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The impact of obesity on the pharmacokinetics of drugs in adolescents and adults

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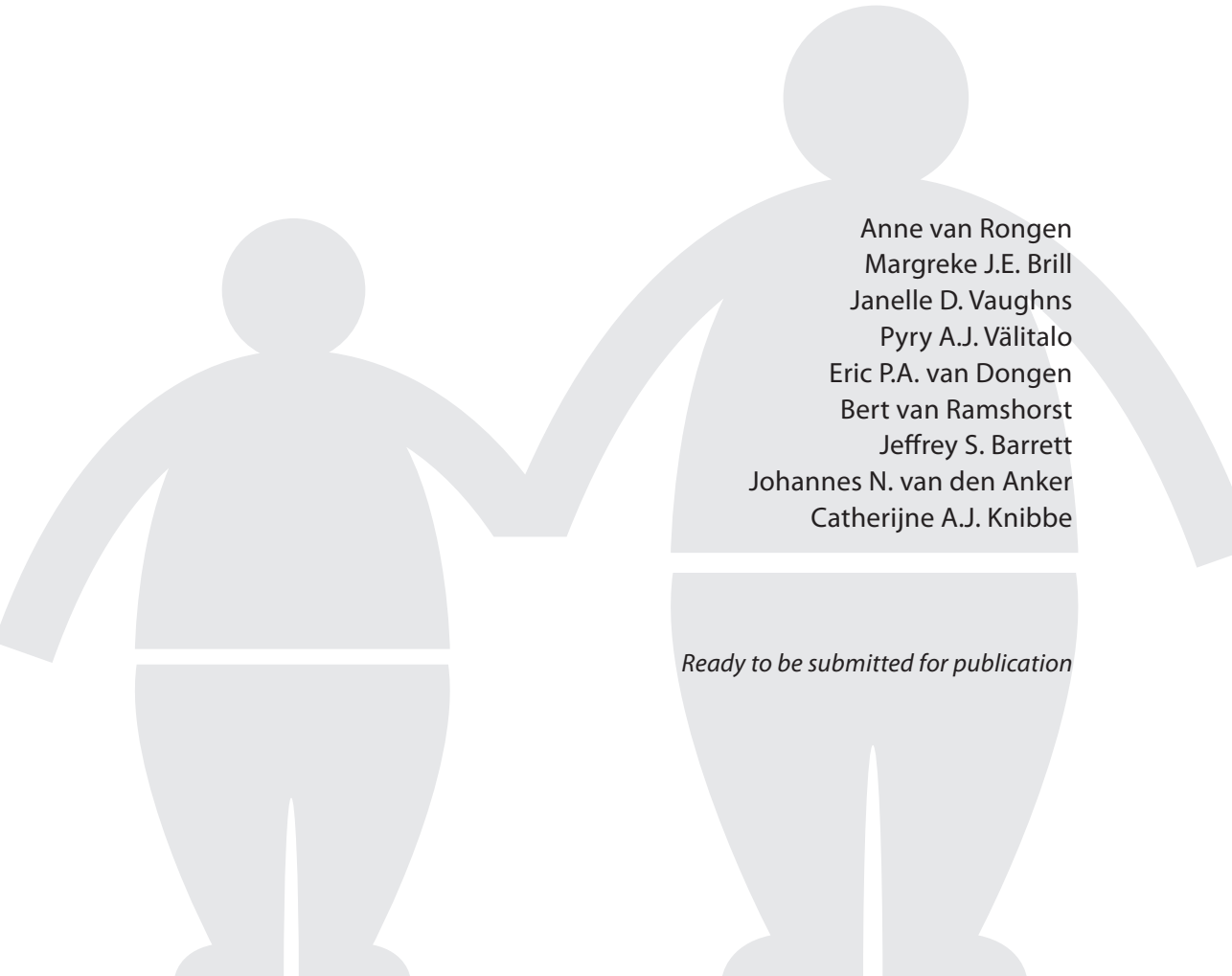
Chapter 9

Higher midazolam clearance in obese adolescents compared to morbidly obese adults



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ABSTRACT

The clearance of CYP3A substrates is known to be reduced with lower age, inflammation and obesity. In a combined study in obese adolescents (15.9 [12.5-18.9] years; 102.7 [62-149.5] kg) and morbidly obese adults (43.6 [26-57] years; 144 [112-186] kg), midazolam clearance was higher in obese adolescents than in obese adults (0.71 [7%] vs 0.44 [11%] L/min, $P < 0.01$). Moreover, in obese adolescents clearance increased mainly with WT_{excess} (= TBW- $WT_{for\ age\ and\ length}$) for which a novel modelling approach was proposed with 0.75 allometric scaling on the basis of $WT_{for\ age\ and\ length}$ and a separate function for WT_{excess}. We hypothesize that the higher midazolam clearance in obese adolescents is explained by less obesity-induced suppression of CYP3A activity, and the increase with WT_{excess} explained by increased liver flow. The approach characterizing the influence of obesity in the paediatric population may be of value for use in future studies in obese adolescents.

