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The pharmacokinetics of midazolam and 1-OH-midazolam during oral premedication in paediatric patients

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ABSTRACT

Aim. Development of midazolam (MDZ) pharmacokinetic model is pivotal for predicting drug response and determining appropriate dosing in patients who undergo surgical procedures. The aim of this study was to provide population pharmacokinetic analysis describing MDZ and its main metabolite 1-OH-midazolam (1-OH-MDZ) used during oral premedication in surgical paediatric patients. The influence of gender, age, and body weight on MDZ pharmacokinetics was also investigated.

Material and methods. The analyzed data set included 27 patients, aged 1 to 17 years, who received oral midazolam syrup before various surgical procedures. The 1-OH-MDZ concentration was approximated by a proportional relationship to MDZ concentration. Population nonlinear mixed-effect modeling was done using NONMEM 7.2. Non-parametric bootstrap and VPC were conducted to evaluate the adequacy of the model to describe the observations.

Results. Midazolam pharmacokinetic model was developed to describe the time course of MDZ and 1-OH-MDZ concentrations. High inter-individual variability in volume of central compartment (93%) and clearance (60%) of MDZ were observed. The effect of body weight was accounted for by the allometric scaling. Significant differences in MDZ pharmacokinetics due to the age and gender were not found.

Conclusions. The population MDZ pharmacokinetic model was successfully developed for paediatric patients. Age, gender do not explain inter-individual variation in the pharmacokinetics of MDZ. No effect of maturation was detected.

Keywords: midazolam; midazolam pharmacokinetic model; 1-OH-midazolam.

Introduction

Midazolam (MDZ) is a sedative drug, which is also commonly used in premedication of general anaesthesia in diagnostic and surgical procedures. It is a member of benzodiazepines family and exhibits anxiolytic, hypnotic, amnesic, myorelaxant and anti-convulsant properties [1]. Sedative effect results from MDZ interaction with ionotropic gamma-aminobutyric acid receptors

($GABA_A$), which causes the opening of chloride channels and increases the penetration of chloride ions inside the neuron. Anti-anxiety properties are linked to the increasing of the glycine inhibitory neurotransmitter [2]. In critically ill children MDZ is administered intravenously, while in the others orally. MDZ is characterized by a rapid onset and short duration of action as well as a constant efficiency. The highest concentration in plasma is achieved within 30 min [3]. Owing to a first-pass hepatic extraction its bioavailability, after oral administration, is estimated at about 50%. Elimination of MDZ occurs mainly by its hydroxylation by intestinal and hepatic cytochrome P450 A4 (CYP3A4) and A5 (CYPA5) enzymes. In this process two metabolites are formed i.e. 1-hydroxymidazolam (1-OH-MDZ, α-hydroxy MDZ) and 4-OH-MDZ [2]. It was shown that 1-OH-MDZ has sedative properties and may significantly contribute to the effects of MDZ, whereas 4-OH-MDZ is quantitatively unimportant [1]. Finally, both metabolites are conjugated with glucuronide acid and excreted into urine [2]. Studies on pharmacokinetics of MDZ have revealed differences in drug half-life ($t_{1/2}$) and weight-corrected clearance between adults, infants and children that are well accounted from by an allometric principle [4]. Neonates have prolonged $t_{1/2}$ and smaller body weight normalized clearance than adults. Between 1 and 2yr higher body weight-normalized clearance is observed, and then a decline to adulthood [5–7]. Pharmacokinetics studies on different populations are essential to proper dosing of MDZ. It is also important to know factors responsible for inter-individual variations in MDZ pharmacokinetics. There are significant differences in pharmacokinetics of many drugs in children and adults, which justify specific studies on paediatric population [8, 9]. Therefore, the aim of this study was to provide population pharmacokinetic analysis describing MDZ and its main metabolite 1-OH-MDZ concentrations after its oral administration for premedication purposes in children. Moreover, the influence of factors as age, gender and body weight on the population MDZ pharmacokinetics in paediatric patients was investigated.

Material and Methods

Patients

Twenty-seven children scheduled for elective surgical procedures, aged between 1 and 17 years, children of Caucasian ancestry, male (n = 20) and female (n = 7), were enrolled in this study (**Table 1**). Surgical procedures included hypospadia, total or partial thyroidectomy, plastic surgery and tumor removal. The local Ethical Committee of the Poznan University of Medical Sciences approved the study (no. 275/12). Parents of all included patients signed the informed consent on the medical records at the hospital. All experiments were carried out in compliance with the relevant laws and guidelines in accordance with the ethical standards of the Helsinki Declaration.

Patients overall health was assessed as I–II, according to the American Society of Anesthesiologists (ASA) physical status classification system. Exclusion criteria included: physical status ASA III and more, active respiratory infection, metabolic or congenital disorders, sedative or anticonvulsive medication. Twenty-four hours before surgical procedure each patient was managed by anesthesiologist according to the preoperative criteria. All patients were made to be fast overnight, but could drink clear fluids up to 2 hours before the induction of anaesthesia.

