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Recently Registered Midazolam Doses for Preterm Neonates Do Not Lead to Equal Exposure: A Population Pharmacokinetic Model

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Abstract

Although midazolam is a frequently used sedative in neonatal intensive care units, its use in preterm neonates has been off-label. Recently, a new dosing advice for midazolam for sedation on intensive care units has been included in the label (0.03 mg/[kg·h] for preterm neonates <32 weeks and 0.06 mg/[kg·h] for neonates >32 weeks). Concentration-time data of a prospective multicenter study (29 patients, median gestational age 26.7 [range 24.0-31.1 weeks]) were combined with previously published data (26 patients, median gestational age 28.1 [range 26.3-33.6 weeks]), and a population pharmacokinetic model describing the maturation of midazolam pharmacokinetics was developed in NONMEM 7.3. Clearance was 73.7 mL/h for a neonate weighing 1.1 kg and changed nonlinearly with body weight (exponent 1.69). Volume of distribution increased linearly with body weight and was 1.03 L for a neonate weighing 1.1 kg. Simulations of the newly registered dosing show considerable differences in steady-state concentrations in preterm neonates. To reach similar steady-state concentrations of 400 μg/mL (±100 μg/mL), a dose of 0.03 mg/(kg·h) is adequate for neonates ≥1 kg and ≤2 kg but would have to be reduced to 0.02 mg/(kg·h) (−33%) in neonates <1 kg and increased to 0.04 mg/(kg·h) (+33%) in neonates weighing >2 kg and ≤2.5 kg. The impact of the observed differences in exposure is difficult to assess because no target concentrations have yet been defined for midazolam, but the current analysis shows that one should be cautious in giving dosage advice based on historical data with a lack of reliable pharmacokinetic and effect data.

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Midazolam is 1 of the most frequently used sedatives in neonatal intensive care units,[1,2] and its use keeps on increasing.[3] Besides acting as a sedative-hypnotic, midazolam is also used for the treatment of refractory seizures and less-frequently for anesthesia.[1] Data on the pharmacodynamics of midazolam are very scarce. Jacqz-Aigrain et al,[4] Anand et al,[5] and Arya and Ramji[6] studied the sedative effect of midazolam in placebo-controlled trials and concluded that it was superior to placebo. A recent meta-analysis of these 3 studies points out the risk of potential severe side effects associated with the use of midazolam.[3] In particular, Ng et al. report a higher incidence of adverse neurological events at 28 days postnatal age when midazolam is compared with morphine as observed in the study performed by Anand.[5] This highlights that more research is urgently needed.

Concerning the pharmacokinetics of midazolam, an influence of maturation in preterm neonates is likely, as midazolam is mainly metabolized by CYP3A.[7] CYP3A activity is known to be very low directly after birth and to increase rapidly during the first weeks of life, reaching values comparable to those in adults around the age of 1 year.[8,9] In accordance with this, the lowest clearance values have been reported in preterm neonates,[10,11] and these increase with age.[12–15] In addition to the influence of maturational status, severity of disease and inflammation may affect midazolam elimination in critically ill neonates and children.[16,17] No target concentration for the use of midazolam in preterm neonates has been defined because quantifying the relationship between plasma concentration and sedative effect has been difficult.[18]

Until recently, the use of midazolam in preterm neonates was off-label because dosing information in this vulnerable population was lacking in the Summary of Product Characteristics.[1,3] Based on a review of the published literature, the drug label has recently been changed, and new dosing advice for midazolam sedation in preterm neonates treated in intensive care units has been included in the label. In the current label, for neonates with a gestational age of less than 32 weeks, lower infusion rates of 0.03 mg/(kg·h) are suggested, as compared with neonates with gestational ages above 32 weeks for whom 0.06 mg/(kg·h) is proposed.

In the current study we analyzed the midazolam concentration-time data of a prospective multicenter study carried out in 4 neonatal intensive care units in the Netherlands. We have combined those data with the data on intravenous administration of midazolam in preterm neonates published earlier by de Wildt et al[19] to develop a population pharmacokinetic model that describes the maturation of midazolam pharmacokinetics in preterm infants. Finally, we used this model to evaluate the performance of the newly registered midazolam dosing for preterm neonates.

