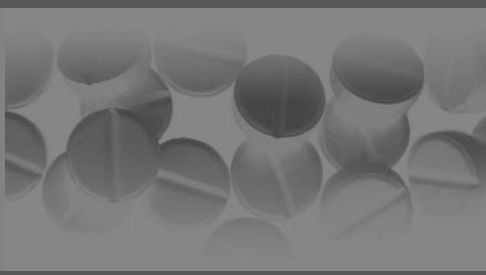
Pharmacokinetics and metabolism of intravenous midazolam in preterm infants

Chapter 4



S.N. de Wildt, G.L. Kearns, W.C.J. Hop, D.J. Murry, S.M. Abdel-Rahman, J.N. van den Anker

Submitted

Summary

Background Midazolam is a benzodiazepine, finding expanded use in neonatal intensive care units. We studied the pharmacokinetics and metabolism of midazolam after a single intravenous dose in preterm infants.

Methods The pharmacokinetics of midazolam and 1-OH-midazolam following a single 0.1 mg/kg intravenous dose of midazolam were determined in 24 preterm infants (gestational age: 26 to 34 weeks, postnatal age: 3 to 11 days). Blood was drawn prior to drug administration and at 0.5, 1, 2, 4, 6, 12 and 24 after the start of the infusion. Midazolam and 1-OH-midazolam concentrations were determined by GC-MS.

Results Total body clearance, apparent volume of distribution, and plasma half-life of midazolam (M) were [median (range)]: 1.8 (0.7-6.7) ml/kg/min, 1.1 (0.4-4.2) L/kg and 6.3 (2.6-17.7) h, respectively. In 19 out of 24 preterm infants, 1-OH-midazolam concentrations could be detected. 1-OH-midazolam (1-OH-M) C_{max}, T_{max} and 1-OH-M/M AUC ratio were [median (range)]: 8.2 (<0.5-68.2) ng/ml, 6 (1-12) h and 0.09 (<0.001- 1), respectively. Elimination half life could be calculated in 13 patients and was found to be [median (range)]: 9.8 (4.9 to 62.2) h. Midazolam plasma clearance was increased in those infants who had indomethacin exposure.

Conclusion Consequent to immature hepatic CYP3A4 activity, midazolam clearance and 1-OH-midazolam concentrations are markedly reduced in preterm infants as compared to previous reports from studies in older children and adults. Indomethacin exposure and its apparent impact on midazolam clearance supports alteration of drug disposition produced by a patent ductus arteriosus.

Introduction

Midazolam, a short-acting benzodiazepine, is used for sedation in newborn infants, requiring prolonged mechanical ventilation and prior to invasive procedures (1,2). Despite the use of the drug in neonatal intensive care units, few data are available on its pharmacokinetics in preterm infants less than 34 weeks of gestation. Moreover, the data describing the pharmacokinetics of intravenous midazolam in preterm infants show marked interpatient variability (3,4).

Midazolam undergoes extensive metabolism by members of the cytochrome P450 3A subfamily (e.g., CYP3A4 and CYP3A5) to a major hydroxylated metabolite (1-OH-midazolam) and several minor metabolites (4-OH, 1,4-OH) (5). In adults, plasma clearance of midazolam is significantly correlated with hepatic CYP3A4/5 activity (6). Cytochrome P450 3A4 (CYP3A4) is the most abundantly expressed cytochrome P450 isoform in adult liver and is responsible for catalyzing the biotransformation of over 50 currently prescribed drugs (7). Hepatic CYP3A5 expression shows large interindividual differences and displays partially overlapping substrate specificity with CYP3A4. In contrast, CYP3A7 is the major isoform expressed in human fetal liver and does not appreciably catalyze the biotransformation of midazolam (7). Lacroix et al. (8) showed that, irrespective of gestational age at birth, CYP3A4 expression is activated during the first weeks after birth, which is accompanied by a simultaneous decrease in CYP3A7 activity. The developmental pattern of CYP3A5 activity is as yet unknown. As one might expect consequent to the impact of ontogeny on CYP3A activity, midazolam plasma clearance is reduced in critically ill newborn infants (3,4,9).

