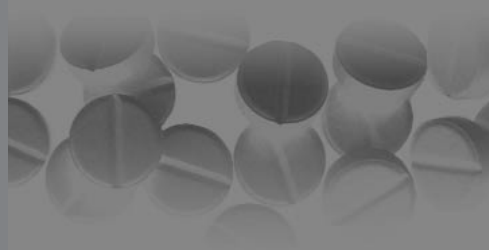# Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients

Chapter 6

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Summary

Aim The aim of this study was to determine the pharmacokinetics and metabolism of midazolam in pediatric intensive care patients.

Methods The pharmacokinetics of midazolam and metabolites were determined in 21 pediatric intensive care patients with ages between 2 days and 17 years who received a continuous infusion of midazolam (0.05-0.4 mg/kg/h) for 3.8 hours to 25 days for conscious sedation. Blood samples were taken at different time points during and after midazolam infusion for determination of midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide concentrations. A population analysis was conducted using a two-compartment pharmacokinetic model using the NPEM program. The final population model was used to generate individual Bayesian posterior pharmacokinetic parameter estimates.

Results Total body clearance, apparent volume distribution in terminal phase, and plasma elimination half-life were [mean ± SD, n=18]: 5.0 ± 3.9 ml/kg/min, 1.7 ± 1.1 L/kg and 5.5 ± 3.5 hr, respectively. The mean 1-OH-midazolam/midazolam ratio and (1-OH-midazolam + 1-OH-midazolam-glucuronide)/midazolam ratio were 0.14 ± 0.21 and 1.4 ± 1.1, respectively. Data from 3 patients with renal failure, hepatic failure and concomitant erythromycin/fentanyl therapy were excluded from the final pharmacokinetic analysis.

Conclusion We describe population and individual midazolam pharmacokinetic parameter estimates in pediatric intensive care patients using a population modeling approach. The derived population model can be useful for future dose optimization and Bayesian individualization. Lower midazolam elimination was observed in comparison to other studies in pediatric intensive care patients, probably due to differences in study design and patient differences such as age and disease state. Co-variates such as renal failure, hepatic failure and concomitant administration of CYP3A inhibitors are important predictors of altered midazolam and metabolite pharmacokinetics in pediatric intensive care patients.

Introduction

One of the most widely used sedative drugs in the pediatric intensive care is the short-acting benzodiazepine midazolam. 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 children (1). Midazolam undergoes extensive metabolism by isoforms of the cytochrome P450 3A subfamily (e.g., CYP3A4 and CYP3A5) to a major hydroxylated metabolite (1-OH-midazolam) (2). 1-OH-midazolam is equipotent to midazolam and its concentrations are the resultant of formation by CYP3A and subsequent metabolism to 1-OH-midazolam-glucuronide by UDP-glucuronosyltransferases (UGTs). 1-OH-midazolam-glucuronide is subsequently renally excreted (3, 4). 1-OH-midazolam-glucuronide also appears to have sedative properties when concentrations are high, as has been observed in adult patients with renal failure (5).

CYP3A4/5 activity reaches adult levels between 3 and 12 months of postnatal age (6). Developmental differences in CYP3A activity may therefore alter the pharmacokinetics of midazolam in pediatric intensive care patients of different ages (7). Similarly, the UGTs exhibit developmental changes in activity. However, as the specific UGTs involved in the conjugation of 1-OH-midazolam are yet unknown, the impact of ontogeny on this reaction remains to be determined.

In addition, the pharmacokinetics of midazolam in critically ill patients can be altered due to single or multiple organ failure (8). The dysfunction of organs such as liver and kidney may affect the pharmacokinetics of midazolam in a different way for each patient (5) (9) (10). In adult intensive care patients, midazolam elimination is impaired in comparison to healthy adults (11) (12). In pediatric intensive care patients, however, no such difference in midazolam elimination between intensive care patients and healthy children has been found (13, 14) (15).