Methods

Data and Studies

The Erasmus Medical Center ethics review board approved the protocols, and written informed consent from parents/legal guardians was obtained before study initiation. The Drug dosage Improvement NeOnates (DINO) study (study 1, MEC-2014-067, NL47409.078.14, ClinicalTrials.gov NCT02421068) prospectively studied a total of 9 drugs, including midazolam, routinely used in preterm infants born before 32 weeks of gestation. The primary objective was to develop pharmacokinetic and pharmacodynamic models from which evidence-based individualized dosing regimens can be derived. From September 2014 to September 2017, 60 midazolam blood samples from 29 children (13 female, 16 male) were collected after intravenous administration in 4 participating Dutch level III neonatal intensive care units (Radboud University Medical Center Nijmegen, Maastricht University Medical Center Maastricht, Máxima Medical Center Veldhoven, and Sophia Children's Hospital Rotterdam). The study made use of sparse opportunistic sampling to reduce the burden on the individual child while the dose was determined by the treating physician. The indication for midazolam was either a stressful procedure or continuous sedation, and bolus doses as well as continuous infusions were administered (Table 1). Additional data (study 2, MEC-171.586/1998/125) after intravenous administration were available from a previously published data set from the neonatal intensive care unit of the Sophia Children's Hospital in Rotterdam.[19] This data set contained 172 samples from 26 neonates (16 female, 10 male) (Table 1) obtained 0.5, 1, 2, 4, 6, 12, and 24 hours after a single intravenous dose of 0.1 mg/kg over 30 minutes for stressful procedures. The combined data set thus consisted of 232 samples from 55 patients after intravenous administration for various doses and indications (Table 1).

Analytic Methods

The plasma concentrations of the de Wildt et al[19] data set were analyzed using gas chromatography with mass spectrometric detection. The lower limit of quantification was 1 μg/L. All samples were analyzed in duplicate, and the resultant mean concentration was used in the pharmacokinetic analysis. For further detail on the analytic method, the reader is referred to the original publication.[19]

Within the DINO study midazolam plasma samples were analyzed using liquid chromatography–tandem mass spectroscopy with electrospray ionization in the

Table 1. Patient Characteristics of the DINO Study Data Set (Study 1) and the Shared Data Set (Study 2)

	DINO Study Data (Study 1)	de Wildt et al[19] (Study 2)	Combined Data Set
Patients	29	26	55
Samples (samples per neonate)	60 (2.1)	172 (6.6)	232 (4.9)
Doses (doses per neonate)	123 (4.2)	26 (1)	149 (2.7)
Doses for stressful procedures (infusion duration ≤30 min)	59 (2.0)	26 (1)	85 (1.5)
Doses for continuous sedation (infusion duration >30 min)	65 (2.2)	0 (0)	65 (1.2)
Female neonates, N (%)	13 (45%)	16 (62%)	29 (53%)
Gestational age, wk[a]	26.7 (24.0–31.1)	28.1 (26.3–33.6)	27.3 (24.0–33.6)
Birth weight, kg[29,a]	0.84 (0.47–1.8)	1.1 (0.75–1.6)	0.95 (0.47–1.8)
Postnatal age (at day of inclusion), d[a]	18 (1–88)	5.5 (3–11)	9 (1–88)
Actual body weight, kg[29,a]	1.3 (0.6–4.3)	1.0 (0.77–1.6)	1.1 (0.6–4.3)

[a]Data provided as medians and ranges.

positive ionization mode. The lower limit of quantification for midazolam was 4 μg/L.[20]

Population Pharmacokinetic Analysis and Model Evaluation

The population pharmacokinetic analysis was performed using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, Maryland), supported by Perl-speaks-NONMEM version 3.4.2 and Xpose version 4.3.5.[21] Model development was performed in 4 steps: (1) selection of a structural model, (2) selection of an error model, (3) covariate analysis, and (4) internal validation of the model. The first-order conditional estimation with interaction method was used throughout model development. In case of missing covariate information, the last value observed in the subject was carried forward. For body weight, linear interpolation between available measurements was performed. The objective function value (OFV) was used to compare models, in which a lower OFV indicated a better fit of the model to the data. A drop in OFV of more than 3.8 was considered statistically significant ($P < .05$) for structural model selection. Standard errors obtained from NONMEM and the confidence intervals of the bootstrap analysis in Perl-speaks-NONMEM (n = 1000) were used to evaluate the precision of the estimated parameters.