Reduced CYP3A4/5 activity after birth will not only limit midazolam elimination but also, the formation of 1-OH-midazolam, an active metabolite (10). In preterm infants, 1-OH-midazolam concentrations following therapeutic midazolam administration demonstrate large interindividual variability (4). However, the pharmacokinetics of this metabolite in preterm infants has not been determined to date.

In order to investigate the pharmacokinetics of midazolam and 1-OH-midazolam in the first two weeks of life, we evaluated its disposition in preterm infants with gestational ages between 26 and 34 weeks following a single intravenous dose of midazolam.

Methods

Patient population

The study was conducted in 24 preterm infants; gestational age: 26 to 34 weeks and postnatal age: 3 to 11 days. The infants were recruited from the Neonatal Intensive Care Unit of the Sophia Children's Hospital. All children received midazolam prior to a stressful procedure (e.g. tracheal tube suction, elective nasopharyngeal intubation) and had a preexisting indwelling arterial catheter placed for purposes of medical care. Patients were excluded if they received morphine, dobutamine, dopamine or a drug known to affect CYP3A activity. In addition, patients were excluded from the study if they had significant underlying hemodynamic, renal, hepatic or neurologic dysfunction. This research protocol was approved by the Human Ethical Committee of the Sophia Children's Hospital. Written, informed consent was obtained from parents or legal guardians prior to enrollment of subjects in the study.

Drug administration and sample collection

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 minutes through microbore tubing into a peripheral vein or into a central venous catheter. Serial arterial blood samples (0.2 ml) were obtained at baseline and at 0.5, 1, 2, 4, 6, 12 and 24 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. The subjects were observed during the infusion for adverse reactions, with vital signs checked prior to infusion and at the time of blood samplings.

Analytical methods

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), 5µl of 500 ng/ml solution, was added to each sample as an internal standard and solid phase extraction was performed using a Varian Bond Elut Column (Varian Inc, Palo Alto, CA). The inter-day coefficient of variation for the low standard (2 ng/ml) was consistently less than 10% for both midazolam and 1-OH midazolam. The intra-day coefficients of variation were also less than 10% for both midazolam and 1-OH-midazolam at a concentration of 2 ng/ml. The lower limit of quantitation was 1 ng/ml for midazolam and 0.5 ng/ml for 1-OH-midazolam using 0.2 ml sample volume. All samples were analyzed in duplicate with the resultant mean concentration used in the pharmacokinetic analysis.

Pharmacokinetic analysis

The maximal concentration of drug in plasma (C_{max}) and time to reach C_{max} (T_{max}) were determined by visual inspection of the plasma concentration vs. time curve. The apparent terminal elimination rate constant (λ_z) was estimated by curve fitting using a nonlinear, least-squares regression analysis with reciprocal (i.e., $1/Y^2$) weighting. Area under the concentration-time curve from time zero to the last sampling time point (AUC_{ot}) was calculated using the log-linear trapezoidal rule. Extrapolation of the AUC to infinity ($AUC_{o-\infty}$) was calculated by the summation of $AUC_{ot} + C_{pt}/ \lambda_z$, where C_{pt} represents the plasma concentration at the last sampling time (t) predicted from the fitted terminal elimination curve. The individual $t_{1/2}$ was calculated as $0.693/\lambda_z$. The apparent steady state volume of distribution (V_{ss}) and total plasma clearance (CL) were calculated using standard noncompartmental techniques. 1-OH-midazolam pharmacokinetic parameters (with the exception of V_{ss} and CL) were determined as described above for midazolam. The 1-OH-midazolam AUC_{ot} /midazolam AUC_{ot} ratio (AUC ratio) was used as a "surrogate" marker of CYP3A activity. All pharmacokinetic analyses were performed using the Kinetica (version 2.0, Innaphase, Inc, Philadelphia, PA, USA) software package.