Pharmacokinetic study design

Oral MDZ syrup was administered in dose of 0.3 mg kg^{-1} (up to maximum of 15 mg) to the patients as a premedication, from 30 to 45 minutes before surgical procedure. Sedation level was assessed in the operating room using the Richmond Agitation-Sedation Scale (RASS, **Table 2**). General anaesthesia was induced with 2–5% sevoflurane via facemask in children with no intravenous (IV) access, or with propofol intravenously in dose of 2–4 mg kg^{-1}, in those with IV access. During the induction fentanyl in dose 1–2 mcg kg^{-1} was administered to all patients. The airways were maintained by endotracheal intubation or laryngeal mask. Intubation was facilitated by miva-

Table 1. Demographic characterization of patients (n = 27). Results are expressed as median and range for continues and as count for categorical variables

Parameter [unit]	Median [Range]
Male/Female	20 / 7
Age [years]	10 [1.75–17]
Weight [kg]	47 [10.625–90]
MDZ dose [mg]	7.5 [2.5–15]

Table 2. Assessment of sedation in study subjects using the Richmond Agitation-Sedation Scale (RASS), n = 27

RASS score	Term	n, %
2	Agitated	1, 3.7%
1	Restless	5, 18.5%
0	Alert and calm	15, 55.6%
-1	Drowsy	5, 18.5%
-2	Light sedation	1, 3.7%

curium 0.2 mg kg^{-1} or rocuronium 0.6–1.0 mg kg^{-1} depending on the expected time of the procedure. The anaesthesia was maintained with sevoflurane (minimum alveolar concentration (MAC) of 1.0–1.4) and nitrous oxide 50% in oxygen using mechanical ventilation. During the maintenance of anaesthesia, the additional doses of 0.5–1 mcg kg^{-1} of fentanyl were given. Throughout the procedure patients were monitored according to standard procedures. To protect patients from hypothermia warming blankets were used. In all children emerging from anassthesia signs of delirium were not present.

After induction, 2.5 ml of peripheral blood was collected at certain points in time: 5 min (T_0), 10 min (T_1), 15 min (T_2), 30 min (T_3), 45 min (T_4), 60 min (T_5), as well as after 90 min (T_6) and 120 min (T_7), if time of procedure exceed 60 min. Plasma was obtained by blood centrifugation (4°C, 3.000 rpm, 10 min) and then stored at -80°C until use.

Drug and metabolite assay

Concentration of MDZ and its metabolite in plasma samples was assessed using validated high-performance liquid chromatography (HPLC, Agilent 1200 series, Waldbronn, Germany) coupled with a triple quadrupole mass spectrometer, equipped with an electrospray ionization source (Agilent 6410B, Wilmington, Delaware, USA), details were described previously [10]. Briefly, three reactions for each compound were recorded. Abselut Nexus (Agilent, USA) solid phase extraction columns (60 mg/ 3 ml) were used for MDZ and metabolite extraction, according to the manufacturer's procedure. Extraction recovery (% + SD) was 91.1 ± 3.5 and 86.8 ± 2.8 for MDZ and 1-OH-MDZ, respectively. Intraday precision (RSD, %) at 20 ng ml^{-1} standard was 5.3 and 7.2 for MDZ and its metabolite. Interday precision was 9.1 and 10.4 for MDZ and 1-OH-MDZ, respectively. The limit of quantification was 10 ng ml^{-1} for both analytes using 0.2 ml sample volume. The method was linear from 10 to 4000 ng ml^{-1}.

Population Pharmacokinetic Analysis

Population nonlinear mixed-effect modeling was done using NONMEM (Version 7.2.0, Icon Development Solutions, Ellicott City, MD, USA) and the gfortran compiler 9.0. NONMEM runs were executed using Wings for NONMEM (WFN720, http://wfn.sourceforge.net). The first-order conditional estimation with interaction (FOCEI) method was used. The self-written differential equations were solved using ADVAN6 PREDPP subroutines. The NONMEM data processing and plots were done in Matlab® Software version 7.0 (The MathWorks, Inc., Natick, MA, USA).

The minimum value of the NONMEM objective function (OFV), typical goodness-of-fit diagnostic plots, and the evaluation of the precision of pharmacokinetic parameter and variability estimates were used to discriminate between various models during the model-building process.

