Chapter 6

Population pharmacokinetics of paracetamol across the human age-range from (pre)term neonates, infants, children to adults

Chenguang Wang[1,2], Karel Allegaert[3], Dick Tibboel[2], Meindert Danhof[1], Caroline D. van der Marel[4], Ron A.A. Mathot[5], Catherijne A.J. Knibbe[1,6]

(1) Division of Pharmacology, LACDR, Leiden University, Leiden, The Netherlands
(2) Erasmus MC Sophia Children's Hospital, Intensive Care and Department of Paediatric Intensive Care, Rotterdam, The Netherlands
(3) Department of Development and Regeneration, KU Leuven and Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium
(4) Erasmus MC, Department of Anesthesiology, Rotterdam, The Netherlands
(5) Departments of Hospital Pharmacy and Clinical Pharmacology, Academic Medical Centre, Amsterdam, The Netherlands
(6) St. Antonius Hospital, Department of Clinical Pharmacy, Nieuwegein, The Netherlands

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Abstract

Introduction: In order to characterize the variation in pharmacokinetics of paracetamol across the human age span, we performed a population pharmacokinetic analysis from preterm neonates to adults with specific focus on clearance.

Methods: A total of 220 (pre)term neonates, infants, children and adults from eight previously published studies on paracetamol pharmacokinetics were analysed using NONMEM 7.2. In the covariate analysis, covariates were tested in linear functions, power functions and a power function with a bodyweight-dependent exponent.

Results: Between preterm neonates and adults, linear bodyweight functions were identified for Q2, Q3, V1, V2 and V3, while for CL a power function with a bodyweight-dependent exponent k was identified ($CL_i = CL_p \bullet (BW/70)^k$). The exponent k was found to decrease in a sigmoidal manner with bodyweight from 1.2 to 0.75, with half the decrease in exponent reached at 12.2 kg. No other covariates such as age were identified.

Conclusions: A pharmacokinetic model for paracetamol characterising changes in pharmacokinetic parameters across the pediatric age-range was developed in which clearance was found to change in a highly nonlinear manner with bodyweight. Based on the final model, dosing guidelines are proposed from preterm neonates to adolescents resulting in similar exposure across all age ranges.

6.1. Introduction

Paracetamol or acetaminophen is an antipyretic and analgesic agent widely used in both adult and pediatric populations. Typically, paracetamol is given to patients orally or rectally [1]. Recently, an intravenous formulation of paracetamol has become available, which is also regularly used as analgesic in neonates even though the USFDA only approved its use for the treatment of acute pain and fever in children aged 2 years and older and adults. In latest years, there has also been great interest in intravenous paracetamol in preterm neonates for closure of neonatal ductus [2-4] at even higher dosages than when used as an analgesic.

To derive evidence based dosing guidelines for intravenous paracetamol across all age ranges including neonates and infants, information is needed on the pharmacokinetics. While the pharmacokinetics of paracetamol have been modeled in neonates and infants [5-7], different models have been derived upon paracetamol or its prodrug given orally, rectally or intravenously [8-10]. Regardless of whether in these analyses data from preterm and term neonates were available [8] or not available [9,10], in all these studies, paracetamol clearance was modeled on the basis of bodyweight with a ¾ allometric function, after which an age-based maturation function was added [8-10]. As the use of both bodyweight and age as covariates on a single parameter was recently reported to potentially harm the predictive performance of the resulting model because bodyweight and age are correlated in a complex and highly nonlinear manner as part of a child's growth and development [11,12], further study on the influence of bodyweight on the pharmacokinetics of paracetamol across the entire human lifespan with inclusion of data from (pre)term neonates seems important. Preferably in this analysis, the influence of bodyweight on clearance is optimized in a way that the inclusion of an additional maturation functions based on age is not required [11,12]. For this purpose, an allometric function on the basis of bodyweight in which the allometric exponent was allowed to vary with bodyweight was proposed for scaling clearance across the human age range[13]. Following the successful application of this so called bodyweight dependent exponent (BDE) model to the scaling of the clearances of propofol [13], morphine [14], busulfan [15] and midazolam [16], the current analysis focuses on the utilization of this model for scaling paracetamol clearance over a large lifespan including

preterm neonates. Given the fact that dosing in children including preterm and term neonates is typically performed on the basis of bodyweight, the results can also be used to derive bodyweight-based dosing guidelines for this drug in all pediatric subpopulations aiming to reach similar paracetamol exposure on the assumption of an identical exposure-effect relationship in pediatrics as in adults. [17]

Therefore, in the current study, we included pharmacokinetic data from eight previously published paracetamol studies [7,18-24] in order to characterize its pharmacokinetics across the entire human lifespan. In the covariate analysis, there was specific focus on the optimization of the influence of bodyweight as predictor of inter-individual variability in clearance.