INTRODUCTION

CYP3A is an important enzyme system, responsible for the primary metabolism of 25% of all clinically used drugs [1]. This enzyme system is known to vary with age, inflammation and obesity [2-6]. Its activity is reported to be low at birth and reaches adult values in the first years of life [6,7], after which the size of the liver and/or liver flow determines the increase in CYP3A clearance. Recently, a study on midazolam, a well-known probe for CYP3A [8,9], showed that this system is also highly influenced by inflammation and sepsis in children [4]. In obesity, which may be seen as a chronic state of inflammation, reduced CYP3A protein expression or CYP3A activity has been reported in vitro and obese mice studies [10-13]. Moreover, in humans, reduced oral clearance of midazolam in obese subjects compared to non-obese subjects was reported for various CYP3A substrates [3], even though no difference in midazolam clearance in obese vs. non-obese individuals was found [14]. Yet, a 1.7 fold increase in midazolam clearance in patients one year after bariatric surgery was reported, indicating a reduced CYP3A hepatic activity in these morbidly obese individuals before their weight loss surgery [15-17].

An important question is how the CYP3A system is influenced by both age and obesity, particularly in view of the increasing prevalence of obesity in both adults and children [18]. Allometric scaling on the basis of body weight with an exponent of 0.75 is often used to describe the finding that clearance in children is generally lower than in adults [19-21]. Especially for adolescents there is agreement on this approach. The US Food and Drug Administration (FDA) already proposed in 2012 that allometric scaling based on adult data, without the use of a dedicated pharmacokinetic study, is a reasonable approach for scaling to adolescents [22]. However, given the increase in body weights of both adults and children that is observed today as a result of the obesity epidemic [18], this approach that uses body weight as a proxy for size, may be questionable in obese individuals.

A combined (covariate) analysis of data from both obese adolescents and obese adults may give an appropriate answer to this question. In this analysis, total body weight can be considered the sum of body weight related to development ($WT_{for\ age\ and\ length}$) and excess body weight related to obesity (WT_{excess}), with potentially a different influence of these types of weight on a specific pharmacokinetic parameter [23]. While for body weight related to size ($WT_{for\ age\ and\ length}$), 0.75 allometric scaling may be applied, WT_{excess} may or may not have an impact. For instance for some drugs, adult clearance is known to vary with obesity while this is not the case for others [3]. Moreover, even when obese adolescents have the same body weight as obese adults, the (patho)physiologic changes associated with obesity, for instance inflammation [24,25], exist for a shorter time, thereby potentially altering their influence.

In this report we aim to study the clearance of the CYP3A substrate midazolam in obese adolescents and morbidly obese adults in a combined analysis. Moreover, we

explore a model that can be used to consider obesity in the paediatric population, given the obesity epidemic we are currently facing.

METHODS

Patients

Model building was based on data from 19 adolescents [26] and 20 adults [14]. The study in obese adolescents was conducted at Children's National Health System (Washington DC, USA) (IRB protocol no 4718) and considered 3 overweight (BMI for age 85th to ≤ 95th percentile) and 16 obese (BMI for age ≥ 95th percentile) adolescents between 12 and 18 years of age undergoing general surgery (such as orthopaedics, tonsillectomy, bariatric surgery) [26]. The study in the morbidly obese adults (BMI > 40 kg/m^2) undergoing bariatric surgery was conducted at St. Antonius Hospital (Nieuwegein, the Netherlands) (VCMO NL35861.100.11, EudraCT 2011-003293-93) [14]. Both studies were conducted in accordance with the principles of the Declaration of Helsinki. Patient characteristics of both studies are summarized in Table 1.

Study procedure for obese adolescents

Obese adolescents received a single intravenous dose of 2 or 3 mg a few minutes before they were taken to the operating room. Blood samples were collected at T=0, (5), 15, 30 min and 1, 2, 4, 6 and occasionally at 8 h. More information on the study procedure can be found in the published paper [26].

Study procedure for morbidly obese adult patients

Morbidly obese adults received 7.5 mg of midazolam orally followed by 5 mg of intravenous midazolam at induction of anaesthesia (159 ± 67 min after the oral dose). Blood samples were collected at T=0, 5, 15, 30, 45, 55, 65, 75, 90, 120, and 150 min after the oral dose and T=5, 15, 30, 90, 120, 150, 180, 210, 270, 330, 390, and 510 min after the intravenous dose. More information on the study procedure can be found in the published paper [14].

Population pharmacokinetic analysis and internal model validation

All data were analysed using non-linear mixed effects modelling with NONMEM version 7.2 (ICON Development Solutions, Hanover, MD, USA) [27]. Pirana (2.9.1) [28], R (3.0.1) [29], Xpose (4.5.0) [28] and Psn (3.6.2) [28] were used to evaluate and visualize the data. Of the 129 midazolam plasma samples of obese adolescents, no observations were below the LOQ (0.5 ng/mL) [26]. Of the total of 434 samples from the morbidly obese adults, 33 values (7.6%) were below the LOD and removed from the analysis. Midazolam

