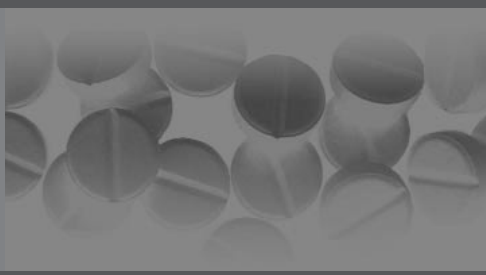
# Pharmacokinetics and metabolism of oral midazolam in preterm infants

# Chapter 5



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

*Submitted*

## Summary

*Introduction* Midazolam is a short-acting benzodiazepine that is finding expanded use in neonatal intensive care units. We studied the pharmacokinetics and metabolism of midazolam after a single oral dose in preterm infants.

*Methods* The pharmacokinetics of midazolam (M) and 1-OH-midazolam (1-OH-M) following a single 0.1 mg/kg oral dose of midazolam were determined in 15 preterm infants (gestational age: 26 to 31 weeks, postnatal age: 3 to 13 days). Blood was drawn prior to drug administration and at 0.5, 1, 2, 4, 6, 12 and 24 after oral administration. In 8 out of these 15 patients the pharmacokinetics of intravenous midazolam were also studied. Midazolam and 1-OH-midazolam concentrations were determined from plasma using GC-MS.

*Results* Apparent oral plasma clearance (CL/F), apparent volume of distribution ($V_{ss}$/F) and plasma half-life of midazolam were [median (range)]: 2.7 (0.67-15.5) ml/kg/min, 1.4 (0.3-12.1) L/kg and 7.6 (1.2-15.1) h, respectively. Midazolam $C_{max}$ and $T_{max}$ were [median (range)]: 64.4 (15.2-204) ng/ml and 2.0 (0.5-12) h, respectively. In 9 out of 15 preterm infants, 1-OH-midazolam concentrations could be detected. 1-OH-M $C_{max}$, $T_{max}$ and 1-OH-M/M AUC ratio were [median(range)]: 10.0 (1.6-22.6) ng/ml, 4 (0.5-24) h and 0.03 (0.01-0.96), respectively. Median elimination half life could only be calculated in four patients and was 3.6 (0.81-10.3) h. Absolute bioavailability could be calculated in 8 patients and was [median (range)]: 0.49 (0.12-1.0), showing a large variability.

*Discussion* Consequent to immature intestinal and 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. The large variability of the bioavailability of midazolam (12-100%) most likely reflects ontogeny and variability in intestinal CYP3A4 activity.

## Introduction

Midazolam, a short-acting benzodiazepine, is used for sedation in newborn infants, requiring prolonged mechanical ventilation and prior to invasive procedures (1). Despite the use of the drug in neonatal intensive care units, few pharmacokinetic data are available in preterm infants less than 34 weeks of gestation. Moreover, data describing midazolam disposition following oral administration in preterm infants are completely lacking. As well, there are no data on the absolute bioavailability of midazolam in preterm infants.

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 (2). CYP3A4 is primarily located in hepatocytes but also is found in the villus tip of enterocytes in the small intestine, the primary site of absorption for orally administered drugs. Therefore, following oral administration, midazolam is subject to hepatic and intestinal metabolism by CYP3A (3). In adults, 1-OH-midazolam concentrations are significantly higher following oral administration of midazolam compared to those seen after intravenous administration of the drug (4). In preterm infants, hepatic CYP3A4 activity is reduced, thereby resulting in prolonged plasma clearance of midazolam after intravenous administration (5). However, it is not known if intestinal CYP3A activity is also reduced as a consequence of age. Since hepatic and intestinal CYP3A are reportedly not co-regulated (6), a similar developmental pattern for intestinal CYP3A may not be assumed. Should the ontogeny of CYP3A4/5 in the small intestine mirror that observed for the liver, a reduction in the rate and extent of 1-OH-midazolam formation could be expected to occur.

Previous studies in adults (6) (7) (4) have used intravenous and oral midazolam to examine the relative contributions of hepatic and intestinal CYP3A4/5 to drug biotransformation. In this investigation, we examined the pharmacokinetics of oral midazolam in preterm infants (26 to 31 weeks of gestational age) who required the drug for pre-procedural sedation. In a cohort of these patients (n=8), midazolam disposition following intravenous administration was also characterized. The pharmacokinetic data from midazolam and its primary metabolite (i.e., 1-OH-midazolam) were used to assess developmental differences in CYP3A4/5 activity and also, to determine the oral bioavailability of midazolam in preterm neonates.