6.2. Methods

6.2.1. Subjects of the original studies

A total of 220 subjects from eight previously published studies [7,18-24] on paracetamol pharmacokinetics were included in the current study, including neonates (1- 76 days), infants (0.11-1.33 years), children (2-7 years) and adults (19-34 years). Detailed information on the studies is given below and summarized in **Table 6-1**.

Neonates [7,18,19]

Study 1: Single dose intravenous propacetamol in neonates [18]

Thirty preterm (gestational age 27 – 35 weeks) and term (gestational age 36 - 40 weeks) neonates aged 1 day and weighing 0.5-4 kg, who received single dose of intravenous propacetamol, were included in the current analysis. Propacetamol dose was 20 mg/kg (10 mg/kg paracetamol) for the first 15 neonates and 40 mg/kg (20 mg/kg paracetamol) for the next 15 neonates. Propacetamol bolus infusion was prepared from a 1 gram propacetamol (500 mg paracetamol) powder-containing vial diluted in 50 ml normal saline. Samples were collected 30, 60, 90, 120, 180, 240, and 600 minutes after the start of intravenous administration.

Study 2: Repeated dose intravenous propacetamol in neonates [19]
Eighteen preterm and term neonates aged 1-76 days (postconceptual age 27 – 42 weeks) and weighing 0.84-4 kg, who received repeated doses of intravenous propacetamol, were included in the current analysis. The dosing regimen consisted of a loading dose (20 mg/kg paracetamol) with a maintenance dosing of 10 mg/kg/dose every 12, 8 or 6 hours for extreme preterm, preterm and term neonates, respectively. Samples were collected 30, 60, 90, 120, 180, 240 and 600 min after initiation of intravenous administration.

Study 3: Repeated dose intravenous paracetamol in neonates [7]
Sixty preterm and term neonates aged 1-28 days and weighing 0.6-4.8 kg, who received repeated dose intravenous paracetamol, were included in the current analysis. The dosing regimen consisted of a loading dose (20 mg/kg) followed by a maintenance dose of 5, 7.5 or 10 mg/kg every 6 hours for extreme preterm, preterm and term neonates, respectively. Samples were collected from an arterial line in the first 48 hours after the paracetamol loading dose.

Infants [20,23]

Study 4: Repeated dose intravenous propacetamol and rectal paracetamol in infants [20]
Twenty-six infants aged 0.11 – 1.33 years and weighing 7.5-12.2 kg after major craniofacial surgery were included in the current analysis. During surgery, all infants received a rectal loading dose of 40 mg/kg paracetamol 2 hours before anticipated extubation. On admittance to the pediatric surgical ICU, the children were randomized to receive either a 15 minutes intravenous infusion of 40 mg/kg propacetamol or 20 mg/kg paracetamol rectally every 6 hours. Blood samples were taken from the arterial catheter at 15 minutes, 1 and 6 hours after the first dose, at 5 minutes, 4 and 6 hours after the third dose, and at 30 minutes, 2 and 3 hours after the fourth dose.

Study 5: Repeated dose rectal acetaminophen in infants [23]
Twenty rectally dosed infants out of forty infants in the original study, aged 0.67 -1.25 years and weighing 7.9-12.2 kg, were included in the current analysis. Approximately 2 hours before anticipated extubation, a loading dose of acetaminophen (40 mg/kg) was administered rectally. Two hours after arrival

in the pediatric surgical ICU, 20-mg/kg acetaminophen was administered rectally at t = 6, t = 12, and t =18 hours. Blood samples were taken at 30, 60, and 90 minutes after the rectal loading dose and at 5, 8, 11, 14, 17 and 20 hours after arrival in pediatric surgical ICU. One individual was excluded from the population pharmacokinetic analysis because specific dosage information was missing.

Children

Study 6: Repeated dose rectal acetaminophen in children [24]
Twenty-nine children, aged 2-7 years and weighing 14-33 kg, received a loading dose of 40 mg/kg rectally resulting in a dose of 600, 700, 800, 900, 1000, 1100, 1200 or 1300 mg when the child was in weight class 14 - 16 kg, 17 - 18 kg, 19 - 21 kg, 22 - 23 kg, 24 - 26 kg, 27 - 28 kg, 29 - 31 kg or in weight class 32 - 33 kg, respectively. The maintenance dose of 30 mg/kg was given rectally every 8 hours and was a dose of 450, 525, 600, 675, 750, 825, 900 or 975 mg when the child was in weight class 14 - 16 kg, 17 - 18 kg, 19 - 21 kg, 22 - 23 kg, 24 - 26 kg, 27 - 28 kg, 29 - 31 kg or 32 - 33 kg, respectively. Samples were taken at the start and at the end of surgery and 1, 2 and 3 hours postoperatively.