plasma concentrations between the limit of quantification (LOQ) (LOQ < 0.8 ng/mL) and limit of detection (LOD) (< 0.3 ng/mL) [14] were kept in the analysis (n=9). The first order conditional estimation method with interaction was used for model development. Discrimination between different models was guided by Likelihood Ratio Test comparing the objective function value (OFV, i.e. -2 log likelihood (-2LL)) between nested models. A *P* value of < 0.05, representing a decrease of 3.84 in OFV for one degree of freedom, was considered statistically significant. In addition, goodness-of-fit plots (observed vs. individual-predicted concentrations, observed vs. population-predicted concentrations, conditional weighted residuals vs. time after dose, and conditional weighted residuals vs. population-predicted concentrations plots) upon midazolam in morbidly obese adults and obese adolescents were used for diagnostic purposes. Furthermore, precision of parameter estimates, the correlation matrix and visual improvement in the individual plots were used to evaluate the model. Pharmacokinetic models incorporating two or three compartments for midazolam were tested. The oral data of the morbidly obese adults were described by optimization of a five transit absorption compartment model, in which the transit compartment rate constant (Ktr) was equalized to the oral absorption rate constant (Ka) [14]. Interindividual variability (IIV) was assumed to follow a log normal distribution. Residual variability was tested using proportional, additive or a combined proportional and additive error models. For internal model evaluation, a stratified bootstrap resampling method using 1000 replicates and normalized prediction distribution errors (NPDE) using 1000 simulations were used.

Covariate analysis

Primarily tested covariates were study population, total body weight (TBW), BMI, lean body weight (LBW) according to the equation of Janmahasatian et al. [30], age, race and gender. Covariates were plotted independently against the eta (η) estimates of the pharmacokinetic parameters to visualize potential relations. Continuous covariates were tested using linear and power equations (Equation 1 and 2):

$$P_i = P_p \times (1 + Y \times (COV - COV_{median})) \quad \text{(Eq. 1)}$$

$$P_i = P_p \times (COV/COV_{median})^X \quad \text{(Eq. 2)}$$

where P_i and P_p represent individual and population parameter estimates, respectively, *COV* represents the covariate, COV_{median} represents the median value of the covariate for the population, *Y* represents the linear relationship between the population pharmacokinetic parameter and the change in covariate value for a linear function and *X* represents the exponent for a power function. The categorical covariates gender and

study population were examined by estimating a separate parameter for each category of the covariate.

Potential covariates were entered into the model one at a time and statistically tested by the Likelihood Ratio Test. In addition, if applicable, reduction in interindividual variability (IIV, omega (ω)) of the parameter was evaluated upon inclusion of the covariate on the parameter. Further, trends in the random effects of the parameter vs. the covariate involved were observed. After forward inclusion ($P < 0.01$), a backward exclusion procedure was applied to justify the inclusion of a covariate ($P < 0.001$). The choice of the covariate model was further evaluated as discussed in the Population pharmacokinetic analysis and internal model validation section.

Excess weight covariate model

To further analyse the influence of excess weight on the pharmacokinetics of midazolam for the obese adolescents, an excess weight covariate model was tested for the parameters for which total body weight proved a covariate, as described under Covariate analysis.

In this model, the total body weight of obese adolescents was considered to be composed of two parts: developmental weight ($WT_{\text{for age and length}}$) and excess body weight (WT_{excess}) [26]. For each individual adolescent of the study $WT_{\text{for age and length}}$, WT_{excess} and relative WT_{excess} ($\%WT_{excess}$) were calculated using Equation 3, 4 and 5 respectively:

$$WT_{\text{for age and length}} = BMI_{\text{without overweight}} \times \text{length}^2 \quad \text{(Eq. 3)}$$

$$WT_{excess} = TBW - WT_{\text{for age and length}} \quad \text{(Eq. 4)}$$

$$\%WT_{excess} = (WT_{excess} / WT_{\text{for age and length}}) \times 100\% \quad \text{(Eq. 5)}$$

in which $BMI_{\text{without overweight}}$ is the BMI derived from the BMI- for-age CDC growth chart (gender specific) at a BMI z score of 0 together with the age of the patient [31] and TBW is the total body weight of the patient.

First, $WT_{\text{for age and length}}$, WT_{excess} and $\%WT_{excess}$ were plotted independently against the eta estimate for clearance to visualize the relation. Then, the impact of $WT_{\text{for age and length}}$ and WT_{excess} on clearance in adolescents was evaluated using Equations 6 and 7:

$$CL_{\text{non-obese adolescent}} = CL_{\text{non-obese adults}} \times (WT_{\text{for age and length}} / 70)^{0.75} \quad \text{(Eq. 6)}$$

$$CL_{\text{(obese) adolescent}} = CL_{\text{non-obese adolescent}} + (Z \times WT_{excess}) \quad \text{(Eq. 7)}$$

in which $CL_{non\text{-}obese\ adolescents}$ represents the clearance estimate of adolescents without overweight with $CL_{non\text{-}obese\ adults}$ representing the population clearance of non-obese adults [14], $WT_{for\ age\ and\ length}$ representing developmental weight and 0.75 being the scaling factor that was previously proposed by the US FDA for scaling clearance in (non-obese) adolescents [22]. $CL_{(obese)\ adolescent}$ represents the individual clearance estimates of (obese) adolescents; *Z* represents the linear relationship between clearance estimates of adolescents without overweight ($CL_{non\text{-}obese\ adolescent}$) and the change in clearance with WT_{excess}.

RESULTS

Patients and data

The pharmacokinetic analysis with NONMEM 7.2 was based on data from 19 obese adolescents [26] and 20 morbidly obese adults (BMI > 40 kg/m^2) [14] and consisted in total of 530 observations. A summary of all patient characteristics is presented in Table 1.

