 245 (770 - 1600)	1040 ± 239 (825 - 1660)
Mechanically ventilated (n)	12	5
Nasal CPAP (n)	7	5

Figure 1 *This bar-graph depicts the proportion of preterm infants who are sedated after a single midazolam dose. The X-axis represents the time before (0) and after (start of) midazolam dosing in hours. The Y-axis represents the proportion of patients sedated (<COMFORT score <17). The black bars represent the patients who received a 30-minute midazolam intravenous infusion (0.1 mg/kg). The white bar represents the patients who received an oral midazolam bolus dose (0.1 mg/kg)*

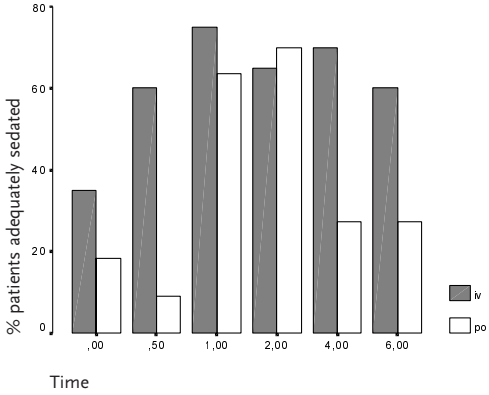
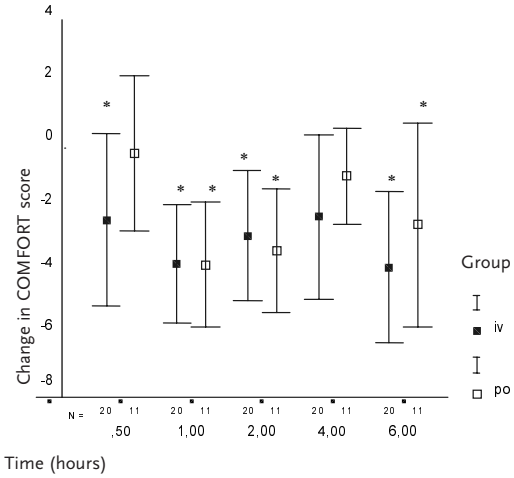
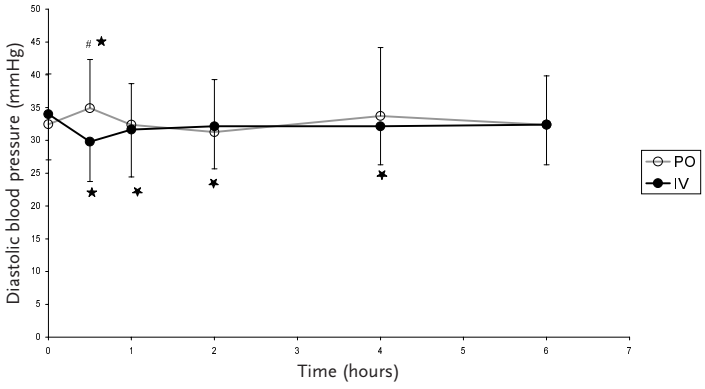


Figure 2 *This graph depicts the change in COMFORT score after 0.1 mg/kg midazolam in preterm infants according to the intravenous (iv) or oral (po) route. The x-axis represents the time after (start of) midazolam dosing in hours. The y-axis represents the mean (± 2 SEM) change in COMFORT score from baseline.*



* = *p<0.05 before vs. after midazolam administration*

Figure 3 *This plot depicts diastolic blood pressure after 0.1 mg/kg of midazolam in preterm infants. The x-axis represents the time before (0) and after (start of) midazolam dosing in hours. The y-axis represents the diastolic blood pressure (mmHg). The dots represent the mean (± 2 SEM) diastolic blood pressure at the various time-points. ∗ p<0.05 before vs after midazolam administration. # p=0.05 intravenous vs oral midazolam administration.*



Nine out of the 20 patients who received intravenous midazolam and five out of the eleven who received oral midazolam were non-responders. First, we determined if differences in drug concentration might account for the difference in response. However, midazolam, 1-OH-midazolam and midazolam plus 1-OH-midazolam concentrations were not statistically different between responders and non-responders. Being a responder or non-responder was also not consistent patients who received midazolam twice by either route. We also did not find an effect of sequence or period of drug administration, postnatal age or mechanical ventilation (present/absent) on the response to midazolam.