Adults [21,22]

Study 7: Intravenous infusion of propacetamol in healthy male adults [21]
Data from twelve healthy male volunteers aged 21-25 years and weighting 63-83 kg from one sub-branch (Study I, Occasion B) in the original study were included in the current analysis. Each subject was given 1 gram of propacetamol HCL (=500 mg paracetamol) intravenously at a constant infusion rate over 15 minutes. Samples were taken before the administration and at 15, 20, 30, 45 minutes, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours after administration.

Study 8: Intravenous infusion of paracetamol in healthy adults [22]
Twenty-six healthy volunteers aged 19-34 years and weighing 49.2-94 kg were included in the current analysis. Each subject received first a 15 minutes infusion of 2 gram of paracetamol (Perfalgan), followed by four additional 15 minutes infusions of 1 gram paracetamol each, at 6 hours intervals. Blood samples were collected before dosing and at 15 minute (the end of infusion), 30 minutes and

1 hour, 1.1 hour, 2, 3, 4, and 6 hour after the 2 gram dose and the first 1 gram dose; before dosing and at the end of infusion of the second and third 1 gram doses; before dosing and at 15 minutes (end of infusion), 30 minutes and 1 hour, 1.5 hours, 2, 3, 4, 6, 8, 10, 12, and 24 hours after the last 1 gram dose.

6.2.2. Pharmacokinetic modelling

Model Building

The population pharmacokinetic analysis was performed with the non-linear mixed effects modeling software NONMEM version 7.2. (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method with the interaction option (FOCEI). Tools like S-PLUS interface for NONMEM (LAP&P Consultants BV, Leiden, NL), S-Plus (version 8.1, Insightful Software, Seattle, WA, USA), XPose and R (version 2.15.1) were used to visualize the output and evaluate the models.

Paracetamol concentrations were logarithmically transformed and fitted simultaneously, since the range in concentrations was more than 1000 fold. Model building was performed in four steps: (1) selection of structural model, (2) selection of statistical sub-model, (3) systematic covariate analysis, (4) model validation. For selection of a structural or statistical model, a difference in objective function (OFV) between models of more than 3.84 points was considered as statistically significant ($p<0.05$ assuming a Chi-square distribution). Furthermore, the goodness-of-fit plots (observed *versus* individual predicted concentrations and *versus* population predicted concentrations, and conditional weighted residuals *versus* time and *versus* population prediction concentrations) of all data and data stratified per age category were evaluated. Finally, the total number of parameters, improvement of the individual concentration-time profiles, the confidence intervals of the parameter estimates and the correlation matrix were assessed. In case the subjects were given propacetamol intravenously, 1 unit propacetamol dose was converted to 0.5 unit of paracetamol as dosing input for the pharmacokinetic analysis.

Structural Model

Based on previous reports [9,20], the distribution and elimination pharmacokinetics of paracetamol were primarily modelled with a two-compartment model, which was parameterized in terms of total clearance (CL), volume of

distribution of the central compartment (V1), volume of distribution of the peripheral compartment (V2) and inter-compartmental clearances between central compartment and peripheral compartment (Q2). To describe the process of rectal absorption for individuals who were given paracetamol rectally, a rectal deposit compartment was incorporated into the model with first-order absorption rate constant (Ka), bioavailability (F), and lag time (Tlag) as parameters. Since we had data upon bolus infusion of paracetamol in our analysis [21], we also explored the performance of a three-compartment model for distribution and elimination of paracetamol, which was parameterized in terms of total clearance (CL), volume of distribution of the central compartment (V1), volume of distribution of the rapidly-equilibrating peripheral compartment (V2) and slowly-equilibrating peripheral compartment (V3), and inter-compartmental clearances between central compartment and two peripheral compartments (Q2, Q3).

Because in some of the studies included in this analysis propacetamol, an intravenous prodrug of paracetamol, was given, we tested a deposit compartment for propacetamol and its first order hydrolysis rate in order to describe the process of conversion from propacetamol to paracetamol. As the half-life of the hydrolysis rate turned out to be very short (<0.0001 hour), this compartment was neglected in the final model.

Statistical Model

Interindividual variability in the pharmacokinetic parameters was tested in the model assuming log-normal distributions, expressed as

$$\theta_i = \theta_{TV} \times e^{\eta_i} \quad , \quad \eta_i \sim N(0, \omega^2) \tag{1}$$

where θ_i is the individual pharmacokinetic parameter value for the *i*th individual, θ_{TV} is the population pharmacokinetic parameter value or typical value, and η_i is a random variable for the *i*th individual from a normal distribution with mean zero and variance ω^2. In addition to testing of the inclusion of interindividual variability on individual parameters, model improvement by inclusion of covariance between these variability parameters was tested as well.