## Methods

### *Patient population*

The study was conducted in 15 preterm infants with gestational and postnatal ages ranging from 26 to 31 weeks and 3 to 13 days, respectively. The infants were recruited from the Neonatal Intensive Care Unit of the Sophia Children's Hospital. All children received midazolam prior to a stressful medical procedure (e.g. tracheal tube suction, elective nasopharyngeal intubation) and had a pre-existing indwelling arterial catheter previously placed for purposes of medical care not related to this pharmacokinetic study. In 8 of these patients the pharmacokinetics of intravenous midazolam were also studied, 72 hours before or after the patients received midazolam orally. Patients were excluded if they received morphine, dobutamine, dopamine or any drug known to affect CYP3A4

activity. In addition, patients were excluded 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 and the Network Steering Committee of the Pediatric Pharmacology Research Unit Network. Written, informed consent was obtained from parents or legal guardians prior to enrollment of subjects in the study.

### *Drug administration and sample collection*

A single oral dose (0.1 mg/kg) of midazolam (Dormicum® injection, Roche Laboratories, The Netherlands) was given as a 0.5 ml glucose 5% solution via nasogastric tube, followed by 0.5 ml of glucose 5% to ensure complete drug delivery. Serial arterial blood samples (0.2 ml each) were obtained from an indwelling arterial catheter at baseline and at 0.5, 1, 2, 4, 6, 12 and 24 h after dosing. In eight of these patients, midazolam was also administered as a single 0.1 mg/kg dose in a 5% glucose solution (0.03 mg/ml) infused into a peripheral or central venous catheter by a syringe pump over 30 minutes through microbore tubing. Serial arterial blood samples were obtained in the same way as after oral 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 study drug administration for adverse reactions, with vital signs checked prior to dosing 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), 5 µl 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 and intra-day coefficients of variation for the low standard (2ng/ml) were less than 10% midazolam and 1-OH midazolam, respectively. 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 for each subject. Initial polyexponential parameter estimates were generated from plasma concentrations vs. time data using a peeling algorithm for each subject. Final estimation of the apparent terminal elimination rate constant ($\lambda_z$) was accomplished by curve fitting using a non-linear, least-squares regression analysis with reciprocal (e.g., $1/Y^2$) 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 ($V_{ss}$/F) and apparent oral plasma clearance (CL/F) 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 $AUC_{0t}$/1-OH-midazolam $AUC_{0t}$ 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 mean ± 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), mechanically ventilated (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 (e.g., postnatal age, gestational age, postconceptional age, Apgar score) and calculated pharmacokinetic parameters are given as Spearman's ($r_s$) correlation coefficients. Finally, absolute oral bioavailability (F) was calculated comparing the AUCs (i.e., $AUC_{0-\infty}$) of midazolam after intravenous and oral administration (i.e., $F = [AUC_{po} / AUC_{iv}]$) in the same patients corrected for both dose (i.e., 0.1 mg/kg) and apparent differences in $\lambda_z$ between evaluation periods (i.e., PO vs. IV). 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*

Fifteen preterm infants (7 female, 8 male) with a mean gestational age of 28 ± 1.6 weeks and a postnatal age between 3 and 13 days, participated in the study (Table 1). Median (range) $FiO_2$ was 0.22 (0.21-0.27) in patients who were mechanically ventilated (n=6) and 0.21 (0.21-0.33) in patients who received continuous positive airway pressure (CPAP) by nasopharyngeal tube (n=8). Fourteen patients were antenatally exposed to indomethacin (to prevent preterm labor) and/or betamethasone (to induce lung maturation). Six patients received both drugs, and 8 received only betamethasone. Nine patients were postnatally exposed to indomethacin. Of these patients, three had a patent ductus arteriosus, for which they received indomethacin during the study and 6 patients had received their last dose of indomethacin at least 24 hours before start of the study. Eleven 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 betalactams and aminoglycosides, were required before or during the study in all patients for suspected or proven infection. Additional drug therapy included

*Table 1* *Demographic and clinical parameters of the study patients (n=15)*

| **Parameters** | | |
|---|---|---|
| GA (weeks) | 28.0 ± 1.6 | (26.0-30.7) |
| PNA (days) | 6.1 ± 2.7 | (3-13) |
| Birth weight (g) | 1076 ± 240 | (745-1630) |
| Study weight (g) | 1070 ± 232 | (825-1660) |
| Apgar 1 min | 6.0 ± 2.0 | (3-9) |
| Apgar 5 min | 7.9 ± 1.3 | (5-10) |