The covariates birth weight, actual body weight at each day in the neonatal intensive care units, gestational age, postnatal age, postmenstrual age (calculated using gestational age and postnatal age), and gender were evaluated using a stepwise covariate modeling procedure.[22] For the covariate analysis, a significance level of $P \le .01$ was used for the forward inclusion and a significance level of $\le.001$ for the backward elimination.

Key models as well as the final model were evaluated using goodness-of-fit plots and normalized prediction distribution errors[23] based on 1000 simulations of the model and a bootstrap analysis based on 1000 samples of the data.

Evaluation of the Recently Registered Dosing Regimen

With use of the final model, 1000 simulations of the newly proposed dosing regimen were performed for 9 hypothetical preterm neonates weighing 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, or 2.5 kg. A continuous infusion of 0.03 mg/(kg·h) was administered over a duration of 72 hours as proposed by the label for preterm infants with a gestational age of less than 32 weeks. Steady-state concentrations were evaluated for their ability to achieve the indicative target concentration of 400 μg/L as proposed by Ahsman et al[24] while allowing for 10% (360-440 μg/L) and 25% (300-500 μg/L) variation in the population-predicted steady-state concentration, respectively.

Results

Population Pharmacokinetic Analysis and Model Evaluation

A 1-compartment model described the available data best. Clearance was best predicted by actual body weight using a power function ($P < .001$; –116 points in OFV). Body weight was also identified as best predictor for volume of distribution ($P < .01$; −9 points in OFV). Because the estimated exponent for volume was close to 1, a linear influence of body weight on volume of distribution was tested for comparison. This led to an equally good fit (+0.2 points in OFV) and was therefore carried forward. No other covariates were found. More details on the covariate analysis can be found in Supplemental Table S1.

Figure 1 shows how clearance was found to change with body weight. The individual post hoc clearance estimates (black dots) are spread evenly around the population value for clearance (black line).

The parameter estimates and their respective bootstrap estimates are provided in Table 2. Figure 2 shows the goodness-of-fit plots of the final model. Model evaluation showed no trends toward a model misspecification and no other remaining trends with respect to time, concentration, and gestational age. An absence
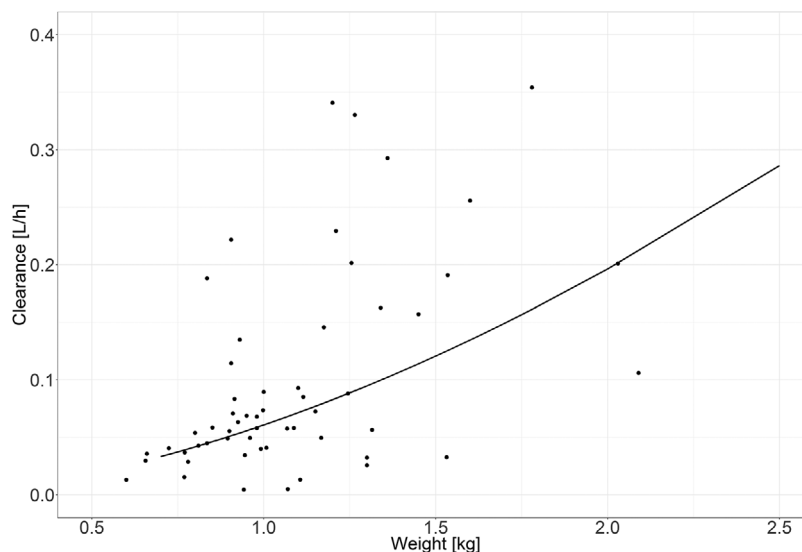
Figure 1. Clearance vs body weight function for the final model: the black line represents the population value for clearance according to the model; the black dots represent the individual post hoc clearance estimates.