Table 1 Demographic parameters of 19 obese adolescents [26] and 20 morbidly obese adults[14].

	Overweight and obese adolescents (n=19)	**Morbidly obese adults (n=20)**
Female/male	13/6	12/8
Overweight/obese [a]	3/16	-
Age (years)	15.9 ± 1.6 (12.5-18.9)	43.6 ± 7.6 (26-57)
Body weight (kg)	102.7 ± 24.9 (62-149.8)	144.4 ± 21.7 (112.3-186.3)
BMI (kg/m^2)	36.1 ± 8.1 (24.8-55)	47.1 ± 6.5 (39.9-67.6)
BMI z-score	2.2 ± 0.4 (1.5-2.7)	-
LBW (kg) [30]	57.3 ± 11.1 (39.8-74.4)	71.5 ± 11.9 (53.4-94.9)
$WT_{for\ (age\ and)\ length}$ (kg)	57.8 ± 7.6 (43-72.3)	-
WT_{excess} (kg)	44.8 ± 21.9 (14.6-92)	70.6 ± 18.9 (45.6-113.4)
$\%WT_{excess}$ (%)	77.4 ± 37.1 (30.8-159.1)	95.8 ± 25.6 (65.2-171.4)

Values are expressed as mean ± standard deviation (range) unless specified otherwise
BMI=body mass index, LBW= lean body weight
[a] Overweight is defined as BMI for age 85th to ≤ 95th percentile and obesity as BMI for age ≥ 95th percentile.

Population pharmacokinetic model and internal model evaluation

Based on the data, a two compartment model was identified, in which study population proved a significant covariate for clearance. Figure 1 shows that midazolam clearance in obese adolescents was significantly higher compared to morbidly obese adults (objective function value (OFV), ΔOFV -8.0, $P < 0.01$). Moreover, in obese adolescents midazolam clearance increased significantly with total body weight (TBW) (ΔOFV -10.6, $P < 0.01$). As a third covariate, the peripheral volume of distribution of morbidly obese

adults increased significantly with TBW in a non-linear manner (ΔOFV -10.9, $P < 0.001$). All three covariates fulfilled the criteria of the backward analysis ($P < 0.001$). No significant trend was found for TBW and clearance in the morbidly obese adult patients, nor for TBW and peripheral volume of distribution of midazolam in the obese adolescents ($P > 0.05$). No other covariates (age, BMI, lean body weight (LBW) [30], race and gender) had a significant influence on any of the pharmacokinetic parameters ($P > 0.05$). The model parameters of the base model without covariates and the final covariate model are summarized in Table 2. Observed vs. individual predicted concentrations and observed vs. population predicted concentrations for midazolam in morbidly obese adults and obese adolescents are shown in Figure 2. The final model was validated by 1000 bootstrap runs, which were successful in 93% of the runs and confirmed the parameter values (Table 2). In addition, a NPDE analysis was performed showing no trends or bias for the two populations (Supplementary Figure 1).

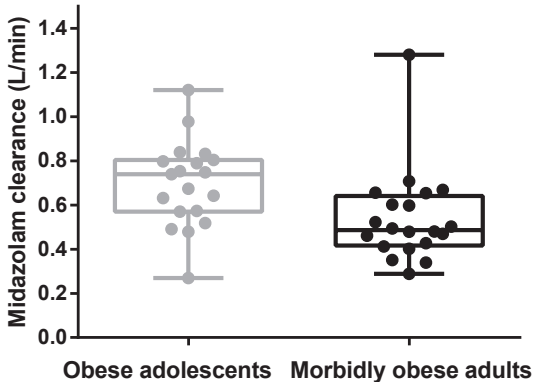

Figure 1 Empirical Bayes estimates (EBEs) of midazolam clearance for obese adolescents (grey) and morbidly obese adults (black) of the base model.

To further analyse the influence of excess weight in obese adolescents, in Figure 3, clearance in obese adolescents is plotted against developmental weight ($WT_{for\ age\ and\ length}$) and excess body weight ($WT_{excess,}$ and $\%WT_{excess}$). In this analysis, $WT_{for\ age\ and\ length}$ was calculated by $WT_{for\ age\ and\ length} = BMI_{without\ overweight} \times length^2$, while WT_{excess} was calculated by WT_{excess} =TBW- $WT_{for\ age\ and\ length}$. Figure 3 shows no obvious trend between $WT_{for\ age\ and\ length}$ and midazolam clearance in obese adolescents, while a positive trend was observed between WT_{excess} or $\%WT_{excess}$ and midazolam clearance (ΔOFV -8.5 and -5.7, $P < 0.01$ and $P < 0.05$, respectively). To capture the potential contribution of these different weight measures in obese adolescents, we propose an excess weight covariate model (Equations 6 and 7, Methods section), in which $WT_{for\ age\ and\ length}$ was scaled on the basis of 70 kg to the power of 0.75 (Equation 6) [22], while for the influence of WT_{excess} a separate function was estimated (Equation 7). Figure 4 shows the results of this excess weight model in which the final covariate model for clearance in obese adolescents (Table 2) was replaced by the excess weight covariate model. This figure illustrates that

using this approach $WT_{for\ age\ and\ length}$ scales allometrically to the power of 0.75 (Equation 6), and that the influence of WT_{excess} was characterized using Equation 7, estimating a Z of 0.00698 (25%), while the other parameters estimates were similar to the final covariate model of Table 2. The excess weight covariate model (Figure 4 and Equations 6 and 7) was as able as the final covariate model (Table 2) to describe the data in terms of OFV (2488.0 vs. 2487.0, $P > 0.05$) and goodness of fit plots.