Statistical analysis

Results are expressed as means ± standard deviation unless stated otherwise. Because most calculated pharmacokinetic parameters did not show a normal distribution, these

are expressed as median (range). Comparison of groups of patients (which were defined according to the following dichotomous co-variates: partus (cesarean section/spontaneous) feeding (parenteral/enteral), prenatal indomethacin exposure (yes/no), prenatal betamethasone exposure (yes/no), postnatal indomethacin exposure (yes/no), mechanically ventilated (yes/no), caffeine therapy (yes/no) and detectable 1-OH-midazolam concentrations (yes/no) with respect to calculated pharmacokinetic parameters was performed using the Mann-Whitney test. Association of continuous co-variates (i.e. postnatal age, gestational age, postconceptual age, Apgar score) and calculated pharmacokinetic parameters are given as Spearman's (r_s) correlation coefficients. These statistical analyses were obtained using the SPSS software (version 9.0.0, SPSS Inc., Chicago, Ill). The level of significance accepted for all statistical analysis was $\alpha = 0.05$.

Results

Clinical results

Twenty-four preterm infants (16 female, 8 male) with a median gestational age of 29 (range 26-34) weeks and a median postnatal age of 5.5 (range 3-11) days, participated in the study (Table 1). Median (range) FiO_2 was 0.21 (range 0.21-0.29) in patients (n=13) who were mechanically ventilated and 0.21 (range 0.21-0.28) in patients (n=10) who received continuous positive airway pressure (CPAP) by nasopharyngeal tube. Twenty patients were antenatally exposed to indomethacin (to prevent preterm labor) and/or betamethasone (to induce lung maturation). Three patients received both drugs, and 17 only betamethasone. Of the eleven patients who were postnatally exposed to indomethacin, four patients had a patent ductus arteriosus, for which they received indomethacin during the study and 7 patients had received their last dose of indomethacin at least 24 hours before start of the study. Thirteen patients received caffeine prior to or during the study for weaning of the ventilatory support or for treatment of neonatal apnea. Antibiotics, in most cases beta-lactams and aminoglycosides, were required before or during the study in all patients for suspected or proven infection. Additional drug

Table 1 *Patient characteristics*

Parameters		
Male / Female	15 / 9	
GA (weeks)	29.1 ± 2.3#	(26.3-33.6)*
PNA (days)	5.8 ± 2.6#	(3-11) *
Birth weight (g)	1092 ± 233#	(745-1630) *
Study weight (g)	1105 ± 230#	(770-1645) *
Postnatal indomethacin	11+, 13-	

*# mean ±SD, * range, GA: Gestational age, PNA: postnatal age*

therapy included surfactant (n=17), morphine (n=11, >12h before midazolam administration) and furosemide (n=3). No serious adverse events due to midazolam were reported throughout the course of the study.

Midazolam and 1-OH-midazolam pharmacokinetics

The mean plasma concentration-time curves for midazolam and 1-OH-midazolam are depicted in Figure 1. Midazolam clearance was [median (range)]: 1.8 (0.7-6.7) ml/kg/min, volume of distribution: 1.1 (0.4-4.2) L/kg and elimination half-life: 6.3 (2.6-17.7) hours (Table 2). In 19 out of 24 patients, 1-OH-midazolam could be quantitated over the sampling interval. Of these patients, median 1-OH-midazolam C_{max} was 8.2 (<0.5-68.2) ng/ml with a median T_{max} reached at 6 (1-12) h. The median 1-OH-midazolam AUC_{ot}/midazolam AUC_{ot} ratio was low (0.09) with large interindividual variation (range: <0.001 – 1, CV 191%). For only 13 patients sufficient data were available to calculate 1-OH-midazolam elimination half-life which was significantly longer than that observed for midazolam [median $t_{1/2}$: 9.8 (range 4.9 - 62.2) vs. 6.3 (range 2.6 - 17.7) h for midazolam, p=0.046].