Although the pharmacokinetics of midazolam have been characterized in healthy children after a single bolus dose, few data are available on the pharmacokinetics of midazolam in pediatric intensive care patients (1, 11, 14, 16). Data on the disposition of 1-OH-midazolam and 1-OH-midazolam-glucuronide are scarce for both sick and healthy children in all age groups. Knowledge of the pharmacokinetics of midazolam and its metabolites may serve as a valuable tool for developing optimal infusion regimens for pediatric patients during intensive care. The aim of our investigation was, therefore, to determine the pharmacokinetics of midazolam and its metabolites in pediatric intensive care patients between birth and 18 years of age during continuous intravenous infusion of midazolam.

Methods

Patient recruitment

The children were recruited from the Pediatric Intensive Care Unit of the Sophia Children's Hospital, Rotterdam, The Netherlands between May 1999 and April 2000. The institutional review board approved this research protocol. Written, informed consent was obtained from patients and/or parents or legal guardians prior to enrollment in the study.

The pharmacokinetic data presented here are part of a prospective pharmacokinetic-pharmacodynamic investigation of intravenous midazolam infusion in pediatric intensive care patients used for conscious sedation.

Patients were eligible for study entry if they were between 0 and 18 years old, needed midazolam for conscious sedation and already had an indwelling arterial catheter placed for purposes of medical care. Patients were excluded if they (1) received concomitant neuromuscular blockade drugs, (2) were exposed to midazolam for longer than 12 hours prior to start of the investigation, (3) were exposed to midazolam prior to start of the investigation without exact information on midazolam dosing, (4) were exposed to recent (i.e. < 24 hours prior to dosing) or chronic treatment with medications known or suspected to alter the pharmacokinetics of midazolam. Since midazolam is a substrate for cytochrome P450 3A enzymes, potential patients were evaluated for exposure to drugs known to affect CYP3A activity (e.g. erythromycin, phenobarbital, dexamethasone, and cisapride) (17).

Study design

Midazolam (0.1 mg/kg in glucose 5%) was given as an intravenous bolus, after which an intravenous midazolam infusion was started at a rate of 0.1 mg/kg/h through microbore tubing into a peripheral vein or central catheter. Subsequently, the infusion rate was adjusted to keep the patient comfortable as estimated by the COMFORT score. The COMFORT score is a previously validated sedation scale for use in the pediatric intensive care patient and postoperative neonates (18) (19). If a patient was not adequately sedated, a bolus dose midazolam (0.1 mg/kg) was given, followed by an increase in infusion rate of 0.05 mg/kg/h. If a patient was too sedated, the infusion rate was decreased by 0.05 mg/kg/h. If sedation was no longer needed clinically, the infusion rate was decreased by 0.1 mg/kg/h every 12 hours.

Blood sampling and drug assay

A blank arterial blood sample was obtained before administration of the loading dose. During the infusion of midazolam, serial arterial blood samples were obtained at the following time points:
1 Prior to and 2 and 30 minutes after each midazolam loading dose
2 every morning at 8.00 am
3 prior to and 10, 30 minutes, 1, 2, 4, 6, 12 and 24 hours after discontinuation of the infusion.

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 validated high-pressure liquid chromatography (HP G13 series, Agilent, Amstelveen, The Netherlands) with diode array UV detection. (HP G1315A, Agilent, Amstelveen, The Netherlands) The column used was Novapak C18 (Waters, Ettenleur, The Netherlands). Diazepam (12.5 ng/100μl H$_2$O, Bufa, Uitgeest, The Netherlands) was added to each sample as internal standard. Solid phase extraction was performed using alkalic extraction with DCM (Rathbun, Walkerburn, Switzerland)

The inter-day coefficients of variation at the low standard concentration (20 ng/ml) were less than 6.9% and 10.3% for midazolam and 1-OH-midazolam, respectively. The lower limit of quantitation was 20 ng/ml for both midazolam and 1-OH-midazolam using 0.5 ml plasma volume.