Pharmacokinetic Model

A standard two-compartment model with first order absorption was used to describe plasma MDZ concentrations:

$$\frac{dA}{dt} = -k_a A \; A(0) = D$$
$$\frac{dA_{MDZ,P}}{dt} = k_a A - \frac{CL/F}{V_P/F} A_{MDZ,P} - \frac{Q/F}{V_P/F} A_{MDZ,P} + \frac{Q/F}{V_T/F} A_{MDZ,P} \; A_{MDZ,P}(0) = 0$$
$$\frac{dA_{MDZ,T}}{dt} = \frac{Q/F}{V_P/F} A_{MDZ,T} - \frac{Q/F}{V_T/F} A_{MDZ,T} \; A_{MDZ,T}(0) = 0 \quad (1)$$

where t denotes time, A, $A_{MDZ,P}$ *and* $A_{MDZ,T}$ denotes MDZ mass in absorption, plasma and peripheral compartment; k_a denotes absorption rate constant; CL and Q denotes the metabolic and inter-compartmental clearance; F denotes bioavailability; and V_P and V_T denotes the volume of distribution of central and peripheral compartment, respectively. MDZ concentration equaled:

$$C_{MDZ,P} = \frac{A_{MDZ,P}}{V_P/F} \quad (2)$$

The MDZ metabolite, 1-OH-MDZ, concentration ($C_{1\text{-}OH\text{-}MDZ}$) was assumed proportional to MDZ concentration according to:

$$C_{1-OH-MDZ} = C_{MDZ,P}\frac{CL/F}{CL_{1-OH-MDZ}/f} \quad (3)$$

where $CL_{1\text{-}OH\text{-}MDZ}$ denotes 1-OH-MDZ clearance and f product of bioavailability and fraction of MDZ to 1-OH-MDZ metabolism. This equation was obtained assuming that elimination rate constant of 1-OH-MDZ is much higher than that of MDZ and assuming a very high absorption rate constant ($k_a >> k$) [10]. All the concentrations were in molar units.

Inter-individual variability (IIV) for the pharmacokinetic parameters was modeled assuming log-normal distribution:

$$P_i = \theta_P \exp(\eta_{P,i}) \quad (4)$$

where P_i is the individual parameter, θ_P is the typical value of this parameter in the population, and η_P is a random effect for that parameter with the mean 0 and variance ω_P^2.

Any j^{th} observations for i^{th} individual of MDZ ($C_{MDZ,P,ij}$) and 1-OH-MDZ ($C_{1\text{-}OH\text{-}MDZ,\,ij}$) were defined by:

$$C_{MDZ,P,ij} = C_{MDZ}(P_i, t_j)\cdot(1+\varepsilon_{prop,ij,MDZ}) \quad (5)$$

$$C_{1-OH-MDZ,ij} = C_{1-OH-MDZ}(P_i, t_j)\cdot \cdot(1+\varepsilon_{prop,ij,1-OH-MDZ}) \quad (6)$$

where $C_{MDZ,P}$ and $C_{1\text{-}OH\text{-}MDZ}$ are defined by basic structural model (Eq. 2 and 3) and $\varepsilon_{prop,ij,MDZ}$ and $\varepsilon_{prop,ij,1\text{-}OH\text{-}MDZ}$, represent the proportional residual random errors of MDZ and 1-OH-MDZ concentrations. It was assumed that ε is normally distributed with the mean of 0 and variances denoted by σ^2.

Covariance Analysis

The covariate search was performed by plotting individual estimates of the pharmacokinetics parameters against time-independent covariates (weight, age) to identify their potential effects. If a relationship was found, it was described by means of linear regression or power model (allometric relationship). The categorical covariate (gender) was included into the model based on indicator variables.

Specifically, the effect of body size on all the volume (V_C, V_T) and clearance (CL, Q) parameters was included a priori based on allometric scaling as follows:

$$P_i = \theta_P \left(\frac{BW_i}{70}\right)^K \exp(\eta_{P,i}) \quad (7)$$

where P_i denotes the individual value of volume and clearance term,, BW_i the individual body weight, 70 is a typical body weight of adult patients, and K is the exponent equal to 0.75 for clearance and 1 for volume of distribution [11].

The difference in the minimum of the NONMEM OFV obtained for two hierarchical models (likelihood ratio) is approximately $\chi 2$ distributed. During the covariate search the effect of each covariate was examined by adding an appropriate equation to the base model. The difference in OFV between models of 3.84 for one degree of freedom was considered to be statistically significant at $p < 0.05$ for the covariate to be included into the base model. This process was repeated until all significant covariates were added. Then, removing one covariate at a time performed backward elimination. The least important covariate was dropped from the model according to the OFV unless that difference in OFV was larger than 6.63 (corresponding to $p < 0.01$). The final model was established when no more covariates could be excluded from the model.

Model Evaluation

The model performance was assessed by means of predicted corrected Visual Predictive Check (pcVPC). The pcVPC was calculated based on 1000 datasets simulated with the final parameter estimates. The pcVPC plots were created by correcting the observed and simulated values for the average population prediction in the time-bin divided by population predictions for each observed and simulated value [12].