The effect of co-variates on midazolam and 1-OH-midazolam pharmacokinetics

No significant relationship was detected between age (gestational, postnatal or postconceptional age) and midazolam CL, V_{ss} or $t_{1/2}$. Newborn infants exposed postnatally

Table 2 *Calculated midazolam and 1-OH-midazolam pharmacokinetic parameters in preterm infants*

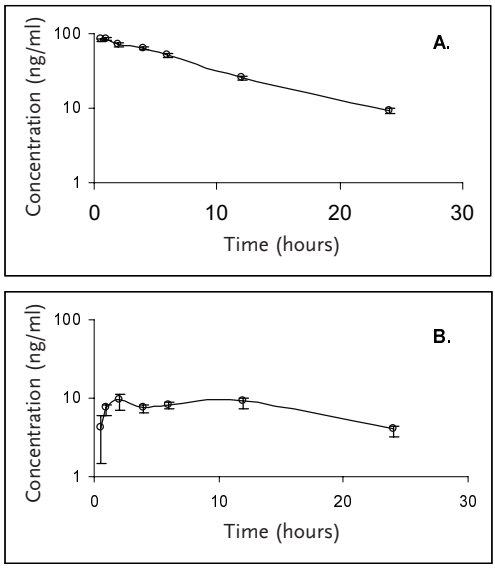
	Midazolam	**1-OH-midazolam**
Parameters		
AUC_{0t} (ng/ml.h)	804 (153 - 2118)	66.7 (<6-997.87)
$AUC_{0-\infty}$ (ng/ml.h)	971 (248 – 2353)	76.0 (<6-1222.4)
$t_{1/2}$ (h)	6.3 (2.6 – 17.7)	9.8 (4.9 – 62.2) #
V_{ss} (L/kg)	1.1 (0.4 – 4.2)	NA
CL (ml/kg/min)	1.8 (0.7 – 6.7)	NA
MRT (h)	10.3 (4.0 – 25.6)	NA
C_{max} (ng/ml)	108 (48.8 – 217.0)	8.2 (<0.5-68.2)
T_{max} (h)	0.5 (0.5 – 4.0)	6 (1-12)
AUC ratio		0.09 (<0.001-1)

Data are expressed as median(range), # = data from 13 patients,
C_{max} = maximal concentration of drug in plasma, T_{max}= time to reach C_{max}, AUC_{ot} = area under the concentration-time curve from time zero to the last sampling time point, $AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity, $t_{1/2}$ = elimination half-life, CL = total clearance and V_{ss} = volume of distribution at steady state, MRT = mean resident time, AUC ratio = 1-OH-midazolamAUC_{ot} / midazolamAUC_{ot}, NA = not available.

to indomethacin (n=11) had a significantly higher mean midazolam clearance as compared to infants who were not exposed to indomethacin (n=13) [0.17 (0.07-0.40) vs. 0.07 (0.04-0.24) ml/kg/min, p=0.003]. This effect of indomethacin on midazolam clearance was also found when only patients who were exposed to indomethacin, but did not have a patent ductus arteriosus at the time of the study (n=7) were compared to patients who were not exposed to indomethacin before [0.14 (0.07-0.40) vs. 0.07 (0.04-0.24) ml/kg/min, p=0.03]. Indomethacin treated infants also had a significantly higher volume of distribution, [1.7 (0.8-4.2) vs. 0.9 (0.4-1.6) L/kg, p=0.001], while mean half-life was not different between both groups [5.8 (3.9-17.7) vs 6.5 (2.6-14.2)h, p=0.93]. In addition, indomethacin-treated infants had a significantly higher postnatal age as compared to non-treated infants [median (range): 6.5 (3-11) days vs. 4.5 (3-9) days, p = 0.04]. Multiple regression was used to determine which factor was most predictive for midazolam plasma clearance. This analysis showed that midazolam clearance was significantly increased after indomethacin exposure (p=0.01) and when adjusted for this effect, there was no predictive value for postnatal age (p=0.43). We did not find an effect of any of the other clinical parameters [(i.e. feeding (enteral feeding n=6), ventilation (mechanically ventilated n=13), Apgar score, partus (spontaneous n=11), prenatal corticosteroid (n=20) or indomethacin administration (n=3), caffeine therapy (n = 15)] on midazolam pharmacokinetic parameters.