Pharmacokinetic-pharmacodynamic relationships

Plasma drug sampling and associated sedation assessment sufficient for examination of possible pharmacokinetic relationships was performed in all 24 patients (216 pairs). No relationship was found between COMFORT scores or change in COMFORT score from baseline and midazolam (p=0.18), 1-OH-midazolam (p=0.50), or midazolam plus 1-OH-midazolam concentrations (p=0.25).

Safety

Overall, during the 6-hour postdose interval, diastolic blood pressure decreased significantly after intravenous (baseline 34.0 ± 7.0 mmHg, $AUEC_{DPB}$= -12.6 ± 4.0 mmHg*h, p=0.003), but not after oral midazolam administration (baseline 32.5 ± 7.7 mmHg, $AUEC_{DBP}$= -2.5 ± 3.7 mmHg*h, p=0. 52, $AUEC_{DBP}$ IV vs. PO p= 0.04), *(Figure 3)*. The maximum decrease in diastolic blood pressure was observed directly after the 30-minute midazolam infusion (- 3.8 ± 0.7 mmHg, p=0.0001) and returned to baseline at 6 hours after start of the infusion (-1.6 ± 0.9, p= 0.08). Although diastolic blood pressure decreased significantly, no hemodynamic instability requiring infusion of crystalloid or colloid or administration of vaso-active drugs, occurred. After oral midazolam administration, diastolic blood pressure never decreased below baseline. In contrast, diastolic blood pressure significantly increased from baseline (2.4 ± 0.9 mmHg, p=0.01) at 30 minutes after oral midazolam administration.

The changes in systolic blood pressure were less pronounced than the changes in diastolic blood pressure. Overall, systolic blood pressure did not decrease significantly after intravenous (baseline 52.8 ± 10.4 mmHg, $AUEC_{SBP}$ = -9.1 ± 7.1 mmHg*h, p=0.21) or after oral midazolam administration (baseline 51.2 ± 9.3 mmHg, $AUEC_{SBP}$ = 3.4 ± 9.4 mmHg*h, p=0.72, $AUEC_{SBP}$ IV vs. PO, p=0.31). After intravenous midazolam, the systolic blood pressure only decreased significantly 30 minutes following midazolam infusion (-4.7 ± 1.4 mmHg), but returned to baseline within one hour (-2.2 ± 1.4 mmHg, p=0.13). After oral midazolam administration, systolic blood pressure did not decrease below baseline at any time point within the 6-hour postdose interval.

Overall, heart rate did not change significantly after intravenous (baseline 150 ± 9.9 bpm, $AUEC_{HR}$ -0.4 ± 1.5 bpm*h, p=0.80) or after oral midazolam administration (144 ± 9.2 bpm, $AUEC_{HR}$ 3.6 ± 0.1 bpm*h, p=0.77) during the 6-hour postdose interval.

The following other adverse events were observed after intravenous and oral midazolam administration: myoclonus (n=1 for intravenous and oral, respectively), apnea (n=2 for IV with O_2sat 61%, n=1 for PO with O_2sat 80%) and bradycardiac episodes

(n=1). Both apneas and bradycardia were defined as 'possibly related' to the study drug, since these symptoms were already present before drug administration, but an effect of midazolam could not be ruled out. Myoclonus was defined as ' probably related' to study drug. All adverse events were categorized as 'mild' and resolved spontaneously without treatment or residua.

Discussion

Sedation

The COMFORT scores decreased significantly (more sedated) in preterm infants after both intravenous and oral midazolam administration. The mean peak sedative effect of midazolam was seen one hour after dosing. As expected, the mean onset of action after intravenous midazolam administration was observed earlier than that of oral midazolam (at 30 minutes after start of the infusion vs. 1 hour after dosing). The onset of action, time of peak effect and duration of effect showed, however, large variation between individual patients.

We found that before midazolam administration, approximately one third of our patients were already oversedated according to the ranges provided by the COMFORT score. A similar high proportion of sedated patients (as defined by a different sedation score) was reported by other investigators before start of a continuous midazolam infusion in preterm infants (5). Moreover, other investigators reported that the mean COMFORT score before start of a continuous midazolam infusion in preterm infants was even lower than observed in our study cohort [18.8 ± 3.6 vs. 15.9 ± 3.8] (6). The COMFORT score has been validated for the assessment of sedation in pediatric intensive care patients and in neonates postoperatively (10, 11). Despite the fact that the COMFORT score has not been validated for use in preterm infants it was used in this study as a quantitative measurement to examine the sedative effect of midazolam and to discriminate between sedated and non-sedated preterm infants. It is important to note that premature infants have a decreased level of alertness and limited muscle development, which suggests a less dramatic visible response to stress (12, 13). Consequently, these developmental differences may confound the use of sedation scores that have been validated in older infants and children and thus, somewhat limit the extrapolation of findings (i.e., the comparison to other older populations) pertaining to the assessment of drug effect. In an attempt to minimize these particular effects, we investigated the change of the COMFORT score in the individual patient as a measure of the sedative effect of midazolam.