In this work the 10^{th}, 50^{th} and 90^{th} percentile were used to summarize the data and for VPC prediction. The pcVPC allows to compare the confidence inter-

vals obtained from prediction with the observed data over time. When the corresponding percentile from the observed data falls outside the 95% confidence interval derived from predictions this is an indication of a model misspecification. Since pharmacokinetics data deviated to some extent from nominal times, binning across time was done.

Bootstrap

Evaluation of model robustness was based on the non-parametric bootstrapping with 1000 replicates. From the bootstrap empirical posterior distribution, 90% confidence intervals (5^{th}–95^{th} percentile) were obtained for the parameters, as described previously [13].

Results

The analyzed data (n = 27) contained 344 MDZ and 1-OH-MDZ concentrations. The raw data are represented in **Figure 1**. Two IDs differed considerably from the other profiles and were excluded from the pharmacokinetic analysis. The brief summary of the analyzed patients is given in **Table 1**. Level of sedation by RASS, was assessed as satisfactory in the majority (55.6%) of patients (**Table 2**).

A two-compartment disposition model with first-order absorption was used to describe the available data. The 1-OH-MDZ concentrations were proportional to MDZ and a simplified direct relationship was used to describe the data, as described earlier [10].

Typical goodness-of-fit plots of the final model are presented in **Figure 2**. The individual and population prediction versus observed concentrations are relatively symmetrically distributed around the line of identity. The conditional weighted residuals versus time and versus individual predicted concentrations do not show any trend and are relatively uniformly distributed around the zero. The VPC plots stratified with respect to the type of measurements and moment during the

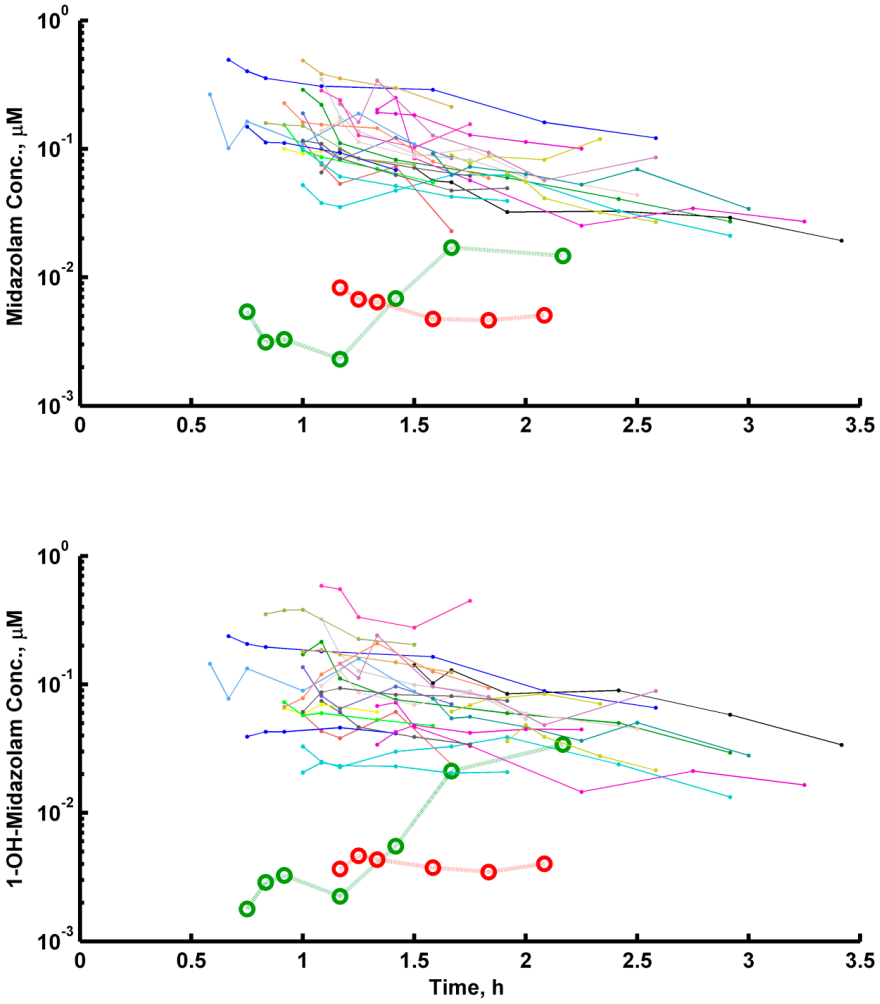

Figure 1. Individual (lines) MDZ and 1-OH-MDZ concentration time profiles. The 2 profiles (dotted line, open symbols) were not included in the analysis