Additionally, there was no relationship detected between 1-OH-midazolam pharmacokinetic parameters (C_{max}, AUC, $t_{1/2}$) and postnatal, postconceptional or gestational age. No relationship was detected between any of the clinical parameters or concomitant drug therapy and 1-OH-midazolam pharmacokinetics. A significant

Figure 1 *Midazolam (A, n=24) and 1-OH-midazolam (B, n=13) concentration versus time curve after a single intravenous dose (0.1 mg/kg) to preterm infants.*



Each dot represents mean ± SEM concentration at each time point.

difference was not found with respect to comparison of demographic parameters between patients with or without detectable 1-OH-midazolam concentrations. In those infants where 1-OH-midazolam could be quantitated, the 1-OH-midazolam/midazolam AUC_{ot} ratio was determined as a surrogate marker for CYP3A activity. No association was observed between any of the demographic parameters and this ratio. Finally, there was not a statistically significant difference in this ratio between patients who were postnatally exposed to indomethacin and those who were not [0.08 (<0.001-0.3) vs 0.15 (<0.001-1), p = 0.90)].

Discussion

In preterm infants, midazolam clearance is lower than previously reported in older children and adults (11,12). Midazolam plasma clearance [1.8 (0.7-6.7) ml/kg/min] in our cohort of preterm neonates was comparable to values previously reported in newborn infants with gestational ages between 34 and 41 weeks (13), but was 1.5 to 5 times lower than reported in infants older than 3 months (3 - 9 ml/kg/min), children (5-13 ml/kg/min) and adults (6 - 11 ml/kg/min) (11,14-16). Accordingly, midazolam elimination half-life was longer in our patients [6.3 (2.6-17.7) h] than in older infants, children and adults (range: 1-2.5 h). This "impaired" midazolam elimination in preterm neonates as compared to older infants and children mirrors the known pattern for the ontogeny of CYP3A4 (7,8).

Interestingly, midazolam plasma clearance in our patients was somewhat higher [1.8 (0.7-6.7) ml/kg/min] than reported by Burtin et al. [1.2 ± 0.96 ml/kg/min] and Lee et al. [1.0 ± 0.2 ml/kg/min] (3,4). These previous investigations estimated clearance using population pharmacokinetics in preterm infants with gestational and postnatal ages similar to our patients, and who received midazolam as either a continuous infusion or as an intravenous bolus dose. This apparent difference between our mean midazolam clearance and those of earlier studies may be due to differences in patient population, co-medication received or simply, greater variability associated with pharmacokinetic parameter estimation from a population-based approach with sparse sampling. First, only about 50% of our infants were ventilated with a relatively low oxygen requirement (FiO_2 range 0.21 –0.29) while in the other studies (3,4) all patients were mechanically ventilated (oxygen demand not reported) suggesting that these patients were, on average, less stable than our patients. In adults, midazolam clearance appears to be reduced in critically ill patients possibly as a consequence of reduced CYP3A activity (17). Therefore, a difference in disease severity may have contributed to the lower midazolam clearance reported by Lee et al. (4) and Burtin et al. (3). Second, the increasing use of betamethasone over the last few years may also have contributed to the higher midazolam clearance reported in our patients compared to older studies. Twenty out of our 24 patients were antenatally exposed to betamethasone. If betamethasone is capable of inducing CYP3A activity as is dexamethasone (18), higher plasma midazolam clearance may have resulted from this particular drug interaction.

Whereas midazolam elimination in preterms shows age-related differences in relation to infants older than six months of age (11,19), we did not find a relationship between age (postconceptional, gestational or postnatal) and midazolam clearance or AUC ratio (as a surrogate marker for CYP3A4/5 activity) within our patient group. This

finding is in agreement with previous reports from preterm and term newborn infants with gestational ages ranging 24 from to 39 weeks (3,4). The lack of relationship between gestational or postnatal age and midazolam elimination mirrors the observation in vitro that CYP3A4 activity increases only marginally during the first two weeks of life (8). However, the lack of a relationship between age and midazolam clearance or AUC ratio in our study should be interpreted with caution given the relatively small sample size (n=24) of our study cohort and the narrow range of gestational (26 to 34 weeks) and postnatal ages (3 to 11 days) that characterized our subjects.