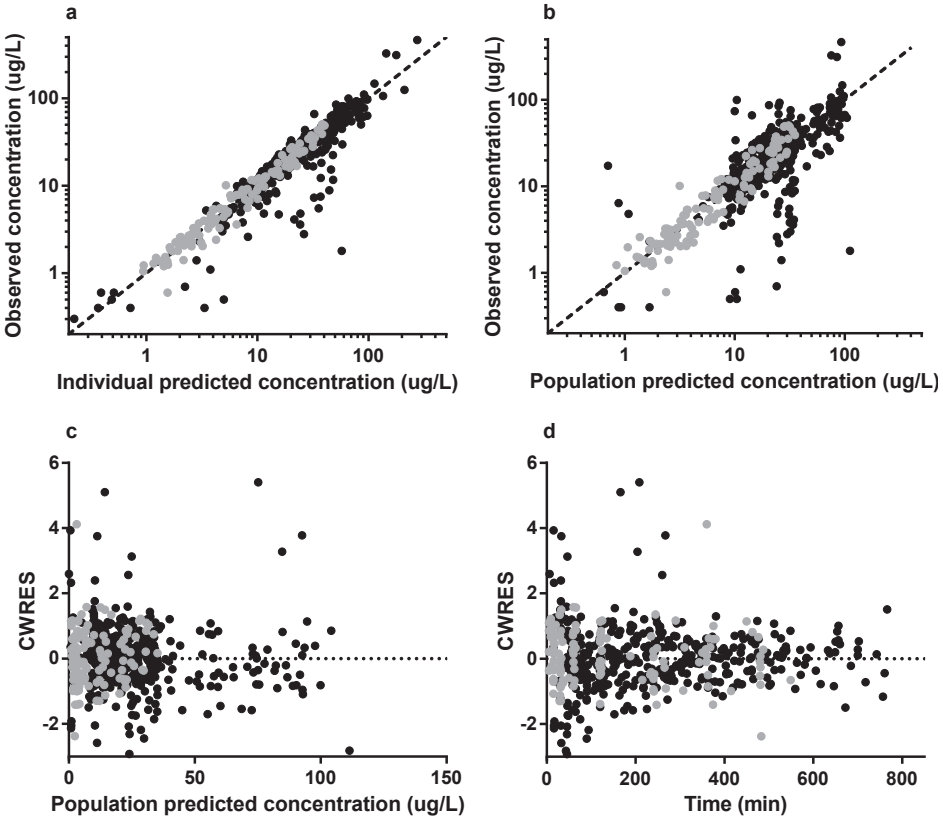

Figure 2 (a) Observed vs. individual predicted concentrations, (b) observed vs. population predicted concentrations, (c) conditional weighted residuals (CWRES) vs. population predicted concentrations and (d) CWRES vs. time of the final pharmacokinetic midazolam model for 19 obese adolescents (grey dots) and 20 morbidly obese adults (black dots).

Table 2 Population pharmacokinetic parameters of the base and final pharmacokinetic model for midazolam in 19 obese adolescents and 20 morbidly obese patients and results of bootstrap analysis of the final model (927/1000 resamples successful).

Parameter	Base model (RSE%)	Final model (RSE%)	Bootstrap (95% confidence interval)
Fixed effects			
CL (L/min)	0.58 (7)	-	
$CL_{obese\ adolescents} = CL_{104.7\ kg} \times (TBW/104.7)^{Y}$			
$CL_{104.7\ kg}$	-	0.71 (7)	0.71 (0.59-0.78)
Y	-	1.2 (31)	1.19 (1.08-1.99)
$CL_{morbidly\ obese\ adults}$ (L/min)	-	0.44 (11)	0.44 (0.33-0.56)
F	0.589 (12)	0.562 (12)	0.563 (0.45-0.74)
Ka = Ktr (min^{-1})	0.114 (11)	0.115 (11)	0.115 (0.09-0.142)
$V_{central}$ (L)	55.4 (11)	55.2 (11)	54.7 (42.2-66.8)
$V_{peripheral}$ (L)	161 (12)	-	
$V_{peripheral\ obese\ adolescents}$ (L)		172 (13)	172.8 (132.9-235.1)
$V_{peripheral\ morbidly\ obese\ adults} = V_{141.8\ kg} \times (TBW/141.8)^{Z}$			
$V_{141.8\ kg}$	-	172 (13)	172.8 (132.9-235.1)
Z	-	3.3 (33)	3.19 (1.08-5.33)
Q (L/min)	1.14 (12)	1.14 (12)	1.14 (0.91-1.47)
Interindivdual variability (%)			
CL	39.9 (14)	21 (26)	17.8 (4.2-33.4)
F	42.9 (23)	39.2 (21)	38.2 (16.7-53.5)
Ka = Ktr	49.2 (17)	49.5 (17)	48.2 (34.9-61.0)
$V_{central}$	62 (11)	58.5 (11)	56.2 (28.1-83.0)
V peripheral	41.9 (20)	42.2 (22)	37.1 (10.7-60.2)
Q	40.9 (17)	42.4 (25)	41.1 (18.7-56.7)
Residual variability (%)			
Proportional error	29.6 (9)	29.7 (9)	29.6 (24.6-35.0)
OFV (-2LL)	2516.6	2487.0	2463.2