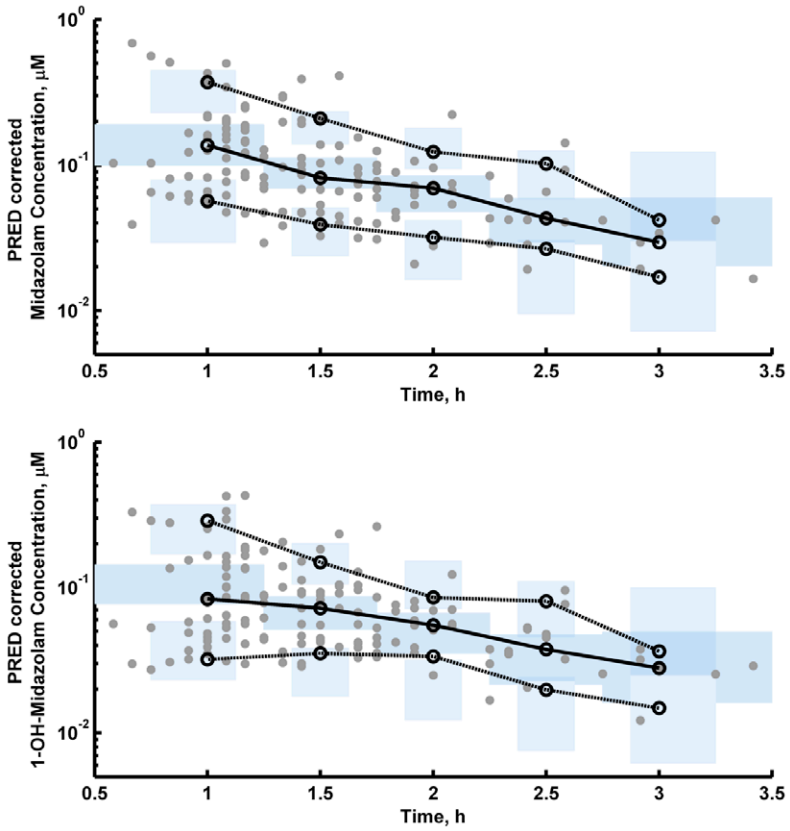

Figure 3. The prediction corrected Visual Predictive Checks (pcVPC). pcVPC plots show the simulation-based 95% confidence intervals around the 10th, 50th, and 90th percentiles of the pharmacokinetics data in the form of blue (50th) and gray (10th and 90th) areas. The corresponding percentiles from the prediction corrected observed data are plotted in black color. The prediction corrected raw data is presented as gray closed symbols

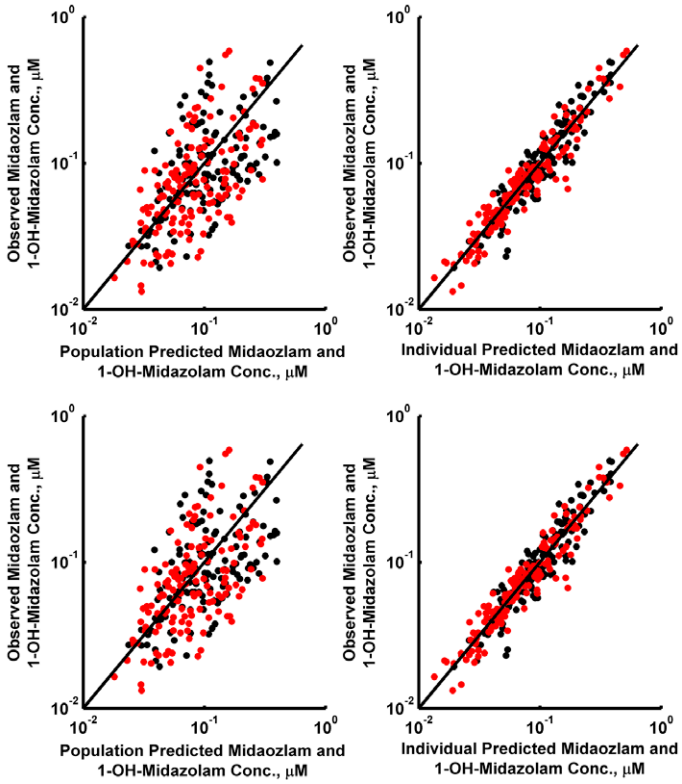

Figure 2. Goodness of fit plots: the observed versus the population predicted concentrations; the observed versus the individual population predicted concentrations; and conditional weighted residuals (CWRES) versus individual predicted concentrations and time. The black symbols denoted MDZ and red 1-OH-MDZ, respectively