As bioavailability should be constrained between 0 and 1, interindividual variability in bioavailability was parameterized in a model proposed by Karlsson *et al*.[25] using the following function:

$$F_i = \frac{e^{ln\left(\frac{TVF}{1-TVF}\right)+\eta_i}}{1+e^{ln\left(\frac{TVF}{1-TVF}\right)+\eta_i}} \quad (2)$$

For the residual error, an additive model for log-transformed concentrations was used which corresponds to proportional error on untransformed data, expressed as:

$$logC_{ij} = logC_{pred_{ij}} + \varepsilon_{ij} \quad , \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad (3)$$

where C_{ij} is the value of the observed paracetamol concentration of *i*th individual at time *j*, $C_{pred_{ij}}$ is the value of the predicted paracetamol concentration of the *i*th individual at time *j*, and ε_{ij} is a random variable for this observation from a normal distribution with mean zero and variance σ^2.

Covariate Model

The covariates bodyweight and age were tested on the pharmacokinetic parameters in a linear function, power function or a power function with a bodyweight dependent exponent. This power function with a bodyweight dependent exponent is called a bodyweight dependent exponent (BDE) model [13] and is shown in equation 4, where it is applied to paracetamol clearance.

$$CL_i = CL_p \times \left(\frac{BW_i}{70}\right)^k \quad , \quad k = k_0 - \frac{k_{max} \times BW_i^{\gamma}}{k_{50}^{\gamma} + BW_i^{\gamma}} \quad (4)$$

In equation 4, Cl_i is clearance in the *i*th individual with bodyweight BW_i; Cl_p is the clearance in a standardized adult with a bodyweight of 70 kg; BW_i is bodyweight of an individual *i*; *k* is the exponent; k_0 is the value of the exponent at a theoretical bodyweight of 0 kg; k_{max} is the maximum decrease of the exponent; k_{50} is the bodyweight at which a 50% decrease in the maximum decrease of exponent value is attained, and γ is the Hill coefficient determining the steepness of sigmoidal decline in the exponent [13].

The significance of a covariate for a parameter in the model was statistically evaluated by the use of the objective function. In the forward inclusion a p

value <0.005 was considered as statistically significant while a more stringent p value <0.001 was used in the backward deletion. When two or more covariates were found to significantly improve the model, the covariate that reduces the objective function the most was retained into the model and served as a basis for subsequent inclusion of additional covariates. The choice of the covariate model was further evaluated as described under Model Building whereby the results of the model validation were also considered.

6.2.3. Model Validation

The model was validated internally using five criteria that were recently proposed for pediatric population model evaluation [26]. (i) The coefficient of variation (CV) of the parameter estimates either from the covariance step in NONMEM or from 200 stratified bootstrap resampling results is less than 50%, (ii) The basic diagnostic plots and particularly the plots of the observed versus population predicted concentrations stratified for age, are visually assessed for bias and precision, (iii) The η-shrinkage is calculated and evaluated according to Karlsson and Savic [27], (iv) The individual and population predicted parameters are plotted against the primary covariate to evaluate whether the individual predicted parameters are equally distributed around the population predicted parameters, (v) The simulation based normalized prediction distribution error (NPDE) proposed by Brendel *et al*. is calculated based on at least 2,000 simulations of the entire dataset and is evaluated visually for bias and precision [28].

Simulations on the basis of the final model

Based on the final model paracetamol concentration-time profiles were simulated for children with bodyweight of 0.5, 1, 1.5, 2, 3, 5, 8, 9, 15, 20, 35 and 50 kg. Two intravenous administration dosing regimens were simulated, i.e. a traditional dosing regimen and a model-based dosing regimen.

The traditional dosing regimen for prematurely born neonates and children was based on the Dutch Children's Formulary [5mg/kg every 6 hours (group 1 with weight 0.5, 1, 1.5 and 2 kg)] [29] while for term neonates and children it was based on the official labeling information in the Netherlands (for term neonates and children weighing less than 10 kg 7.5 mg/kg every 6 hours (group 2 with weight 3, 5, 8 and 9 kg) and for children weighing between 10 and 50 kg 15mg/kg every 6 hours (group 3 with weight 15, 20, 35 and 50 kg).

In the model-based dosing regimen, model based doses were derived for children of all bodyweights on the basis of a loading dose and a maintenance dose every 6 hours while aiming for steady state concentrations attained in group 3 using the traditional dosing regimen.

6.3. Results

For the analysis, data of 220 subjects varying from preterm and term neonates, infants, children and adults receiving paracetamol intravenously or rectally or propacetamol intravenously were available. An overview of the data of the eight paracetamol studies was summarized in **Table 6-1**.