To measure 1-OH-midazolam-glucuronide in plasma, plasma samples were prepared with 50 µl β-glucuronidase (IBF Biotechnics, Villeneuve-la-Garenne, France, 100.000 Fishmann units/ml) and incubated at 40°C for 16 hours. Samples were processed and quantitated for total 1-OH-midazolam (conjugated plus unconjugated) in the same manner as described earlier. 1-OH-midazolam-glucuronide concentrations were then determined by using the following equation: [1 -OH-MG]= d[1-OH-M] x [M 1-OH-MG/M 1-OH-M], where: [1-OH-MG] = 1-OH-midazolam-glucuronide concentration, d[1-OH-M] = concentration difference of 1-OH-midazolam before and after hydrolysis, M 1-OH-MG = molecular weight of 1-OH-midazolam-glucuronide (517,9) and M 1-OH-M = molecular weight van 1-OH-midazolam (341,8).

Pharmacokinetic analysis
Population modeling
Midazolam concentration data were used to develop a population model by using the nonparametric expectation maximization algorithm developed by Schumitzky (NPEM program, USC*PACK clinical collection version 10.7, LAPK, Los Angeles, CA) employing all available data points per patient (20) (21).The model was parameterized in terms of volume of distribution of the central compartment V_1 (L/kg), elimination rate constant k_{el} (h^{-1}), and distribution constants k_{12} (h^{-1}) and k_{21} (h^{-1}). In order to weight each serum concentration correctly by the reciprocal of its variance an assay error pattern was used, fitted by the following equation: SD= 0.02 + 0.05C, where SD is the standard deviation of the assay and C represents the measured midazolam serum concentration (ng/ml). This error pattern was multiplied by gamma of 2.81, a factor determined by NPEM program to capture additional environmental noise, before calculating the population model. (22).

The modeling process consisted of two steps. The front part of the NPEM program was used to calculate individual parameter estimates for V_1, k_{el}, k_{12} and k_{21} in a two-compartment model with an iterative 2-stage Bayesian (IT2B) algorithm. The ranges for the parameter estimates were then used as input for the actual NPEM program resulting in the calculation of the entire probability density function (PDF). NPEM also provided mean and median population parameter estimates, SD's and the covariance and correlation matrices.

Population model and Bayesian feedback
The NPEM derived population model was entered into the MW\Pharm program (MW\Pharm, version 3.30, MediWare; Groningen, The Netherlands) and was used to generate the following individual Bayesian posterior pharmacokinetic parameter estimates: clearance (CL), volume of distribution of the central compartment and volume of distribution in terminal phase (V_1 and $V_β$, respectively), distribution half-life ($t_{1/2α}$) and elimination half-life ($t_{1/2β}$). To test the internal consistency of the individual pharmacokinetic parameter estimates generated by the MW/Pharm program, we compared predicted and measured midazolam serum concentrations in individual patients by calculating bias and precision (23). The mean 1-OH-midazolam/midazolam ratio [OHM/M] and (1-OH-midazolam + 1-OH-midazolam-glucuronide)/midazolam ratio [(OHM+OHMG)/M] were calculated with and without correction for molecular weight of midazolam and metabolites.

Statistical analysis

Data are expressed as means ± SD unless stated otherwise. Mean drug and metabolite concentrations and metabolite: drug ratios were determined from the mean concentrations or ratios from each patient. Because the assumption of normality was not fulfilled for all pharmacokinetic parameter estimates, we calculated a Spearman's correlation coefficient to investigate a correlation between age and pharmacokinetic parameters. These 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 α = 0.05.