Table 2. Parameter Estimates of the Final Model and Their Corresponding Bootstrap Estimates

Parameter	Final Model Estimate (RSE%) [Shrinkage]	Bootstrap Estimate (95%CI)
Fixed effects		
CL [L/h] = CL_p	0.0737 (13%)	0.0787 (0.0550–0.102)
$CL_i = CL_p \times (WT_i/Median\ WT)^{\Theta WT}$		
ΘWT	1.69 (10%)	1.67 (0.406–2.47)
V [L] = V_p		
$V_i = V_p \times (WT_i/Median\ WT)$	1.03 (21%)	1.11 (0.877–1.37)
Interindividual variability (η)		
On CL [%]	91.9 (15%) [8%]	96.6 (67.5–128)
On V [%]	67.2 (16%) [17%]	72.7 (47.4–96.8)
Residual variability		
Proportional (%)	33.8 (16%)	34.0 (28.6–39.4)
Additive (µg/L)	0.218 (56%)	0.283 (0.0800–0.585)

CL indicates clearance; i, individual; p, population mean value of a parameter for an individual with body weight of 1.12 kg; RSE, residual standard error; V, central volume of distribution; WT, actual body weight (median WT = 1.12 kg); ΘWT, exponent for influence of WT on CL .
Bootstrap convergence rate was 83.1%.

of trends in the individual deviation of clearance and volume of distribution (η) versus covariate plots shows that covariates have been successfully implemented (Supplemental Figure S1). The normalized prediction distribution error shows that the variability in the observed data has been adequately described (Supplemental Figure S2).

Evaluation of the Recently Registered Dosing Regimen

Figure 3A illustrates concentration-time profiles of preterm infants with different body weights when dosed according to the new dosing regimen (0.03 mg/[kg·h] for 72 hours). The dashed line represents a target concentration of 400 µg/L. The plots show that midazolam plasma concentrations in children with lower body weights are higher than those of children with higher body weights (Figure 3A). Seventy-two hours after start of therapy the mean concentration was predicted to be 754 µg/L, 421 µg/L, and 262 µg/L for preterm infants with body weights of 0.5, 1.25, and 2.5 kg, respectively. At this time point 27.8%, 10.6%, and 5.4% of the individual simulated concentrations were above 1000 µg/L, and 5.7%, 19.6%, and 37.6% were below 200 µg/L, for a preterm infant weighing 0.5 kg, 1.25 kg, and 2.5 kg, respectively. This added up to a total of 11.6% and 23.2% of all simulated concentrations above 1000 µg/L and below 200 µg/L, respectively, from all simulations. Moreover, the time to reach steady state differed for different body weights. Whereas steady state is reached after 24 hours in neonates weighing 2 kg or more, it takes more than 48 hours in children weighing 1 kg or less and between 24 and 48 hours in children between 1 and 2 kg (Figure 3A).