In our subjects, the COMFORT score decreased significantly from baseline after a single midazolam dose. This observation is in agreement with data from older preterm infants (gestational age 34 to 40 weeks) where a change in sedation level was observed 10 to 20 minutes after an IV midazolam bolus (0.2 mg/kg) and appeared to last more than 2 hours (3). Moreover, in a placebo-controlled study on the effect of continuous sedation on neurological outcome, the mean COMFORT score was lower during midazolam infusion than during placebo (p=0.04) (6, 7). In contrast, these investigators did not find a significant decrease in COMFORT score 24 hours after start of the continuous midazolam infusion in preterm infants (6). In comparing preterm infants

to older children and adults, the time to peak effect (30 minutes vs. 2-3 minutes) and duration of effect (2-6 hours vs. 0.5-1 hour) for intravenous midazolam appear to be longer and more variable (14) (15).

In contrast to the rather uniform response reflected by the mean COMFORT scores in our patients, only 55% of the preterm infants demonstrated a sedative response after midazolam administration; a proportion which is lower than observed with the use of the absolute COMFORT score of < 17 (i.e., 65% and 76% after oral and intravenous midazolam, respectively). Several reasons may explain these apparent discrepant findings. First, as discussed earlier, the COMFORT score has not been validated in preterm infants and may lack sufficient sensitivity to accurately detect changes in distress in preterm infants. Second, physiologic instability associated with prematurity and its attendant disease states, may leave the preterm infant too weak to respond and consequently, blunt observations. We therefore propose that the lack of response to midazolam in many of our subjects may have been due to physical instability of these particular infants. Another potential limitation of our study resides with the fact that we did not determine severity of illness as measured, for example, by the Clinical Risk Index for Babies (6) but rather, relied upon the need for mechanical ventilation as a surrogate measure for illness which revealed that the proportion of ventilated patients was not higher in the non-responder as compared to the responder group [p=0.7 (IV) and p=1.0 (PO), Fisher Exact test). Finally, another potential reason for the lack of sedative response to midazolam in some preterm neonates may reside in developmental differences in benzodiazepine receptor density and functional activity. Benzodiazepine-binding sites are expressed early in life, with the overall benzodiazepine receptor densities increasing three- to fourfold postnatally in cortices and cerebellum (16). However, the exact ontogeny of the different benzodiazepine receptor subtypes during human development has not been elucidated.

Pharmacodynamic-pharmacokinetic relationship

The lack of an apparent relationship between midazolam plasma concentrations and change in sedation level in our subjects corroborates the results of other investigators who determined the relationship between midazolam plasma concentrations and sedation levels at 24 and 48 hours after the start of a continuous infusion of the drug in preterm infants (5). In older children and adults, however, a relationship between midazolam concentrations and level of sedation is apparent (14, 17). The apparent absence of a definable pharmacokinetic-pharmacodynamic relationship in preterm infants as compared to older children and adults supports our assertion that the lack of response to midazolam in a substantial portion of preterm infants is due to developmental differences in drug action and/or the relative inability of sick infants to demonstrate distress at levels sufficient to be detected with the operative constraints of the COMFORT score.

Safety

Midazolam was administered as a 30-minute infusion or as an oral bolus dose in an attempt to minimize the increased risk of hypotension in preterm infants given intravenous bolus doses of the drug (18). As a consequence, we expected midazolam peak plasma concentrations to be lower and thus, to obviate or attenuate any adverse

hemodynamic effects of midazolam. Our data support that this particular safety objective of the investigation was attained. Following intravenous infusion of midazolam, plasma concentrations were higher after intravenous as compared to oral administration [median (range): 108 (48-217) vs. 64.4 (15.2-204) ng/ml]. Only after intravenous midazolam administration did blood pressure decrease slightly, albeit significantly. A previous study (24) suggested that hypotension may reduce cerebral blood flow velocity; a finding that has been disputed with regard to its significance (25). While we did not specifically evaluate cerebral blood flow in or study, evaluation of our subjects suggested that the reduction in blood pressure following a 30 minute intravenous infusion of midazolam was not clinically significant as it was transient and did not require pharmacologic or fluid treatment. Thus, a 30 minute intravenous infusion of a single 0.1 mg/kg dose of midazolam in preterm neonates appears to be well tolerated.