Results

Patient clinical characteristics

21 patients were enrolled in this study ranging in age from 2 days to 17 years. The characteristics of the individual patients are listed in Table 1. All patients received concomitant drug therapy inherent in intensive care. Four patients required analgesia in the form of opioids (morphine, codeine, and fentanyl) during the midazolam infusion. Three additional patients received acetaminophen for fever reduction. Although the prescription of a drug known to affect CYP3A activity, was an exclusion criteria before entry in the study, two patients received such a drug after inclusion in the study. One patient (no 8) received a bolus of the CYP3A4 inducer dexamethasone (corticosteroid) on the second and third study day before a scheduled extubation (24). Another patient (no 11) received both the CYP3A4 inhibitor erythromycin (macrolide antibiotic) and the CYP3A4 substrate fentanyl during the whole study period (25-27). Other prescribed drugs were amphotericin B, amoxicillin, cefotaxime, cefuroxime, tobramycin, vancomycin, etomidate, furosemide, spironolactone and prostaglandin E1.

Midazolam dosing

In eleven patients study participation ended before midazolam was discontinued, for the following reasons: a) neuromuscular blockade (n=1), b) death (n=1), c) arterial line removal (n=4) and d) discharge from the intensive care unit (n=4). One patient (no 4) was withdrawn from the study by his guardian. In ten patients a (partial) washout curve could be established.

The median duration of infusion was 3.4 days (range 3.8 hours to 25 days) with a median infusion rate of 0.09 mg/kg/h (range 0.05 – 0.27 mg/kg/h). The median total dose of midazolam infused was 2.9 mg/kg (range 0.40 – 46.0 mg/kg). On average, patients received two (range 0 – 12) bolus injections of midazolam during the study period, and underwent 3 (range 1 – 10) infusion rate changes. In two patients the midazolam infusion was started without a loading dose. The reason for this protocol violation was that the attending physician considered possible hypotension associated with a midazolam bolus contraindicated given the patient's condition.

Midazolam pharmacokinetics

A two-compartment model was used to model the midazolam pharmacokinetics (28). We first modeled midazolam pharmacokinetics using data from all 21 patients. Three patients were excluded from the final population pharmacokinetic analysis, as their PK

Table 1 *Patient characteristics*

Patient	Sex	Age	Weight (kg)	Origin	ICU admission reason
1	Male	0.04 mths	3.5	Caucasian	Congenital heart disease
2	Male	0.12 mths	3.8	Caucasian	Congenital heart disease
3	Female	0.36 mths	3.6	Caucasian	Congenital heart disease
4	Male	0.48 mths	2.8	African	Postcardiac surgery
5	Female	0.60 mths	3.7	Caucasian	Congenital heart disease
6	Female	0.96 mths	4.3	Mediterranean	Respiratory insufficiency eci
7	Female	1.9 mths	4.8	Afro-Caribbean	Upper airway infection
8	Male	2.0 mths	3.6	Caucasian	Upper airway infection
9	Male	4.1 mths	7.5	Caucasian	Meningitis
10	Male	8.2 mths	20	Caucasian	Upper airway infection
11	Male	1.1 yrs	9.3	Asian	Pneumonia
12	Male	2.8 yrs	13	Asian	Empyema
13	Male	3.9 yrs	15	Afro-Caribbean	Acute laryngotracheobronchitis
14	Female	4.5 yrs	19	Caucasian	Pulmonary hypertension
15	Female	5.5 yrs	24	Caucasian	Staphylococcal scalded skin syndrome
16	Female	8.9 yrs	22	Middle-Eastern	Pulmonary hypertension
17	Male	9.1 yrs	25	Caucasian	Measles pneunomia
18	Female	13.1 yrs	40	Caucasian	Final stage ALL with multiple organ failure
19	Male	14.8 yrs	50	Caucasian	Ebstein-Barr virus infection
20	Female	15.1 yrs	52	Hispanic	Malignant hypertension
21	Male	17.0 yrs	60	Mediterranean	Postcardiac surgery

ALL = acute lymphatic leukemia, mths = months, yrs = years

parameters were very different in comparison to the other patients, as a result of renal failure, hepatic failure and erythromycin co-medication, respectively. Exclusion improved the final model (log-likelihood) and resulted in better estimates for the individual Bayesian pharmacokinetic parameter estimates, due to reduced inter-subject variability in the final population model.