The model predicts that a median steady-state concentration of 400 µg/L (±10%) can be achieved by reducing the dose by 50% from 0.03 mg/(kg·h) to 0.015 mg/(kg·h) in preterm neonates weighing 0.5 kg, by 33% to 0.02 mg/(kg·h) in neonates weighing 0.75 kg, and to 0.024 mg/(kg·h) in neonates weighing 1 kg (Figure 3B). For preterm infants with a body weight of 1.25 kg or 1.5 kg, the proposed dose would be adequate. In preterm infants with a body weight of 1.75 kg, a dose increase of 20% (0.036 mg/kg) was suitable, whereas in neonates weighing 2 to 2.25 kg the dose had to be increased by 33% (0.04 mg/[kg·h]) and by
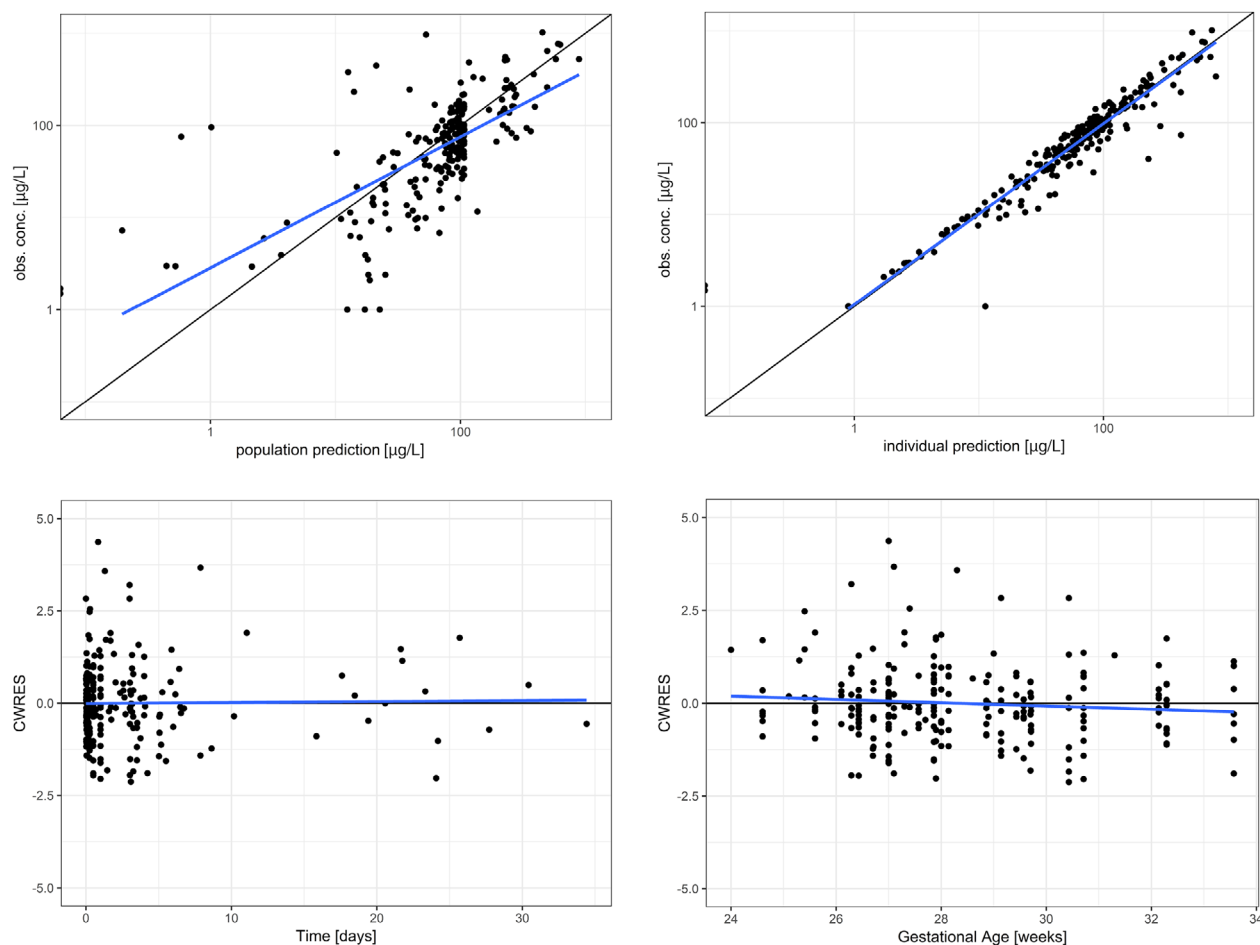
Figure 2. Goodness-of-fit plots for the final model. Top, population-predicted (left) and individual predicted (right) concentrations vs observed values on a log scale. Bottom, conditional weighted residuals (CWRES) vs time on study (left) and gestational age (right).

50% in a child weighing 2.5 kg (Figure 3B). If one would consider a target range between 300 µg/L and 500 µg/L (400 µg/L ± 25%) as adequate, a dose of 0.03 mg/(kg·h) would be adequate in neonates between 1 and 2 kg. This dose would have to be reduced by one third (0.02 mg/[kg·h]) in children below 1 kg and increased by one third in children weighing more than 2 kg and less or equal to 2.5 kg (0.04 mg/[kg·h], data not shown).

Discussion

In this study we successfully developed a population pharmacokinetic model for midazolam in preterm neonates with a gestational age of 24-33 weeks on the basis of previously published data[19] and newly available data from the prospective multicenter DINO study. The results of this study show that clearance nonlinearly increases with body weight (Figure 1), whereas central volume of distribution linearly increases with body weight (Table 2). Only due to the utilization of data from different sources was it possible to develop a population pharmacokinetic model of this drug.

Although the data of de Wildt et al were very densely sampled, they only contained data on 1 intravenous bolus administration per patient.[19] The DINO data made use of sparse opportunistic sampling, which allowed for the collection of the most informative data while putting the least burden on this vulnerable population. This practice resulted in a very low number of observations per administration, but patients were followed over a long period of time (up to 30 days) and received intravenous bolus administrations, continuous intravenous infusions, or both (Table 1). The combined data set thus contains sufficient information to describe the whole postnatal and gestational age range of preterm neonates, which can support identifying maturational processes and eventually aids dose finding.