Table 6-1 Summary of studies included in this analysis

Study	Population	Administration	N	Age	Weight	Reference
1	preterm and term neonates	i.v. propacetamol	30	1 day	0.505–4 kg	(18)
2	preterm and term neonates	i.v. propacetamol	18	1-76 days	0.81–4 kg	(19)
3	preterm and term neonates	i.v. paracetamol	60	1-28 days	0.6–4.3 kg	(7)
4	infants	rectal paracetamol i.v. propacetamol	26	0.11-1.33 yrs	7.5-12.2 kg	(20)
5	infants	rectal paracetamol	19	0.67-1.25 yrs	7.9-12.2 kg	(23)
6	children	rectal paracetamol	29	2-7 yrs	14-33 kg	(24)
7	Male adults	i.v. propacetamol	12	21-25 yrs	63-83 kg	(21)
8	adults	i.v. paracetamol	26	19–34 yrs	49.2-94 kg	(22)

Table 6-2 presents the results of the final model. The results demonstrated that a three-compartment structural model for distribution and elimination of paracetamol was superior over a two-compartment model, based on the improvement of the goodness of fit plots and a decrease of 639 points ($P<0.0001$) in objective function value. The population lag time (Tlag) of the rectal dose was estimated to be 0.409 hour without interindividual variability. The rectal bioavailability was estimated to be 0.962 with a large interindividual variability of 205.9%. The rectal absorption rate constant (Ka) was estimated to be 0.28 (1/hour) with an interindividual variability of 86.7%. The population value for clearance in a typical adult with a bodyweight of 70kg was estimated

17.6 L/hr and the corresponding population volume of distribution of the central compartment was 25.1 L (**Table 6-2**).

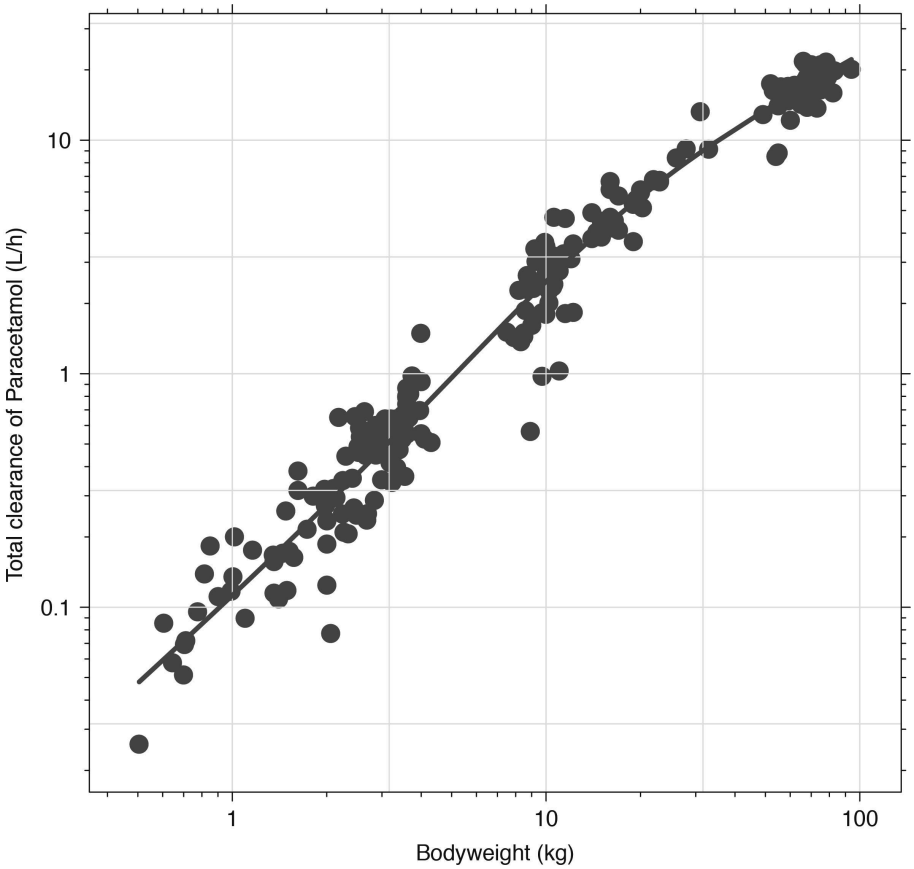

Figure 6-1 Plot of paracetamol clearance of all individuals (*post hoc* parameter estimates) against bodyweight in log-log scale.

Filled circles: *post hoc* individual paracetamol clearance; Solid line: model predicted paracetamol clearance as defined by $CL_i = CL_p \times (BW/70)^{k}$ with $k = k_0 - k_{max} \times BW^{\gamma} / (k_{50}^{\gamma} + BW^{\gamma})$ with parameters as shown in **Table 6-2**.