The mean population pharmacokinetic parameter estimates provided by NPEM were: V_I 0.43 ± 0.20 L/kg; k_{el} 0.70 ± 0.40 /h; k_{12} 1.49 ± 0.84 /h and k_{21} 0.90 ± 0.48 /h. The mean individual Bayesian posterior pharmacokinetic parameter estimates were:

clearance (CL): 5.0 ± 3.9 ml/kg/min, volume of distribution (V_β): 1.7 ± 1.1 L/kg, distribution half-life ($t_{1/2\alpha}$): 0.24 ± 0.06 h and elimination half-life ($t_{1/2\beta}$): 5.5 ± 3.5 h. The median bias and precision of the observed vs. predicted midazolam concentrations, using the individual Bayesian pharmacokinetic parameter estimates was 12 ng/ml (3.8 %) and 47 ng/ml (14.6 %), respectively.

1-OH-midazolam and 1-OH-midazolam-glucuronide

Mean 1-OH-midazolam and 1-OH-midazolam-glucuronide concentrations were 60 ± 30 ng/ml and 556 ± 262 ng/ml, respectively. The mean 1-OH-midazolam/midazolam ratios were 0.21 ± 0.20 (not corrected for molecular weight, MW) and 0.14 ± 21 (corrected for MW). The mean (1-OH-midazolam +1-OH-midazolam-glucuronide)/midazolam ratios were 2.1 ± 1.5 (not corrected for MW) and 1.4 ± 1.1 (corrected for MW).

Effect of age on midazolam pharmacokinetics

No relationship could be detected between age and for body size corrected midazolam pharmacokinetic parameters or between age and for body size and dose corrected metabolite: drug ratios. We excluded patient 7, 16 and 19 from the analysis on the effect of age on midazolam disposition, as the pharmacokinetics of these patients were confounded by other co-variates than age (i.e. renal failure, hepatic failure and erythromycin co-administration).

Outliers

We also used the population model to estimate the individual Bayesian pharmacokinetic parameters for the three patients who were excluded from the final modeling. Patient 20 had renal insufficiency secondary to a non-functioning transplant kidney (creatinin 691 μmol/l). Elimination half-life was prolonged (40 hours), volume of distribution was large (16 L/kg), but midazolam clearance was within the population range (4.7 ml/kg/min). Her mean (1OHM+1OHMG)/M ratio was more than three times above the standard deviation of the population (i.e.: 14.8). Patient 18 had acute lymphatic leukemia and died within 24 hours after inclusion in the study of a secondary systemic aspergillosis infection. She had hepatic failure based on liver function tests (increased γGT, ASAT, ALAT, LD, reduced serum albumin concentration and impaired clotting function). Elimination half-life was extremely long (>100 hours), clearance very slow (<0.001 ml/kg/min), but volume of distribution (V) in the population range (1.4 L/kg). Her mean 1OHM/M and (1OHM+1OHMG)/M ratios were very low (0.06 and 0.09). Patient 11 received the CYP3A4 inhibitor erythromycin and CYP3A4 substrate fentanyl; consequently his midazolam elimination was also impaired [$t_{1/2\beta}$ 24.0 h, CL 2.2 ml/kg/min, OHM/M ratio 0.03 and (OHM +OHMG)/M ratio 0.40].