CL= clearance of midazolam, F= oral bioavailability, Ka= absorption rate constant, Ktr= transit compartment rate constant, OFV= objective function value, Q=inter-compartmental clearance of midazolam between the central and peripheral compartment, RSE = relative standard error, TBW=total body weight, V= volume of distribution

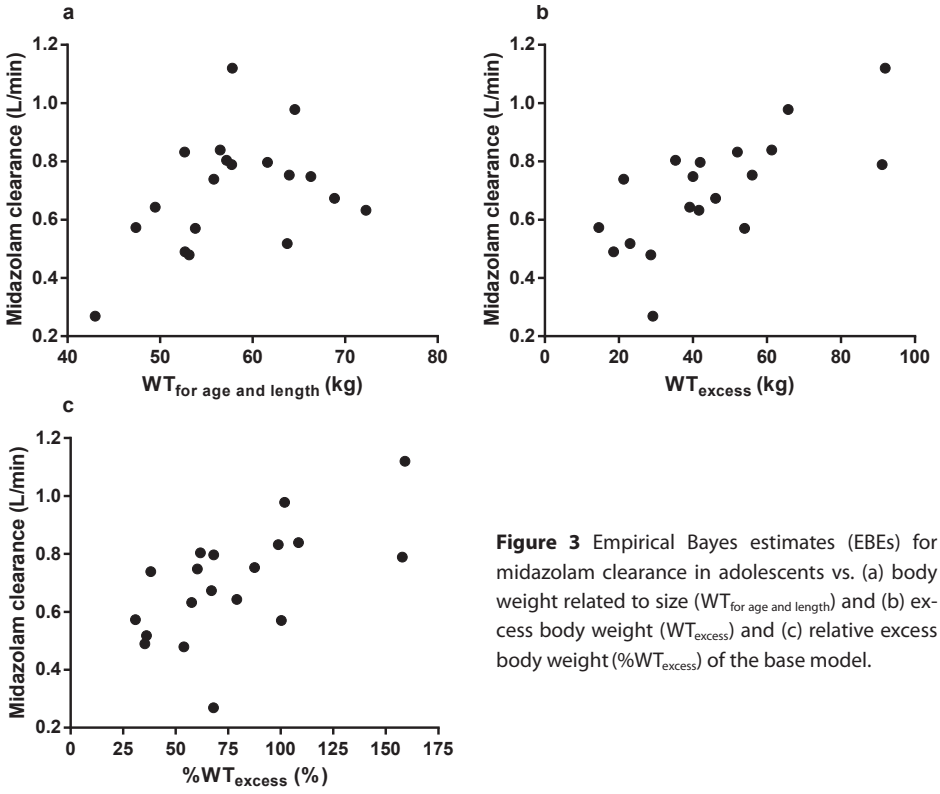

Figure 3 Empirical Bayes estimates (EBEs) for midazolam clearance in adolescents vs. (a) body weight related to size ($WT_{for\ age\ and\ length}$) and (b) excess body weight (WT_{excess}) and (c) relative excess body weight ($\%WT_{excess}$) of the base model.

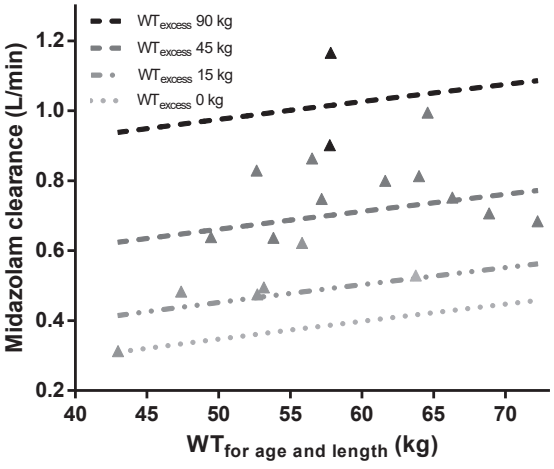

Figure 4 Midazolam clearance (population predicted (line) and Empirical Bayes estimates (triangles)) in obese adolescents vs. $WT_{for\ age\ and\ length}$. Population clearance values of adolescents without overweight ($WT_{excess\ 0\ kg}$, dotted line) is calculated by scaling the clearance of adults on the basis of 70 kg to the power of 0.75 (Equation 6) [22]. Population clearance values of the obese adolescents (WT_{excess} of 15, 45 and 90 kg, dark grey/black lines) are composed of the clearance of adolescents without overweight ($WT_{excess\ 0\ kg}$) supplemented by WT_{excess} of the obese adolescent times Z (Equation 7). Observed individual values of obese adolescents are represented by triangles with grey colours varying according to the degree in WT_{excess}.