In our study the AUC ratio was used as a surrogate "marker" of CYP3A4/5 activity *in vivo*. Due to technical limitations (i.e. small sample volume), we were not able to measure the plasma 1-OH-midazolam-glucuronide concentrations (20). Therefore, the AUC ratio we calculated is not "corrected" for glucuronidation. Nonetheless, as the rate-limiting step in the formation of 1-OH-midazolam is catalyzed by CYP3A4, it was reasonable to assess the potential impact of development on enzyme activity using this AUC ratio.

Unexpectedly, postnatal indomethacin exposure, during or at any time before the study, was associated with a higher midazolam plasma clearance and a larger apparent volume of distribution. This may be an effect of altered pharmacokinetics as a result of resolution of a patent ductus arteriosus consequent to indomethacin treatment as has been reported for aminoglycosides, indomethacin and vancomycin (21). However, most of the patients received indomethacin more than 24 hours prior to midazolam administration and, based on clinical data, did not have a patent ductus arteriosus at the time of the study. As shown by van den Anker et al (22), indomethacin treatment of patent ductus arteriosus in the first days postnatally was associated with a larger apparent volume of distribution of ceftazidime up to two weeks of age. Hemodynamic consequences of the transition from fetal to neonatal circulation with resultant alterations in extracellular fluid dynamics and/or glomerular filtration may be sufficient to alter midazolam distribution and/or the clearance of 1-OH-midazolam as reflected by the increased elimination half-life in our patients.

Although 1-OH-midazolam concentrations have been measured in preterm infants (23, 24), the pharmacokinetics of 1-OH-midazolam in preterm infants have, to our knowledge, not been previously reported. The metabolite:drug AUC ratio appears to be lower in preterm infants than in older children and adults consequent to expected developmental reductions in CYP3A4/5 activity [0.09 (<0.001-1.0) vs. 0.13-0.26] (10,26). The increased median 1-OH-midazolam elimination half-life was longer in our neonates as compared to previous values from adults, where 1-OH-midazolam has a shorter half-life than the parent drug (10). This difference in 1-OH-midazolam elimination half-life may reflect lower renal clearance of 1-OH-midazolam and/or reduced glucuronidation in the neonate.

1-OH-midazolam concentrations and AUC ratio showed considerable interpatient variability (Table 2) and in five of our 24 patients, no 1-OH-midazolam could be detected. The intersubject variability in the AUC ratio is much larger in our cohort of preterm infants than the variability reported for midazolam and other CYP3A4/5 substrates in both pediatric and adult populations (10,25,26,27). This larger intersubject variability in newborns as compared to the intersubject variation in adults indicates that CYP3A4/5 activity in the newborn is certainly as variable as documented in adults, but probably

CYP3A4/5 activity in the newborn has a larger variability as compared to CYP3A4/5 activity in adults. Given the small age range of the preterm infants investigated in our study, it is highly unlikely that development per se is producing the aforementioned variability. Moreover, the lack of correlation between CYP3A4/5 activity and postconceptional age further supports that development does not explain the difference between variability in the newborn and adult in this study. Importantly, the larger variability in the newborn has potentially important implications for the treatment of newborns with CYP3A4/5 substrates.

Our inability to detect 1-OH-midazolam in a subset of patients may have been consequent to virtually absent constitutive CYP3A4/5 expression (ie. CYP3A7 predominance) with the production of metabolite concentrations below the limit of detection for the analytical method.

In conclusion, the elimination of midazolam in preterm infants between 26 and 34 weeks gestational age and less than two weeks of postnatal age is impaired relative to older infants, children and adults consequent to reduced CYP3A4/5 activity. Therefore, midazolam dosing regimens may need to be altered in young preterm neonates to prevent overdosing consequent to accumulation of midazolam and 1-OH-midazolam with repeated dosing. Part of the large variability in midazolam pharmacokinetics in this neonatal population could be explained by postnatal indomethacin exposure for closure of a patent ductus arteriosus and its effects on hemodynamic and/or renal function. Finally, as reflected by examination of the pharmacokinetic data for 1-OH-midazolam in the first two weeks of life, developmental dependence of CYP3A4/5 activity is either absent or alternatively, obscured by the marked interindividual variability in this enzyme.

References

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

2 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.