The frequency and type of adverse events observed in our patients after midazolam administration are comparable to those described in a previous investigation (2). We qualified apneas and bradycardia as possibly related to midazolam administration because these symptoms are inherent in prematurity and they were also observed with the same frequency and severity in the 24-hour pre-study period. Myoclonus was observed in one patient in each formulation group after midazolam administration. In newborn infants, myoclonus following midazolam administration has been reported by several investigators. (19). However as shown previously (26), EEG recording during myoclonus episodes in 6 newborn infants following midazolam administration did not show any epileptic activity.

In summary, midazolam (0.1 mg/kg) as a 30-minute intravenous infusion or a single oral bolus dose appears to be well tolerated in preterm infants but produces effective sedation in only a small majority of patients. This developmental difference (as compared to older infants and children) appears to have a pharmacodynamic basis as opposed to a pharmacokinetic basis. Further evaluation of midazolam pharmacodynamics in the neonatal period is warranted as is the validation of scoring "systems" that are both sensitive and specific enough to better quantitate drug effects. Finally, it is unclear whether dose escalation (i.e., doses > 0.1 mg/kg) might produce sedation in those preterm infants who have apparent therapeutic failure with the 0.1 mg/kg dose. Caution in this regard would be prudent given the potential for higher midazolam doses to produce potentially significant adverse effects (e.g., hypotension, desaturation) that may not be well tolerated in a small, sick preterm infant.

References

1 Anand KJS, Phil D, Hickey PR. Pain and its effects in the human neonate and fetus. N Engl J Med 1987;317(21).

2 Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. Clin Pharmacokinet 1996;31(6):423-43.

3 Jacqz-Aigrain E, Wood C, Robieux I. Pharmacokinetics of midazolam in critically ill neonates. Eur J Clin Pharmacol 1990;39:191-192.

4 Blumer JL. Clinical pharmacology of midazolam in infants and children. Clin Pharmacokinet 1998;35(1):37-47.

5 Jacqz-Aigrain E, Daoud P, Burtin P, Desplanques L, Beaufils F. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. Lancet 1994;344:646-650.

6 Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med 1999;153(4):331-8.

7 Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database Syst Rev 2000(2):CD002052.

8 Whyte S, Birrell G, Wyllie J. Premedication before intubation in UK neonatal units. Arch Dis Child Fetal Neonatal Ed 2000;82(1):F38-41.

9 Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 1998;18(1):84-112.

10 Marx CM, Smith PG, Lowrie LH, Hamlett KW, Ambuel B, Yamashita TS, et al. Optimal sedation of mechanically ventilated pediatric care patients. Crit Care Med 1994;22(163-170).

11 van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 2000;84(2-3):367-77.

12 Bozzette M. Observation of pain behavior in the NICU: an exploratory study. Perinat Neonatal Nurs 1993;7(1):76-87.

13 Phillips P. Neonatal pain management: A call to action. Ped Nurs 1995;21(2):195-199.

14 Marshall J, Rodarte A, Blumer J, Khoo KC, Akbari B, Kearns G. Pediatric pharmacodynamics of midazolam oral syrup. Pediatric Pharmacology Research Unit Network. J Clin Pharmacol 2000;40(6):578-89.

15 Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62(3):310-24.

16 Reichelt R, Hofmann D, Fodisch H-J, Mohler H, Knapp M, Hebebrand J. Ontogeny of the benzodiazepine receptor in human brain fluorographic, immunochemical, and reversible binding studies. J Neurochem 1991;57:1128-1135.

17 Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. Clin Pharmacol Ther 1992;51(6):715-28.

18 Burtin P, Daoud P, Jacqz-Aigrain E, Mussat P, Moriette G. Hypotension with midazolam and fentanyl in the newborn. Lancet 1991;337:1545-1546.

19 Van Straaten HLM, Rademaker CMA, De Vries LS. Comparison of the effect of midazolam or vecuronium on blood pressure and cerebral blood flow velocity in the premature newborn. Dev Pharmacol Ther 1992;19:191-195.