So far, to our knowledge, only 2 population pharmacokinetic models including preterm neonates have been published. In 1994 Burtin et al[10] studied 187 critically ill neonates with a gestational age of 26 to 42 weeks, a birth weight of 700 to 5200 g and a postnatal age of 0 to 10 days and found that clearance and
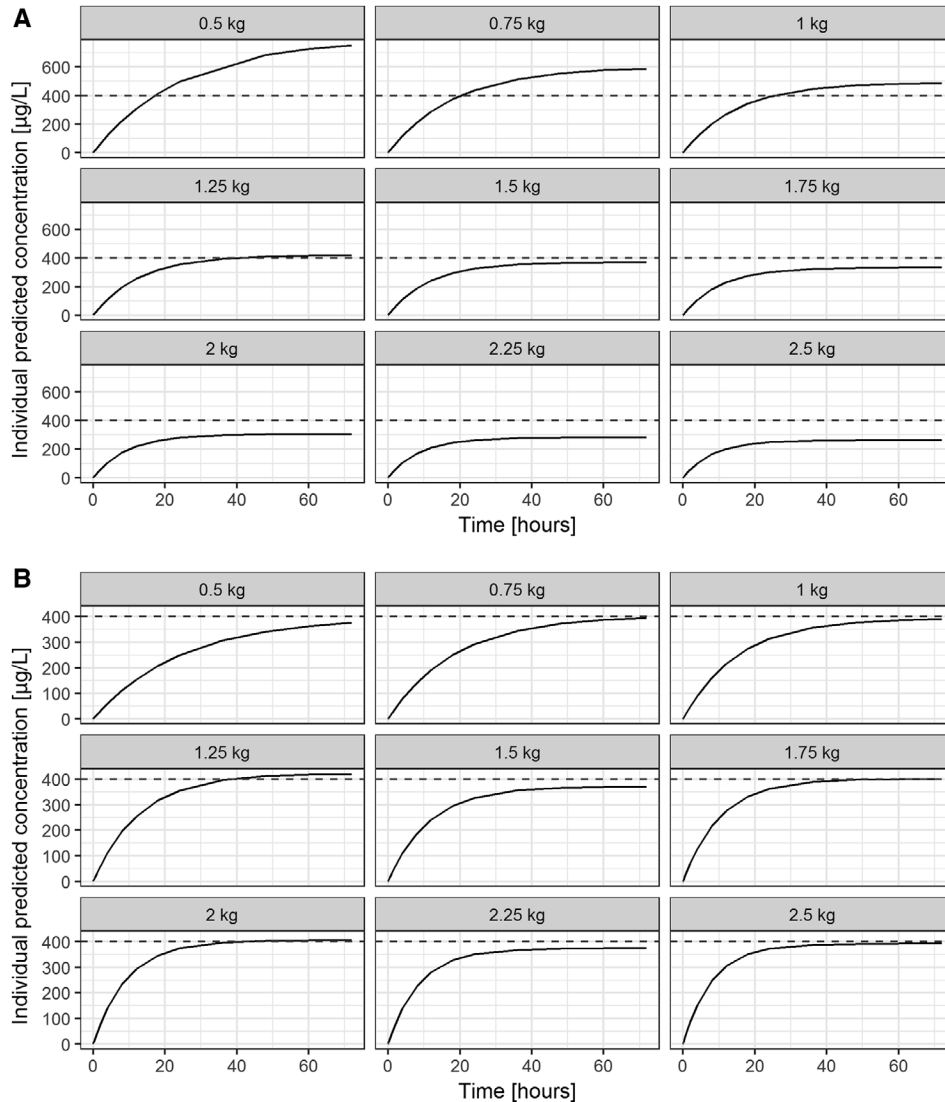
Figure 3. Population-predicted midazolam concentration-time profiles over 72 hours for preterm infants with body weights of 0.5 kg, 0.75 kg, 1 kg, 1.25 kg, 1.5 kg, 1.75 kg, 2 kg, 2.25 kg, and 2.5 kg; dashed lines represent indicative target concentration proposed by Ahsman et al[24] for (A) a dose of 0.03 mg/(kg·h) according to the current label and (B) an adjusted dosing regimen to reach a concentration of 400 μg/L at 72 hours postdose.