*Data are expressed as means ±SD (range) GA: gestational age, PNA: postnatal age*

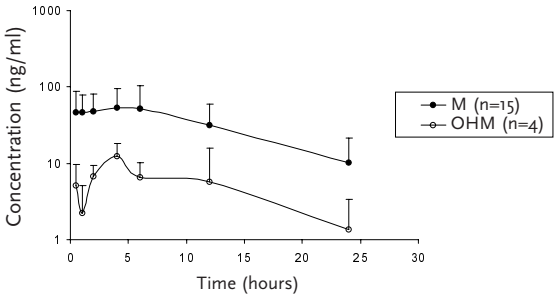
*Table 2* *Oral midazolam calculated pharmacokinetic parameters in 15 preterm infants*

| | **Midazolam** | **1-OH-midazolam** |
|---|---|---|
| **Parameters** | | |
| $AUC_{0t}$ (h.ng/ml) | 613 (90-2286) | 68.9 (<0.01-272.6) |
| $AUC_{0-\infty}$ (h.ng/ml) | 642 (108-2465) | 71.8 (1.6-305.0)# |
| $T_{1/2}$ (h) | 7.6 (1.2-15.1) | 3.6 (0.81-10.3)# |
| $V_{ss}/F$ (L/kg) | 1.4 (0.3-12.1) | NA |
| CL/F (L/kg/h) | 0.16 (0.04-0.93) | NA |
| MRT (h) | 12.0 (3.7-22.7) | 9.7 (3.3-15.5)# |
| $C_{max}$ (ng/ml) | 64.4 (15.2-204.0) | 10.3 (<0.01-22.1) |
| $T_{max}$ (h) | 2.0 (0.5-12.0) | 4.0 (0.5-24.0) |
| AUC ratio | | 0.03 (<0.01-0.96) |
| F (%) | 0.49 (0.12-1.0) | |

*Data are expressed as: median (range), # data of four patients*

*$C_{max}$ = maximal concentration of drug in plasma, $T_{max}$= time to reach $C_{max}$, AUCot = 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/F = total apparent clearance and $V_{ss}/F$ = apparent volume of distribution at steady state, MRT = mean resident time, AUC ratio = 1-OH-midazolam$AUC_{ot}$ / midazolam$AUC_{ot}$, F = oral bioavailability, NA = not available.*

*Figure 1* *Midazolam and 1-OH-midazolam mean concentration-time curves*




*Concentration-time curve of midazolam and 1-OH-midazolam after 0.1 mg/kg oral midazolam: mean (SEM) concentrations of midazolam (n=15) and 1-OH-midazolam (n=4).*

surfactant (n=9), morphine (n=4, >12 h before midazolam administration) and furosemide (n=1). 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. Apparent midazolam CL/F was [median (range)]: 2.7 (0.7-15.5) ml/kg/min, $V_{ss}$/F was: 1.4 (0.3-12.1) L/kg and $t_{1/2}$ was 7.6 (1.2-15.1) hours (Table 2). $C_{max}$ was [median (range)]: 64.4 (15.2-204.0) ng/ml with a median $T_{max}$ reached at 2 (0.5-12.0) h. In 9 out of 15 patients, 1-OH-midazolam could be quantitated over the post-dose sampling interval. Of these patients, median 1-OH-midazolam $C_{max}$ was 10.3 (1.6-22.1) ng/ml with a median $T_{max}$ reached at 4.0 (0.5-24) h. The median AUC ratio was low (0.03) with an almost 100-fold interindividual variation (range: 0.01-0.96). Sufficient concentration vs. time data were available in only four patients to reliably calculate the 1-OH-midazolam elimination half-life [mean (range)] which was 3.6 (0.81-10.3) h. In the 8 patients who received midazolam orally and intravenously the mean absolute oral bioavailability was 0.49 with a range of values (0.12-1.0) that also reflected considerable intersubject variability.

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

No significant relationship was detected between age (postnatal, gestational or postconceptual age) and midazolam CL/F, $V_{ss}$/F or elimination half-life. We did not detect an effect of any of the clinical parameters or concomitant drug therapy [(i.e., feeding (enteral feeding n=3), ventilation (mechanically ventilated n=6 ), Apgar score, manner of delivery (spontaneous n=11 ), prenatal exposure to corticosteroids (n=14) or indomethacin (n=6), postnatal treatment with indomethacin (n=9), and caffeine therapy (n= 11)] on midazolam pharmacokinetic parameters.