Discussion

Midazolam pharmacokinetics

This is the first report describing midazolam pharmacokinetics in pediatric intensive care patients using a population modeling approach. An additional advantage of the approach used is that, based on the derived model, we were able to estimate

pharmacokinetic parameters (CL, $t_{1/2\alpha}$, $t_{1/2\beta}$, V_1 and V_β) in individual patients with a high degree of precision using a Bayesian feedback algorithm. Moreover, using this approach, there will be no need for complete sets of post-infusion midazolam concentrations to estimate midazolam pharmacokinetic parameters in individual patients. Because three patients had a clinical condition associated with altered midazolam pharmacokinetics (renal failure, hepatic failure and concomitant erythromycin therapy), we excluded these patients from the final population pharmacokinetic analysis. A limitation of this study is that we did not validate our model prospectively in a separate group of patients, consequent to the limited sample size. Therefore, before using this model to predict midazolam pharmacokinetic parameters from other sparse data sets, prospective validation is needed

Midazolam undergoes extensive metabolism by members of the cytochrome 450 3A subfamily, i.e. CYP3A4, CYP3A5 and to a lesser extent by CYP3A7, to its main metabolite 1-OH-midazolam (2) (29). CYP3A4 activity is low at birth, with an increase thereafter to reach adult levels at one year of age (6). Therefore, midazolam clearance may alter as a function of age. Mean clearance rate in this study, with half of our patients less than 6 months of age, is lower than reported in patients older than two years of age (9.6 ± 3.5 ml/kg/min and 13.0 (range 2.3-66.7) ml/kg/min (14, 15). In contrast, mean midazolam clearance rate is higher in this study than reported in neonatal intensive care patients [median 1.8 (range 0.6-2.7) ml/kg/min] (3) (14, 30). Midazolam clearance in our study was comparable to data from another study in pediatric intensive care patients between 26 days and 5 years of age, when studied during the first 24-48 hours of midazolam infusion (5.8 ± 3.8 ml/kg/min vs. 5.0 ± 3.9 ml/kg/min) (16). Hence, our data in addition to data from other studies in pediatric patients, support an age-related increase in midazolam clearance, consequent to an age-related surge in CYP3A4/5 activity (7). Since our patient population covers the whole pediatric age range, we also studied the relationship between age and midazolam elimination in our patient sample. However, mean midazolam clearance was not statistically different between patients younger and older than 6 months of age (3.8 ± 1.9 ml/kg/min vs. 6.2 ± 5.0 ml/kg/min, p=0.39). Moreover, none of the other pharmacokinetic parameters showed a relationship with age.

Other differences in study design may also contribute to the disparate results on midazolam disposition. First, we used a population modeling approach to calculate pharmacokinetic parameters, while others calculated midazolam clearance by dividing infusion rate by 'steady-state' plasma concentration. Our data show that midazolam half-life appears to be longer than in healthy children (5.5h vs. 1.2h) (13). Since time of steady-state was defined as 6 or 24 hours after an infusion rate change, steady-state may not have been reached in patients in those studies (14, 16). This may very well have resulted in an overestimation of midazolam clearance values. In this study, clearance rates estimated using steady-state (>24 hours) do not differ significantly from clearance rates estimated using population pharmacokinetics (data not shown). Second, differences in disease state may also contribute to reported differences in midazolam pharmacokinetic parameters. Intrinsic hepatic disease or cytokines associated with systemic infection have been shown to alter CYP3A activity (10) (8). Moreover, disease-related changes in body composition or hepatic blood flow may alter midazolam pharmacokinetics of intensive care patients (9) (11). (10).

Midazolam elimination half-life (5.5 ± 3.5h) is longer than reported for healthy children between 3 and 10 years of age (1.2 ± 0.3 h) (13). These data are in agreement with adult data, where midazolam elimination is also impaired in critically ill patients as compared to healthy adults (11) (12). Hence, midazolam can not be considered a drug with a short elimination half-life in pediatric intensive care patients. Without a loading dose, steady-state of a midazolam infusion will only be reached after approximately 20 hours. Therefore, midazolam sedation should be initiated with a bolus followed by a continuous infusion in pediatric intensive care patients.