volume of distribution were directly proportional to birth weight. They also found a categorical influence of gestational age, with children with a gestational age of 39 weeks or older having 1.6 times higher clearance values. In our analysis we did not find an additional influence of gestational or postnatal age after body weight was implemented, which may be explained by the correlation between age and weight and the fact that the range in gestational age was low in our data set. In 1999 Lee et al[11] analyzed data of 60 mechanically ventilated preterm neonates with a gestational age of 24 to 31 weeks, a birth weight of 523 to 1470 g, and a postnatal age of 2 to 15 days. They found that clearance and volume of distribution were significantly lower in infants with a birth weight below 1 kg. We compared the 2 clearance × weight functions described

in these publications with the function that we identified (Figure 4). Because the data of Burtin et al[10] mainly included infants during the first week of life and the population of Lee et al had a median postnatal age of 4.5 days,[11] we assumed that the current body weight was approximately equal to birth weight, as preterm infants do not gain weight during the first 10 days of life.[25] This made us able to depict all clearance maturation functions in 1 figure, which shows that the estimates of previous population pharmacokinetic studies were in close agreement with our results. This is also true for the clearance estimate in the original publication of the de Wildt data, which was obtained using standard noncompartmental techniques.[19] On the basis of these results and the successful model evaluation, the developed model is suitable for the data
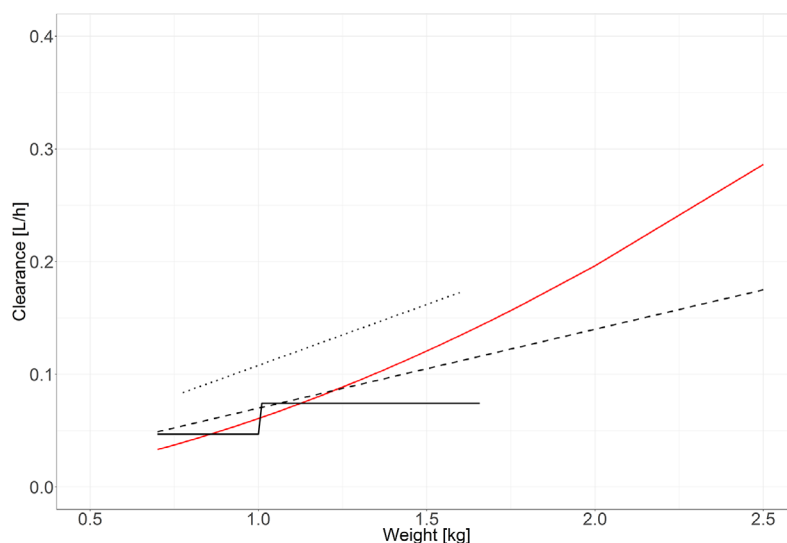
Figure 4. Comparison of clearance vs weight of the current analysis with literature; the red line represents the function of the current model; the solid black line represents the clearance estimates of Lee et al[11]; the dotted line represents the clearance estimates of de Wildt et al[19]; the dashed line represents the clearance estimates of Burtin et al.[10] All estimates are displayed for the population ranges included in the respective studies only.

used (Table 2, Figure 2, Supplemental Figure S1) but should also be suitable to describe intravenous data from other preterm neonatal populations. The fact that body weight and not gestational age or birth weight was the best covariate to describe the data in our model is most likely related to the broader range in postnatal age and the longer observation period, resulting in body weight undergoing significant changes over time. With the low postnatal age range in the 2 previous studies,[10,11] it might have been difficult to detect an influence of postnatal maturation. Previous studies in older children have shown that clearance might be lower in children with systemic inflammation.[16,17] Because the data set of de Wildt et al did not contain information on inflammation, and C-reactive protein values have been infrequently sampled in the DINO population,[19] we were not able to test this covariate, but it seems possible that it might be able to explain some of the high interindividual variability in clearance.