Additionally, there was no relationship detected between age (postnatal, postconceptional or gestational) and 1-OH-midazolam pharmacokinetic parameters ($C_{max}$, AUC, $t_{1/2}$). Likewise, no relationship was detected between any of the clinical parameters or concomitant drug therapy and 1-OH-midazolam pharmacokinetics. A significant difference was not found with respect to comparison of age (i.e., both postnatal and postconceptional) between patients with or without detectable 1-OH-midazolam concentrations. In those infants where 1-OH-midazolam could be quantitated, the AUC ratio was used as a surrogate marker to assess total CYP3A activity. No association was observed between any of the demographic parameters and this ratio.

## Discussion

In preterm infants, midazolam apparent oral clearance [2.7 (0.7-15.5) ml/kg/min] following oral administration was nearly 10-fold lower than previously reported in older children and adults (14.0-40.0 ml/kg/min) (8)). Accordingly, midazolam mean elimination half-life was longer in our patients (7.6 h) as compared to values reported in older children and adults (1.9-3.2 h) (6, 9, 10). This “impaired” midazolam elimination in preterm infants mirrors the recognized pattern for the ontogeny of CYP3A4 (11).

Moreover, in preterm infants, reduced midazolam clearance is also observed after intravenous administration consequent to low hepatic CYP3A activity shortly after birth (5). However, while intravenous midazolam clearance mainly reflects hepatic CYP3A activity (10), oral midazolam clearance is dependent on both intestinal and hepatic CYP3A activity (8). Therefore, the reduced midazolam clearance after oral administration to preterm infants suggests low hepatic ánd intestinal CYP3A4/5 activity directly after birth, which is supported by our observation that the median metabolite: drug AUC ratio is substantially lower [0.03 (0.01 - 0.96)] as compared to adults [0.43 ± 0.03 (mean ± SD)] (4).

In adults, 1-OH-midazolam plasma concentrations and the metabolite: drug AUC ratio were significantly higher following oral as compared to intravenous administration consequent to the role of intestinal 3A4 activity in midazolam biotransformation (4,14). Moreover, recent data indicate that the oral bioavailability of midazolam is almost entirely determined by CYP3A activity in the small intestine (7). Accordingly, low intestinal CYP3A4 activity would be expected to result in an increased oral bioavailability of midazolam, the converse being true for individuals with high intestinal CYP3A4 activity. This is further supported by the observation that oral administration of the CYP3A4 inhibitor clarithromycin resulted in a significant increase (from 31% to 75%) in the mean oral bioavailability of midazolam in healthy adult volunteers (17). Mexican adults with a systemic midazolam plasma clearance comparable to newborn infants (2.5 ± 0.4 vs. 2.0 ± 1.2 ml/kg/min) also demonstrated a relatively high oral absolute bioavailability [54 ± 6.1% (mean ± SEM)] of midazolam, confirming the aforementioned relationship between low CYP3A activity and increased absolute bioavailability of oral midazolam (15,16).

We were able to determine the absolute bioavailability of oral midazolam in approximately half of our study patients. Overall, the bioavailability of midazolam in these 8 patients averaged 49% which compares favorably with previous reports using a similar dose (per kilogram) given as an oral tablet or solution formulation in adult populations (24-38%) (4,10). Thus, it would appear that in preterm infants, both the rate and the extent of oral bioavailability may contribute in a substantial way to the substantial intersubject variability observed in the dose vs. plasma concentration relationship seen with oral administration of this drug. In preterm infants during the first two weeks of postnatal life, this most likely reflects intersubject variability in the constitutive expression of CYP3A4/5 in both the liver and the small intestine (18).

Whereas midazolam elimination shows a positive, linear association with age over the first years of life (11), we did not find a relationship between age (postconceptional, gestational or postnatal) and either the CL/F or AUC ratio within our study cohort. This finding is in agreement with previous reports from preterm and term newborn infants with gestational ages ranging from 24 to 39 weeks (5),13). This observation suggests that CYP3A4 activity increases only marginally during the first two weeks of postnatal life (12). However, the lack of a relationship between age and midazolam CL/F or AUC ratio in our study should be interpreted with caution given the relatively small sample size (n=15) of our study cohort in the face of apparent wide intersubject variability in the aforementioned parameters and the narrow range of gestational (26 to 31 weeks) and postnatal ages (3-13 days) that characterized our subjects.