DISCUSSION

In this analysis we report on the clearance of the CYP3A substrate midazolam in obese adolescents and morbidly obese adults. Throughout paediatric life, clearance is known to increase for which allometric scaling with an exponent of 0.75 is often used[19-21]. Particularly for adolescents there is hardly any debate on the use of this type of scaling [22]. In obesity, CYP3A activity seems to be suppressed, which was not only supported by in vitro and obese mice studies [10-13], but also by the reported increased CYP3A-mediated midazolam clearance after substantial weight reduction upon bariatric surgery in morbidly obese patients [15-17]. However, an important question is whether these results apply to obese adolescents, particularly in view of the increasing prevalence of obesity in children and adolescents.

This current study shows that obese adolescents have a higher midazolam clearance compared to morbidly obese adults. This finding is unexpected, because adolescents are anticipated to have a lower clearance compared to adults, since they have a lower age and immature physiology. However, the higher clearance in obese adolescents may perhaps not be so unexpected when recent studies on midazolam in morbidly obese patients before and after bariatric surgery are taken into consideration [14,15]. In one study, morbidly obese adults showed no change in clearance compared to non-obese adults [14]. These results are explained by postulating that a higher liver volume and/or liver blood flow will counteract the previously reported lower CYP3A protein expression or activity [10-13] caused by an increased inflammation state [12,24,25,32], ultimately resulting in a similar absolute hepatic CYP3A metabolizing capacity in both groups [14]. This hypothesis was supported by another study, in which the pharmacokinetic study was repeated one year after bariatric surgery in 18 of the 20 patients of the morbidly obese study group, when they had on average lost 44.5 ± 10.2 kg of body weight [15]. Using the exact same study design, the bariatric patients showed a 1.7 higher midazolam clearance compared to the situation before surgery [15] (Figure 5). This increase was anticipated to result from the recovery of obesity-suppressed hepatic CYP3A activity as a consequence of the decreased inflammation status after weight loss from bariatric surgery [15]. A semi-physiologically based pharmacokinetic model (PBPK) including the 1-OH-midazolam metabolite confirmed this finding, where the intrinsic hepatic clearance of midazolam was 1.5 times higher in bariatric patients compared to morbidly obese patients before surgery [16]. As such, our finding of a higher total midazolam plasma clearance in obese adolescents compared to morbidly obese adults, can in our opinion be explained by the hypothesis that the CYP3A activity in obese adolescents is not (yet) suppressed to the same extent as morbidly obese adults. Perhaps the duration of (morbid) obesity and thereby the inflammatory status that goes with obesity, is of influence on the final CYP3A activity in the liver.

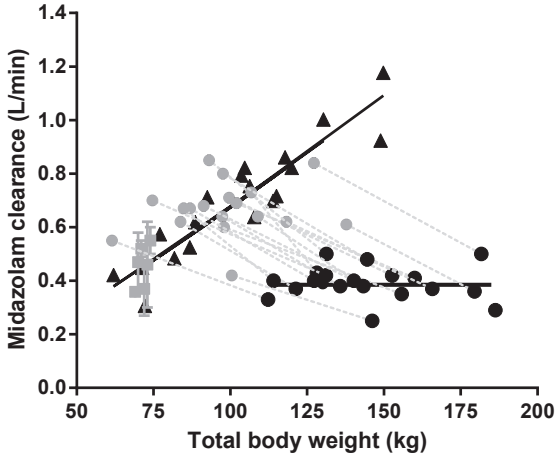

Figure 5 Empirical Bayes estimates of midazolam clearance of 19 obese adolescents (black triangles) and 20 morbidly obese patients (black dots) and population mean estimates (black lines) of the final pharmacokinetic model vs. body weight. Values reported for 18 of the 20 morbidly obese patients one year after bariatric surgery [15] (grey dots, with dotted lines for corresponding values of these individuals at bariatric surgery) and in healthy volunteers studies (grey squares) [14,33-39] are added for comparison. Adapted from Brill et al. [15] with permission.

The results of this study also show that the midazolam clearance in obese adolescents seems even higher than in healthy non-obese volunteers (Figure 5) [14]. Based on this finding, it is hypothesized that obese adolescents have – besides the (yet) unaffected CYP3A activity – an increased liver size or increased liver blood flow and/or perfusion like morbidly obese adults [16,40,41]. This is further substantiated by the result that within the obese adolescent population, midazolam clearance increases with total body weight (Figure 5), which was mainly explained by excess body weight (WT_{excess}) instead of developmental weight ($WT_{for\ age\ and\ length}$) (Figure 3 and 4). Concerning the increase in liver blood flow with body weight in obese adolescents, there is some evidence from a study on propofol, which is a high extraction ratio drug of which the clearance is mainly defined by liver blood flow [42]. In this study, propofol clearance was found to increase with body weight in (morbidly) obese adolescents indicating an increase in liver blood flow in this population. This would point at a combination of an increase in liver blood flow and unaffected CYP3A activity being responsible for the elevated midazolam clearance in obese adolescents.