1-OH-midazolam and 1-OH-midazolam-glucuronide

The mean 1OHM/M ratio (0.21 ± 0.20) in our patients is in agreement with the OHM/M ratio in pediatric patients who received midazolam after cardiac surgery [mean 0.25 (SEM ± 0.03)] (31). In contrast, the OHM/M ratio was higher in our patients than in newborn infants less than two weeks of age during continuous infusion of midazolam (0.06 ± 0.05) (3). Since the OHM/M ratio may be a surrogate measure of CYP3A activity, these findings also imply rapid developmental changes in CYP3A4/5 activity between birth and the first weeks of life.

The ratio between the plasma concentrations of 1-OH-midazolam + 1-OH-midazolam-glucuronide and midazolam is governed by the metabolic rate of midazolam and 1-OH-midazolam and the renal excretion rate of 1-OH-midazolam-glucuronide, which is in turn related to the glomerular filtration rate of the patient (9). Therefore, the OHM/M and (OHM+OHMG)/M ratios will provide insight in the contribution of the different metabolic pathways. The following observations suggest that the metabolism of 1-OH-midazolam to 1-OH-midazolam-glucuronide by UGT isoforms is not importantly impaired in children between 2 days and 17 years of age compared to adults. First, the mean (OHM+OHMG)/M ratio in our patients (2.1 ± 1.5) is higher than reported in adult intensive care patients [median 0.96 (range 0.1-23.2)] (9). Second, the OHM/M ratio is almost 7 times lower than the (OHM+OHMG)/M ratio. Finally, the (OHM+OHMG)/M ratio did not differ between children younger or older than 6 months of age (Mann-Whitney p=0.754). However, reduced renal excretion of 1-OH-midazolam-glucuronide consequent to immature renal function in the first weeks after birth, may obscure lower UGT activity in this period (32).

Outliers

Three patients had clinical characteristics, which are associated with altered midazolam pharmacokinetics. Pharmacokinetic analysis of data from these patients did indeed show altered midazolam pharmacokinetics.

First, consequent to renal failure the elimination half-life of patient 20 was extremely long, volume of distribution was extremely large, but midazolam clearance was in the normal range of our patient group. As discussed by Reves et al. (33), the free fraction of midazolam is significantly increased in renal-failure patients. Consequently, after correction for free-fraction no significant difference in midazolam pharmacokinetics will remain (33). Also consequent to renal failure, her mean 1-OH-midazolam-glucuronide concentration was high (1100 ng/ml) as well as her (OHM+OHMG)M ratio. Since this patient received midazolam for only 12 hours, the metabolite did not accumulate to a great extent (5). However, if renal-failure patients receive higher doses

of midazolam or an infusion for a longer period of time, prolonged sedation (> 3 days after cessation of the infusion) may occur due to accumulation of the 1-OH-midazolam-glucuronide in the absence of detectable concentrations of midazolam or 1-OH-midazolam (5).

In patient 18, who was critically ill with hepatic failure, midazolam elimination was significantly impaired due to impaired midazolam metabolism (low metabolite : drug ratios). This impairment in midazolam metabolism was most likely due to liver failure, as has been shown in critically ill adult patients (8). In addition, inflammatory mediators in serum may also have impaired midazolam metabolism consequent to reduced CYP3A activity (10).

The concomitant administration of the CYP3A4 inhibitors erythromycin and fentanyl in patient 11 also reduced midazolam elimination as a result of inhibition of midazolam metabolism (14, 34).

In summary, using a population pharmacokinetic approach we were able to estimate pharmacokinetic parameters for individual patients. The derived population pharmacokinetic model can be useful for future dose optimization and Bayesian individualization in pediatric intensive care patients. Lower midazolam elimination was observed in comparison to other studies in pediatric intensive care patients, probably due to differences in study design and patient differences such as age and disease state. Renal insufficiency, hepatic failure and concomitant administration of CYP3A inhibitors are important predictors of altered midazolam and metabolite pharmacokinetics in pediatric intensive care unit patients for which alternative dosing strategies have to be developed.

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