3 Burtin P, Jacqz-Aigrain E, Girard P, Lenclen R, Magny J, Betremieux P, et al. Population pharmacokinetics of midazolam in neonates. Clin Pharmacol Ther 1994;56(6):615-625.

4 Lee TC, Charles BG, Harte GJ, Gray PH, Steer PA, Flenady VJ. Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. Anesthesiol 1999;90(2):451-7.

5 Gorski JC, Hall SD, Jones DR, VandenBranden M, Wrighton SA. Regioselective biotransformation of midazolam by members of the human cytochrome P450 3A (CYP3A) subfamily. Biochem Pharmacol 1994;47(9): 1643-1653.

6 Thummel KE, Shen DD, Podoll TD, Kunze KL, Trager WF, Hartwell PS, et al. Use of midazolam as a human cytochrome P450 3A probe: I. In vitro-in vivo correlations in liver transplant patients. J Pharmacol Exp Ther 1994;271:549-556.

7 de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: ontogeny and drug disposition. Clin Pharmacokinet 1999;37(6):485-505.

8 Lacroix D, Sonnier M, Monion A, Cheron G, Cresteil T. Expression of CYP3A in the liver. Evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. Eur J Biochem 1997;247:625-634.

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

10 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.

11 Payne K, Mattheyse FJ, Liebenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. Eur J Clin Pharmacol 1989;37(267-272).

12 Smith MT, Eadie MJ, O'Rourke Brophy T. The pharmacokinetics of midazolam in man. Eur J Clin Pharmacol 1981;19:271-178.

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

14 Hughes J, Gill AM, Mulhearn H, Powell E, Choonara I. Steady-state plasma concentrations of midazolam in critically ill infants and children. Ann Pharmacother 1996;30:27-30.

15 Mathews HM, Carson IW, Lyons SM, Orr IA, Collier PS, Howard PJ, et al. A pharmacokinetic study of midazolam in paediatric patients undergoing cardiac surgery. Br J Anaesth 1988;61(3):302-7.

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

17 Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolise midazolam. Anaesthesiol 1987;42(6):619-26.

18 Pascussi JM, Drocourt L, Fabre JM, Maurel P, Vilarem MJ. Dexamethasone induces pregnane X receptor and retinoid X receptor-alpha expression in human hepatocytes: synergistic increase of CYP3A4 induction by pregnane X receptor activators. Mol Pharmacol 2000;58(2):361-72.

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

20 Vree TB, Shimoda M, Driessen JJ, Guelen PJ, Janssen TJ, Termond EF, et al. Decreased plasma albumin concentration results in increased volume of distribution and decreased elimination of midazolam in intensive care patients. Clin Pharmacol Ther 1989;46(5):537-44.

21 Gal P, Gilman JT. Drug disposition in neonates with patent ductus arteriosus. Ann Pharmacother 1993;27(11): 1383-8.

22 van den Anker JN, Hop WC, Schoemaker RC, van der Heijden BJ, Neijens HJ, de Groot R. Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. Br J Clin Pharmacol 1995;40(5): 439-43.

23 Lee TC, Charles B. Measurement by HPLC of midazolam and its major metabolite, 1-hydroxymidazolam in plasma of very premature neonates. Biomed Chromat 1996;10:65-68.

24 Jacqz-Aigrain E, Daoud P, Burtin S, Maherzi S, Beaufils F. Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. Eur J Clin Pharmacol 1992;42:329-332.

25 Krecic-Shepard ME, Barnas CR, Slimko J, Gorski JC, Wainer IW, Schwartz JB. In vivo comparison of putative probes of CYP3A4/5 activity: erythromycin, dextromethorphan, and verapamil. Clin Pharmacol Ther 1999;66(1): 40-50.

26 Lloyd-Thomas AR, Booker PD. Infusion of midazolam in paediatric patients after cardiac surgery. Br J Anaesth 1986;58(1):1109-1115.

27 Bailey DG, Dresser GK, Kreeft JH, Munoz C, Freeman DJ, Bend JR. Grapefruit-felodipine interaction: effect of unprocessed fruit and probable active ingredients. Clin Pharmacol Ther 2000;68(5):468-77.