As denoted previously, we used the AUC ratio of primary metabolite and parent

compound as a surrogate "marker" to assess 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. Therefore, the AUC ratio we reported is not "corrected" for glucuronidation (13). Nonetheless, given that the rate-limiting step in the formation of 1-OH-midazolam is catalyzed by CYP3A4, it was reasonable to evaluate the potential impact of development on enzyme activity using this AUC ratio.

Although 1-OH-midazolam concentrations have been measured in preterm infants (14), the pharmacokinetics of 1-OH-midazolam in preterm infants given an oral formulation of midazolam have, to our knowledge, not been previously reported. Despite considerable intersubject variability, the AUC ratio (Table 2) appears to be lower in preterm infants than values for this ratio previously reported in adults (4). The intuitive explanation for this finding would be reduced CYP3A4/5 activity in both liver and small intestine associated with immaturity of organ function. While midazolam is reportedly not a substrate for p-glycoprotein (15), it is unlikely that potential developmental differences associated with the functional competence of this transporter could have influenced the results of the AUC ratio. However, we can not rule out other "factors" (e.g., differences in gastrointestinal motility, loss of drug in stool) that could potentially impact either the rate or extent of midazolam absorption from the small intestine which, in turn, would influence the reliability of using the aforementioned AUC ratio as an indirect pharmacokinetic "surrogate" method.

The plasma concentrations of 1-OH-midazolam and the AUC ratio showed considerable interpatient variability (Table 2) and in 6 of our 15 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 after oral administration in adult populations (16). This variation may reflect organ-specific (i.e., intestine, liver) or CYP3A isoform-specific (i.e., CYP3A4, CYP3A5) differences in ontogeny. In addition to CYP3A4/5 activity, ontogenic differences in UGT activity may have contributed to the observed large intersubject variation in AUC ratios and 1-OH-midazolam plasma concentrations. Furthermore, although midazolam is almost completely metabolized in adults (10), renal excretion of unchanged midazolam may also contribute to the large intersubject variation in midazolam metabolism in preterm infants as is the case for caffeine, which is extensively metabolized in adults vs. approximately 90% renally excreted in preterm infants (22). Due to practical limitations (i.e., difficult and therefore, incomplete urine collections in preterm infants) we were not able to reliably quantitate midazolam and its metabolites in urine. Our inability to detect 1-OH-midazolam in a subset of patients may have been consequent to virtually absent constitutive CYP3A4/5 expression (i.e., CYP3A7 predominance) with the production of metabolite concentrations below the limit of detection for the analytical method. As well, the extreme intersubject variability in the AUC ratio may have been produced, in part, by non-enzymatic events (e.g. drug loss into stool, developmental differences in gastrointestinal motility capable of influencing the mean residence time of the drug at the absorptive surface area, intersubject differences in the size of the potential absorptive surface area in the small bowel) capable of influencing both the rate and extent of midazolam absorption.

The $T_{max}$ for midazolam appears greater and more variable in preterm infants as compared to values previously reported in older children and adults [e.g., 2.0 (0.2-24)

h vs.: 0.90 ± 0.36 h and 0.37 ±0.05 h (mean ± SD), respectively](6, 17). Several factors, in addition to intestinal drug metabolism, may affect the rate of oral drug absorption in preterm infants (e.g., feeding, gastric pH, intestinal transit time) (18). While three out of our 15 patients received enteral feedings, we did not observe a difference in midazolam pharmacokinetics between patients who received oral feedings and those who did not. Our patient group may, however, have been too small to detect a truly significant difference in the pharmacokinetics of midazolam absorption associated with feeding *per se* or type of infant feeding. Finally, given that the median midazolam $T_{max}$ is only reached after 2 hours and shows large interindividual differences, this route of administration is not suitable in preterm infants when a rapid sedative effect is needed for pre-procedural use.

In conclusion, the elimination of midazolam in preterm infants between 26 and 31 weeks gestational age and less than two weeks of postnatal age is impaired relative to older infants, children and adults consequent to reduced hepatic and intestinal CYP3A4/5 activity. Consequently, 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. Based on absolute bioavailability of orally administered midazolam of approximate 49%, oral dosing in some infants may need to be increased to compensate for incomplete absorption as compared to the routine intravenous doses employed in clinical practice today. However, an apparent delayed rate of midazolam absorption in preterm neonates may limit the practical utility of the oral route when the drug is being given as a pre-procedural sedative agent. 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.

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