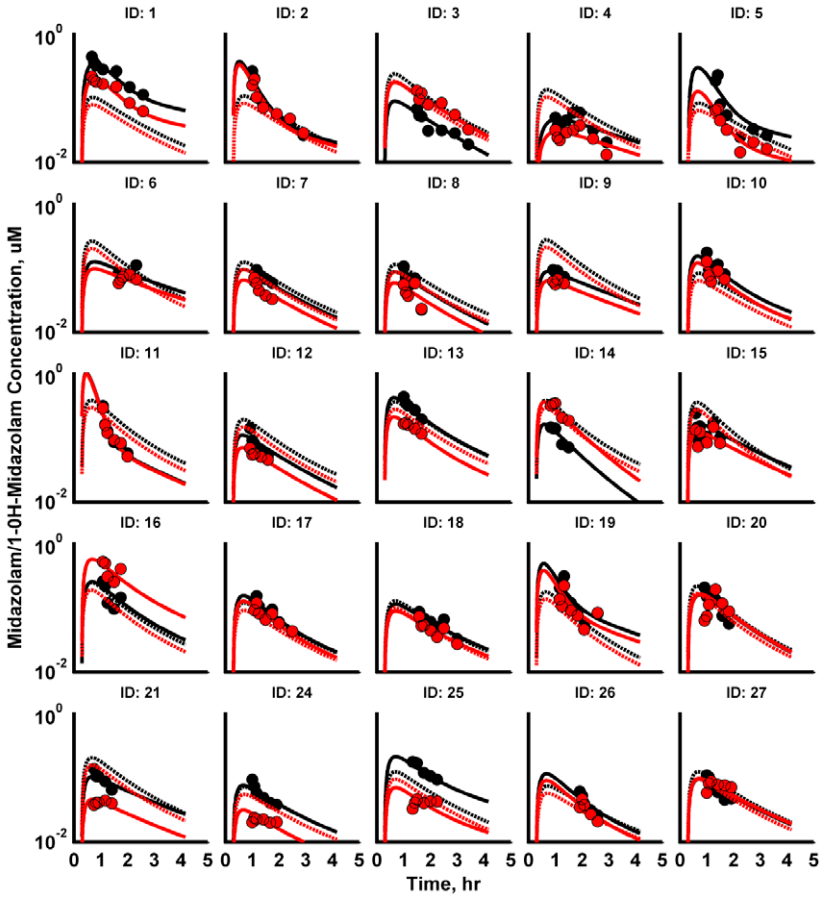

Figure 4. Experimental (red symbols), individual (black dotted) and population model predictions (red dotted) of MDZ (black) and 1-OH-midaozlam (red) concentrations

Table 3. Final model parameter estimates. 90% confidence interval (CI) of the parameter estimate derived from a nonparametric bootstrap analysis (n = 1000, unsuccessful = 79)

Parameter	Estimate	%RSE	Shrinkage%	Bootstrap median	Bootstrap 90% CI	
					Lower	Upper
k_a [1/h]	6.11 FIXED[a]	–	–	–	–	–
t_{lag} [h]	0.29 FIXED[a]	–	–	–	–	–
V_P/F [L]	176	18	–	191	122	280
Cl/F [L/h]	93.6	16	–	88.7	53.8	127
V_T/F [L]	67.8	64	–	90.7	23.5	493
Q/F [L/h]	27.0	35	–	30.7	12.3	71.6
$Cl_{1\text{-}OH\text{-}MDZ}/f$ [L/h]	123	15	–	114	67.7	157
$\omega^2_{VP/F,\ \%}$	93.1	34	1.0	116	80.8	165
$\omega^2_{CL/F,\ \%}$	59.4	26	3.6	68.8	43.6	119
$\omega^2_{CL\text{-}OH\text{-}MDZ,\ \%}$	58.9	54	3.9	63.5	40.2	104
$\omega^2_{Ka,\ \%}$	65 FIXED*	–		–	–	–
$\omega^2_{tlag,\ \%}$	15 FIXED*	–		–	–	–
$cor_{VP/F\text{-}\ CL1\text{-}OH\text{-}MDZ/f}$	0.82	38		0.88	0.66	0.99
$cor_{VT/F\text{-}\ CL1\text{-}OH\text{-}MDZ/f}$	0.59	45		0.75	0.46	0.97
$cor_{CL/F\text{-}CL1\text{-}OH\text{-}MDZ/f}$	0.63	28		0.75	0.48	0.92
$\sigma^2_{Prop,MDZ}$	0.24	10		0.238	0.192	0.277
$\sigma^2_{Prop,1\text{-}OH\text{-}MDZ}$	0.23	15		0.218	0.161	0.27