Table 6-2 Parameter estimates of the final model

Parameter	Model Estimates	RSE	Bootstrap Mean	Bootstrap RSE
Fixed effect				
CL	$= TVCL \times (BW/70)^{k}$			
TVCL (L/hr•70kg)	17.6	3.2%	17.5	2.8%
k	$=k_0 - k_{max} \times BW^{\gamma} / (k_{50}^{\gamma} + BW^{\gamma})$			
k_{max}	0.454	5.4%	0.44	5.7%
$k_0 - k_{max}$ §	0.75 FIX	-	-	-
k_{50} (kg)	12.2	27.2%	28.3	202.9%
γ	1.4 FIX	-	-	-
V1	$= TVVc \times (BW/70)$			
TVV1 (L/70kg)	25.1	11.2%	24.4	16.1%
Q2	$= TVQ \times (BW/70)$			
TVQ2 (L/hr•70kg)	96.8	12.6%	103.7	19.5%
V2	$= TVVp \times (BW/70)$			
TVV2 (L/70kg)	36.1	5.5%	36.8	7.3%
Q3	$= TVQ \times (BW/70)$			
TVQ3 (L/hr•70kg)	1.36	9.8%	1.37	8.1%
V3	$= TVV3 \times (BW/70)$			
TVV3 (L/70kg)	21.6	12.8%	22.2	13.9%
Ka (1/hr)	0.252	13.8%	0.29	25.9%
Tlag (h)	0.409	5.7%	0.409	6.4%
F	0.962	8%	0.9	11.7%
Random effect (%)				
ω CL	35.4%	9.1%	34.6%	17.6%
ω Vc	63.6%	12.6%	68.4%	36.6%
ω Ka	86.7%	14%	95.7%	42.5%
ω F	205.9%	76.4%	311%	110%
σ	21.4%	8.8%	21.4%	15.9%

k = bodyweight dependent exponent ; k_{max} = maximum decrease of *k*; k_0 = value of k at a theoretical bodyweight of 0 kg; k_{50} = the bodyweight at which a 50% decrease in the maximum decrease of *k* is attained; γ = the Hill coefficient determining the steepness of sigmoidal decline in *k*; Ka = rectal absorption constant rate; Tlag = lag time in rectal absorption; F= rectal bioavailability; ω= standard deviation of the inter-individual variability (η); σ = standard deviation of the proportional residual error (ε); § k_0-k_{max} was parameterized as a fixed effect parameter (THETA) in NONMEM

Concerning the covariate analysis, bodyweight was identified a significant covariate for all structural pharmacokinetic parameters except for Ka, F and Tlag. For the parameters Q2, Q3, V1, V2 and V3, the influence of bodyweight was best described by a linear function (**Table 6-2**). For clearance, a power function in which the exponent *k* varied with bodyweight in a sigmoidal function (BDE model, eq.5) proved superior over a linear or a power function with a fixed exponent *k*. The bodyweight-dependent exponent *k* was estimated to decrease

from a value of 1.2 (k_0) at the theoretical bodyweight of zero kilogram to 0.75 (k_0-k_{max}) and reached half this decrease at 12.2 kilogram (k_{50}) (**Table 6-2**). The minimum exponent, which equals k_0-k_{max}, was fixed to 0.75, since this exponent proved successful in a separate pre-analysis based on adult data only. The Hill factor (γ) was found to be 1.4 and was fixed to this value in the final model in order to get the covariance step (**Table 6-2**). **Figure 6-1** shows that on the basis of this BDE model, the change in individual paracetamol clearance over bodyweight of all individuals of this analysis was very well captured. As η-shrinkage was low (12.8%), the reliability of the individual clearance values in the subjects can be considered high [27]. Concerning the evaluation of the implementation of the covariate model for clearance in the final model by the bodyweight-dependent exponent (BDE) model, **Figure 6-2** shows that there were no remaining trends in the *post hoc* eta of clearance versus bodyweight, postnatal age (PNA), postmenstrual age (PMA) and gestational age (GA) plots. As the data of PMA and GA were only availabe in neonates, corresponding plots were limited to 50 weeks in the x-axes.

With respect to model validation, goodness of fit plots stratified by age (1. birth to 1 month; 2. 1 month to 2 years; 3. 2-12 years; 4 12-16 years) showed that the population predicted paracetamol concentrations of the final model were in good agreement with the observed paracetamol concentrations for the different age ranges (Supplemental **Figure 6-S1**). As a simulation based validation method, the normalized prediction distribution error (NPDE) showed that paracetamol concentrations in the models were normally distributed (mean=-0.02462, variance= 0.7756, $p<0.001$) around the median prediction and that there was no trend in the NPDE versus TIME and *versus* the logarithm of the individual predicted concentrations (Supplemental **Figure 6-S2**). In addition, the results of the bootstrap validation of the final model are listed in **Table 6-2**.