When analysing pharmacokinetic data in obese adolescents, it is important to be able to distinguish between the influence of body weight resulting from development or size and from obesity on the pharmacokinetic parameters [23]. Particularly because the numbers of obese individuals are increasing also in the paediatric population complicating scaling on the basis of body weight. Previously, a model was proposed evaluating busulfan pharmacokinetics in under-, normal and overweight children, adolescents and adults (median age of 4 (0.1-35) years) [43] introducing a division of the body weight of each patient into body weight related to growth (body weight-for-age, $BW_{for\ age}$) and body weight related to under/overweight (body weight Z score, $BW_{z\ score}$) with separate functions for each of these weights. This exploratory model showed that both $BW_{for\ age}$ and $BW_{z\ score}$ influenced busulfan clearance, each in their own way [43]. For the analysis of midazolam data in overweight and obese adolescents [26], this exploratory model

was adjusted into the (over)weight covariate model, in which body weight for age and length ($WT_{for\ age\ and\ length}$) was used instead of $BW_{for\ age}$ since the influence of length is more relevant for adolescents. Another approach was reported by Diepstraten et al. who performed a population pharmacokinetic meta-analysis on propofol data from morbidly obese adults, adolescents, children and their non-obese controls (body weight 37-184 kg, age 9-79 years) [44]. In that report, propofol clearance was found to increase with body weight, while age was implemented as a second covariate using a bilinear function [44]. As such, propofol clearance values were found to increase with body weight but were systematically lower in adolescents as compared to adults, which is in contrast with the current results on the CYP3A substrate midazolam for which higher values in obese adolescents were found. The excess weight covariate model we proposed here, may in our opinion provide guidance on how to analyse data in obese adolescents or children in future paediatric studies, as the influence of weight from developmental growth and obesity are separated and the influence of weight excess can theoretically be positive or negative (Equation 7). Such a model is particularly of relevance because the prevalence of obesity is not only increasing in adults but also in children, thereby complicating the analysis of (often scarce) paediatric data even further.

It has been stated before that when dosing information is not available in obese children, data can be extrapolated from obese adults [45-47] as long as practitioners consider the effects of growth and development on the pharmacokinetics relevant to the child's age [46-48]. However, based on our results, we can conclude that data of morbidly obese adults cannot be extrapolated to obese children as the duration of obesity is probably of influence on the (patho)physiological changes upon obesity. Using the excess weight covariate model we propose here, TBW is divided in $WT_{for\ age\ and\ length}$ and WT_{excess} ($TBW = WT_{for\ age\ and\ length} + WT_{excess}$). Clearance for non-obese adolescents is calculated on the basis of 70 kg to the power of 0.75 using clearance values in non-obese adults (Equation 6). While this approach is generally accepted, particularly for adolescents [22], an advantage of this approach is that data from non-obese adolescents are not per se needed even though visual inspection may be useful as we showed in Figure 3a. Then the influence of WT_{excess} on clearance can be separately identified using visual inspection (Figure 3b and c) after which implementation of this covariate in the model can be applied. Using this approach both the influence of size resulting from development/growth (i.e. $WT_{for\ age\ and\ length}$) and size resulting from obesity (WT_{excess}) can be separately studied and accounted for (Figures 3 and 4). It seems that this function needs to be considered when clearance is scaled to adolescents, as the percentage of obesity is still increasing, especially in this age group.

To conclude, this study shows that midazolam clearance is higher in obese adolescents compared to morbidly obese adults. A possible explanation is that the CYP3A activity in obese adolescents is not (yet) suppressed to the same extent as in morbidly obese adults.

As in obese adolescents WT_{excess} was found to substantially influence clearance and their clearance is also higher than that of non-obese adults, it seems that this finding may be the result of an increased liver size, liver blood flow and/or perfusion. From these results it seems that obesity is a significant issue to consider when scaling from adults to adolescents.

CONFLICT OF INTEREST/DISCLOSURE

The authors declare no conflict of interest.

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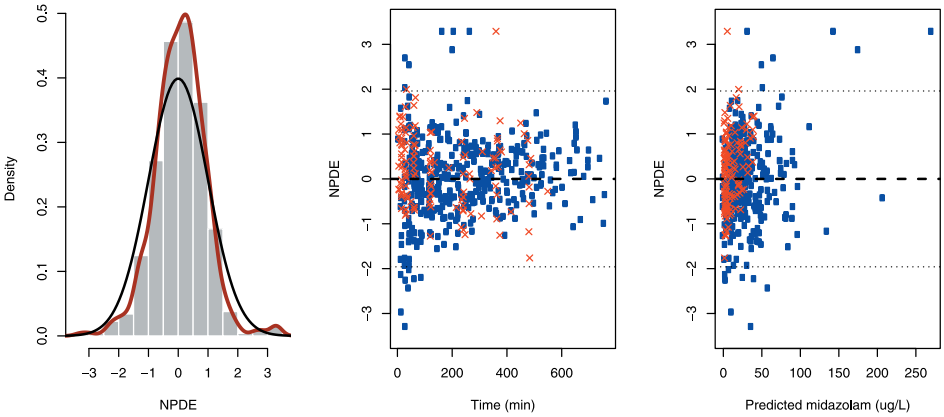
SUPPLEMENTARY MATERIAL



Supplementary Figure 1 Normalized prediction distribution errors plots of the final pharmacokinetic model of midazolam in 19 obese adolescents (red crosses) and 20 morbidly obese adults (blue dots).