[a] Fixed based on work [21] Abbreviations: k_a – absorption rate constant; t_{lag} – lag-time; V_P/F – volume of central compartment of midazolam; Cl/F – oral clearance of midazolam; V_T/F – volume of peripheral compartment of midazolam; Q/F – intercompartmental clearance of midazolam; $Cl_{1\text{-}OH\text{-}Mid/f}$ – clearance of 1-OH-midazolam; $\omega^2_{VP/F}$ – inter-individual variance of VP/F; $\omega^2_{CL/F}$ – inter-individual variance of Cl/F; $\omega^2_{CL\text{-}OH\text{-}MDZ}$ – inter-individual variance of 1-OH-midazolam clearance; ω^2_{Ka} – inter-individual variance of ka; ω^2_{tlag} – inter-individual variance of Tlag; $cor_{VP/F}$ – CL-1-OH-MDZ/f – correlation between volume of central compartment of midazolam and clearance of 1-OH-midazolam; $cor_{VT/F}$- **CL-1-OH-MDZ/f** – correlation between volume of peripheral compartment of midazolam and clearance of 1-OH-midazolam; $cor_{CL/F}$- **CL-1-OH-MDZ/f** correlation between clearance of midazolam and clearance of 1-OH-midazolam; $\sigma^2_{Prop,MDZ}$ – residual variance for midazolam; $\sigma^2_{Prop,1\text{-}OH\text{-}MDZ}$ – residual variance for 1-OH-midazolam

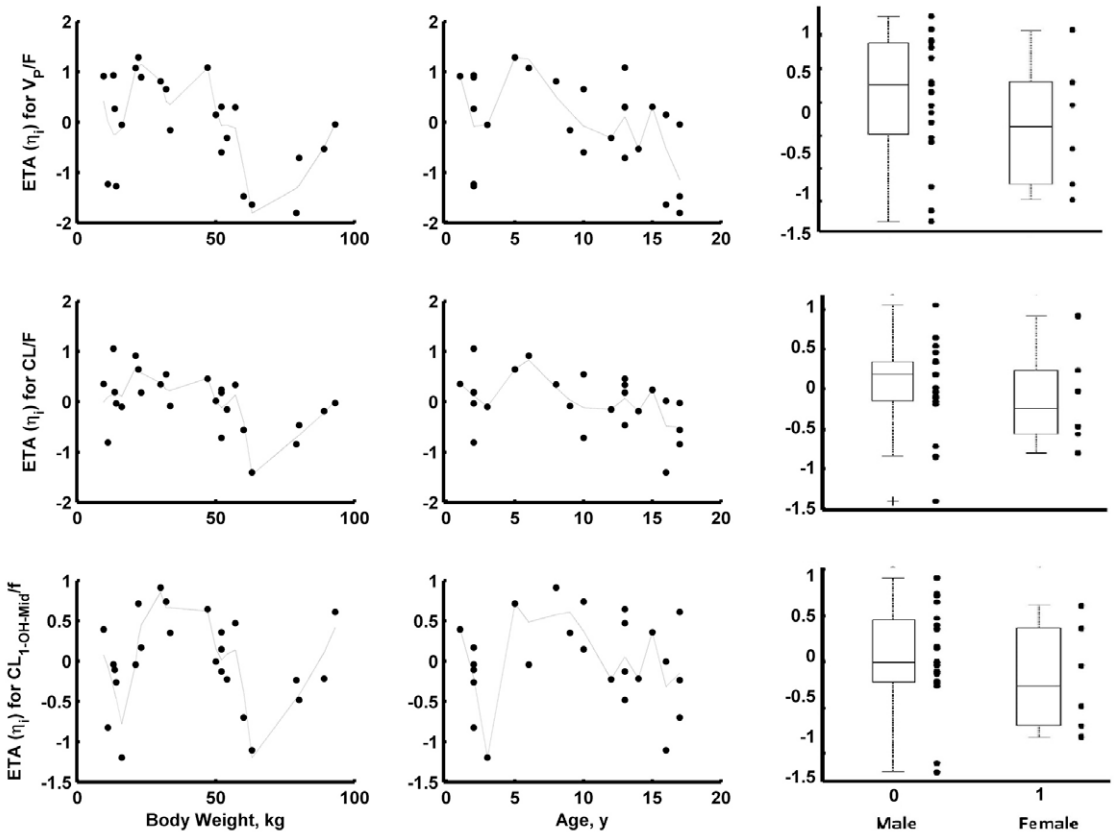

Figure 5. The individual estimates for eta (deviation of the individual estimate from the population mean) of the final pharmacokinetics/ parameters in relation to the patients' body weight, age and gender. The dotted line indicates the trend in the data (loess smooth)

infusion are presented in **Figure 3**. They all indicate that both the central tendency of the data and the variability at a particular sampling time were recaptured very well. Similarly, most of the individual predicted concentrations versus time profiles were very close to the experimental data as presented in **Figure 4**. **Table 3** shows parameter estimates of the final population pharmacokinetic model of MDZ along with their bootstrap estimates. All pharmacokinetics parameters, inter-subject, and residual error variances were estimated well with CVs lower than 64%.