Table 6-3 Model-based dosing regimen of intravenous paracetamol aiming for a target paracetamol concentration of 9 mg/L in individuals weighing between 0.5 and 50 kg. Both maintenance doses administered 4 times daily (MD) and loading doses (LD) are presented. For the maintenance dose expressed per kg (MD/kg) the difference with a traditional dosing regimen is given.

BW (kg)	CL (L/h)	V (L)	$t_{1/2}$ (h)	Target Cavg (mg/L)	MD (mg)	MD/kg (mg/kg)	Traditional MD/kg (mg/kg)	% DIFF MD/kg	L/M Ratio	LD (mg)	LD/kg (mg/kg)
0.5	0.047	0.179	2.641	9	2.5	5.1	5	+2%	2.2	5.6	11.2
1	0.112	0.359	2.223	9	6.0	6.0	5	+20%	2	12.1	12.1
1.5	0.188	0.538	1.982	9	10.2	6.8	5	+36%	1.8	18.3	12.2
2	0.274	0.717	1.813	9	14.8	7.4	5	+48%	1.8	26.7	13.3
3	0.473	1.076	1.576	9	25.5	8.5	7.5	+13%	1.5	38.3	12.8
5	0.958	1.793	1.297	9	51.8	10.4	7.5	+39%	1.3	67.3	13.5
8	1.836	2.869	1.083	9	99.1	12.4	7.5	+65%	1.3	128.9	16.1
9	2.151	3.227	1.039	9	116.2	12.9	7.5	+72%	1.3	151.0	16.8
15	4.109	5.379	0.907	9	221.9	14.8	15	-1%	1.3	288.4	19.2
20	5.689	7.171	0.874	9	307.2	15.4	15	+3%	1.2	368.7	18.4
35	9.870	12.550	0.881	9	533.0	15.2	15	+1%	1.2	639.6	18.3
50	13.422	17.929	0.926	9	724.8	14.5	15	-3%	1.2	869.8	17.4

BW is body weight; CL is the predicted clearance from final model; V is the predicted volume of distribution from final model; $t_{1/2}$ = ln(2) / (CL/V); Target Cavg is the target average concentration used for the model-based dosing regimen which was taken from the average steady state concentrations observed in individuals weighing 15, 20, 35, 50 kg upon the traditional dosing regimen; MD is the final model optimized Maintenance Dose = Target Cavg*CL*6h; MD/kg is the final model optimized Maintenance Dose Per Kilogram = MD/BW; TraditionalMD/kg is the Maintenance Dose per kilogram of the traditional dosing regimen; % DIFF MD/kg is the change of model based MD/kg from the TraditionalMD/kg in percentage =100%* (MD/kg – TraditionalMD/kg)/ TraditionalMD/kg; L/M Ratio is the ratio of loading dose to maintenance dose in the model-based dosing regimen; LD is the model-based Loading Dose = MD * L/M Ratio; LD/kg is the final model optimized Loading Dose per kilogram

Simulations on the basis of the final model for both a traditional dosing regimen and a model-based dosing regimen are presented in **Figure 6-3**. For the traditional dosing regimen, 3 different maintenance doses were used 6 hourly, i.e. 5 mg/kg, 7.5 mg/kg and 15 mg/kg for neonates with a body weight between 0.5 - 3 kg, 3 – 10 kg and children with weight 10 - 50 kg, respectively, according to the official label and the Dutch Childrens Formularium [29]. The simulations upon the traditional dosing regimen in group 3 (**Figure 6-3 a**, buttom row, 10-50 kg) show that on average a concentration of 9 mg/L was attained (**Figure 6-3 a**, dotted reference line). For the other groups, a variety of average concentrations was attained upon this traditional mg/kg dosing regimen (**Figure 6-3 a**, upper two rows).