One of the major advantages of population pharmacokinetic modeling is that it offers the possibility of performing simulations based on the developed model.[26] In this case we were able to review the recently proposed dosage advice for midazolam in preterm neonates. Our results show that when 1 fixed body weight–based dose is used for all preterm neonates up to 32 weeks of gestation, and another for preterm neonates above 32 weeks of gestation, steady-state concentrations differ considerably. The steady-state concentration after a 72-hour infusion of 0.03 mg/(kg·h) was nearly 3 times as high for a child of 0.5 kg when compared with a child weighing 2.5 kg (754 vs 262 µg/L). Moreover, when performing our analysis, we were faced with the problem of defining the cutoff between the dosage advised below 32 weeks

and that for above 32 weeks. We could not determine for how long after birth the dosage advice should be applicable. For example, if a child is born at 30 weeks of gestation and weighs 1.5 kg, should the dosage be changed from 0.03 mg/(kg·h) to 0.06 mg/(kg·h) if the child is 2 weeks old (postmenstrual age 32 weeks) and weighs 1.8 kg. Our developed model would not support such a sharp cutoff, because clearance increases gradually with body weight (Figure 3A). Also, the newly registered dosage does not give advice on suitable loading doses. With regard to the considerably long and weight-dependent time to reach steady state, this seems desirable (Figure 3A).

No target concentration for the use of midazolam in preterm neonates has been defined as quantifying the relationship between plasma concentration and sedative effect. One publication related COMFORT scores to midazolam concentrations but did not find a significant correlation. In addition, the authors concluded that comedication might be of considerable influence to this relationship.[18] Nevertheless, different authors have attempted to define indicative target concentrations. Jacqz-Aigrain et al[4] calculated their midazolam doses to obtain plasma concentrations between 200 and 1000 µg/L but without directly relating this target range to a specific effect. Although substantial variability was observed, only 2 of 46 infants with a gestational age of less than 32 weeks had a value above 1000 µg/L, and none had a value below 200 µg/L. The dosing schedule they used in this study was 0.06 mg/(kg·h) during the first 24 hours in all neonates and a dose reduction to 0.03 mg/(kg·h) from 24 hours onward in neonates younger than 33 weeks. Again, no correlation between sedation score and midazolam concentrations could be

found. Ahsman et al proposed a target concentration of 400 µg/L for continuous infusions in term neonates because this was the median plasma concentration observed in their study. They did, however, assume that all of the patients included had been successfully titrated to their target sedation.[24] To date, no clear concentration-effect relationship for midazolam can be found; it is difficult to assess the impact of the observed differences. If we can assume a very broad target range of 200-1000 µg/L, 65.2% of the simulated infants treated with the newly registered dosing regimen would be within this therapeutic window. Part of the reason for the rather large proportion of treated infants outside the therapeutic window is the large interindividual variability observed in the studied population, which has also been observed in the 2 other population pharmacokinetic models developed up to now.[10,11] This large unexplained interindividual variability may partly be caused by the use of 2 assays for quantification of midazolam and the limited (additional) covariate data available in our study, which did not enable us to study potentially interesting factors such as interacting comedication, ethnicity, severity of disease, and inflammation. Inflammation and disease severity have been reported to affect midazolam elimination in critically ill neonates and children[16,17] and thus may explain some of the variability. However, because the data set of de Wildt et al did not contain information on inflammation, and because C-reactive peptide values have been infrequently sampled in the DINO population,[19] we were not able to test this covariate. Physiologically based PK modeling, which can incorporate variation in CYP3A4 activity as a function of maturation or inflammation, can be used for simulations of the consequences of these variables. This approach has been used in pediatric PK assessments, including midazolam.[27]

When aiming for a comparable exposure in all preterm infants, the dosage of 0.03 mg/kg/h would have to be reduced in children weighing 1 kg or less and would have to be increased in children weighing 1.75 kg or more (Figure 3B). For a median child born at 33 weeks of gestation weighing around 2 kg,[28] we would recommend an increase in dose by 33%, thus to 0.04 mg/kg/h and not to 0.06 mg/kg/h. The proposed dosing regimen could not be evaluated beyond a gestational age of 34 weeks because the population did not include individuals above that gestational age.

Conclusion

In conclusion, the newly registered dosage advice does not lead to uniform exposure in preterm infants resulting in considerable differences in typical steady-state concentrations and time to reach steady-state. The impact of this is difficult to assess, as no target concentrations have yet been defined for midazolam, but the current analysis shows that one should be cautious in giving dosage advice based on historical data with a lack of reliable pharmacokinetic and effect data.

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Declaration of Conflict of Interest

All authors have no conflicts of interest to declare.

Data Accessibility Statement

The final data set and the accompanying code are available on request.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.