The typical values of apparent (due to unknown bioavailability) volume of central and peripheral compartment were, respectively 176 and 67.8 L for MDZ. The apparent elimination and inter-compartmental clearance equaled 93.6 L h^{-1} and 27 L h^{-1}. For 1-OH-MDZ the apparent clearance equaled 123 L h^{-1}. The inter-individual variability was high and equaled about 93% for volume of central compartment and 60% for clearance, respectively.

The effect of body weight on MDZ and 1-OH-MDZ pharmacokinetics was well explained by an allometric relationship with theoretical exponents. Age and gender were not found to be independently significant covariates in this study. The relationship between the individual estimates for eta (deviation of the individual estimate from the population mean) of the *CL/F, VP/F*, and $CL_{1\text{-}OH\text{-}MDZ}$ and the individual values of the covariate (eta-plots) are presented in **Figure 5**. The lack of any trend in the data indicates that the above mentioned covariates do not explain the remaining unexplained ones between patients variability for *CL/F*, V_p/F, and $CL_{1\text{-}OH\text{-}MDZ}$.

Discussion

Development of MDZ pharmacokinetic model is pivotal for predicting drug response and determining appropriate dosing as a premedication in patients who undergo surgical procedures. It is also important to establish which factors are responsible for inter-individual variations in MDZ clearance. In this study the population pharmacokinetic model was successfully developed to describe the time course of MDZ and 1-OH-MDZ concentrations in paediatric patients. The influence of age, gender and weight on MDZ and 1-OH-MDZ clearance was also investigated. We were unable to show any statistically significant

differences in the studied population due to the gender. No maturation could be identified, that for this weight was included as covariate according to allometric scaling principles. The allometric principle well accounted for the body weight effects on MDZ and 1-OH-MDZ pharmacokinetics parameters.

Based on the literature data, inter-individual variation in the pharmacokinetics of MDZ, especially in its clearance, may result from differences in many factors such as age [5–7, 14], weight [15, 16], disease occurrence [17] as well as ethnicity/genotype [16, 18]. Some of studies on age-related changes in pharmacokinetics of MDZ administrated intravenously have demonstrated altered pharmacokinetics parameters depending on the patient's age. Prolonged $t_{1/2}$ and a decreased weight-corrected clearance of MDZ were observed in neonates [5, 6] as well as MDZ clearance was higher in children aged 3 years and older, than in infants and children from 1 to 2 years [7]. On the other hand, some studies on weight-corrected oral MDZ clearance have not revealed age-related changes [19, 20]. Moreover, it was shown that weight-adjusted MDZ clearance decreases according to the power-low relationship with body weight [21]. Increased weight-normalized MDZ clearance in children of lower weight is sometimes explained by their greater liver volume relative to total body weight (4% of the body in 1-year-old children compared to 2.5% in adults) [22, 23] or by higher concentration of catalytically active cytochrome P450 3A4 (CYP3A4) per gram liver weight in children. Despite the underlying mechanism all the literature reported findings consistently suggest that age affects MDZ clearance up to second year of life, and later changes in pharmacokinetics of MDZ can be well explained by body weight differences [4].

In a systematic review, in which the extent of inter-individual variation in MDZ clearance in children and factors responsible for this variation were determined, it was shown that variation in MDZ clearance is greatest in critically ill children and neonates [24, 25]. There are several factors that may affect the pharmacokinetics of drugs in critically ill patients including: hypoxia, shock, systemic inflammatory responses, stress, changes in diet, endocrine changes and other drugs [25–28]. Moreover, it was determined that the degree of inter-individual variation in these patients is far greater than the variation in administered doses of MDZ. As a result, it is likely that some of these paediatric patients may receive inadequate dose of MDZ and as a consequence be underdosed or overdosed with this sedative [24]. Two patients were removed from the analysis, as they had considerably different pharmacokinetics that could not be associated with available covariates. The presence of outlying concentration-time profiles confirms the existence of large inter-individual variability in MDZ metabolism. The variability may be determined by many factors, including genetic, environmental and demographic ones. Excluded patients received the same dose of MDZ (7.5 mg), were of the same age, one was a man and one was a woman weighing 69 kg and 56 kg, respectively. Level of sedation assessed according to the Richmond Agitation-Sedation Scale (RASS) had the value of 0 (described as alert and calm, patient spontaneously pays attention to caregiver) for both patients. It could indicate that the observed differences in pharmacokinetics-profiles are more likely caused by other mechanism, like patients noncompliance or delayed gastric emptying.

Moreover, in this age group of patients (1–17 years) effect of age and gender is minimal and if it would be visible, it can be well explained by differences in body weight. There may be a number of factors contributing to the variation in MDZ pharmacokinetics, thus further studies are necessary to determine the influence of particular covariates (demographic, genetic, environmental, diseases occurrence) on pharmacokinetics of MDZ.

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Conflict of interest statement
The authors declare no conflict of interest.

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