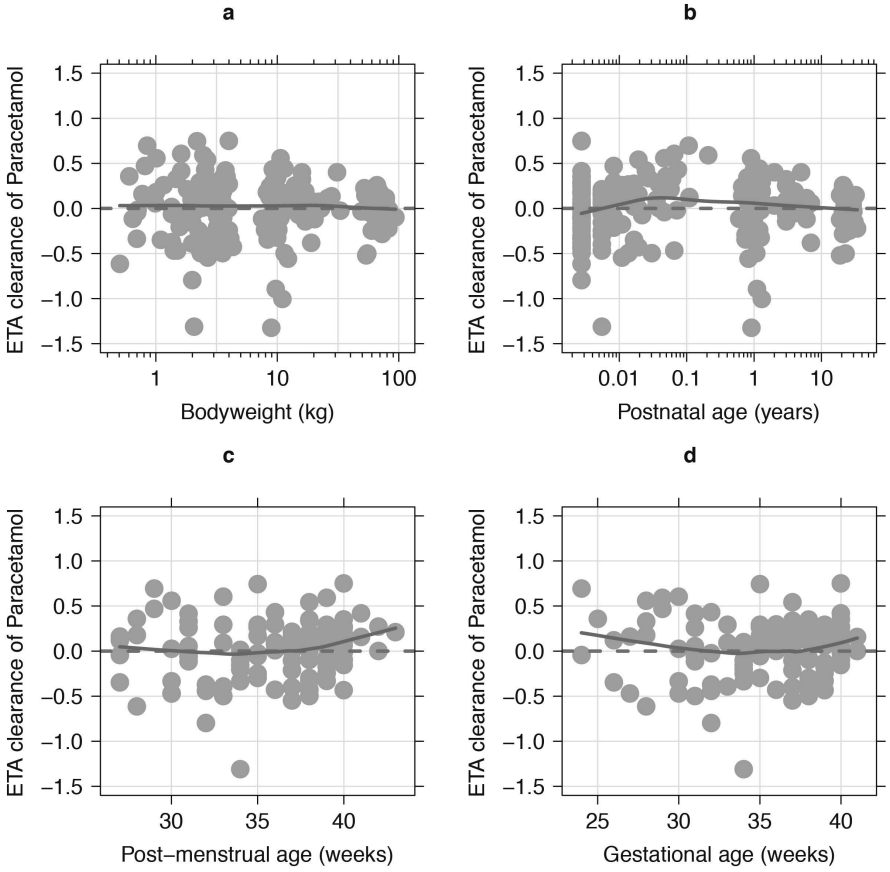

Figure 6-2 Plot of interindividual variability (ETA) in paracetamol clearance of the final model versus candidate covariates, including bodyweight, postnatal age, postmenstrual age (only for neonates) and gestational age (only for neonates).

Table 6-3 shows the loading and maintenance doses for the model-based dosing regimen aiming for a concentration of 9 mg/L in all groups with individuals varying in bodyweight between 0.5 and 50 kg. **Figure 6-3 b** shows the simulated concentrations in all individuals upon this model-based dosing regimen.

6.4. Discussion

In this meta-pharmacokinetic analysis we studied the pharmacokinetics of paracetamol using data from eight different clinical studies in (pre)term neonates, infants, children and adults. The results show that, whereas changes in most pharmacokinetic parameters were linearly related to bodyweight, developmental changes in clearance were best described on the basis of a power function with an exponent that varied with bodyweight. This exponent was found to vary from the value of 1.2 for neonates to 0.75 for older children and adults. Using this function, the influence of bodyweight on clearance was implemented in an optimal way which was confirmed by advanced internal validation procedures, being particularly important for pediatric studies where datasets are often sparse and variability due to age is large [26]. Most importantly, the Empirical Bayes Estimates (EBE) based *post hoc* interindividual variability of clearance had no trend against either bodyweight or age (including PNA, PMA and GA) (**Figure 6-2**), confirming that an appropriate final model has been reached [30]. These results demonstrate that the influence of bodyweight on clearance as described by the highly nonlinear bodyweight dependent exponent (BDE) function also takes the influence of age (PNA, PMA or GA) into account. However, caution is needed in case of obese individuals. In our datasets, there were no obese individuals, and therefore the derived function should not be used in obesity. A graphical comparsion of clearance predictions between the BDE model and literature models [8-10] shows that the predictions of these four models were in reasonable agreement with each other, such despite the fact that different functions and covariates were used (Supplemental **Table 6-S1**, **Figure 6-S3**).

The bodyweight-dependent exponent (BDE) function was originally developed on the basis of a very large and rich dataset from preterm neonates to adults on propofol [13]. Later on, it was applied for scaling morphine across the entire human lifespan [14] and in the current study. Concerning the results from propofol, morphine and paracetamol from the current study, it seems that relatively similar values for k were found (exponent of 1.35 to 0.56, 1.47 to 0.88 and 1.2 to 0.75, respectively). We think that this may be explained by the fact that glucuronidation is the main pathway for these drugs upon which the question rises whether this function could be seen as a semiphysiological function for glucuronidation in humans.

For a previously developed function for morphine glucuonidation from preterm neonates to 3 year old children, this has recently been proposed and evaluated using phsyiologically based modelling principles [31,32]. On the other hand, the current function for paracetamol differs from propofol and morphine by the k_{50} being 12. 2 kg for paracetamol vs 3.78 and 4.01 kg for propofol and morphine, respectively, indicating that paracetamol clearance maturates at a slower rate than glucuronidation of propofol and morphine. An explanation for this finding is that paracetamol is not entirely metabolised through glucuronidation as sulphation plays an important role, particularly in neonates [9]. Therefore the currently derived function is probably a mixture of glucuronidation and sulphation which each mature at their own rate. At least, it seems that the BDE model in which the exponent is allowed to vary with bodyweight is of relevance for scaling clearance across a large range in bodyweight on the basis of a single covariate.

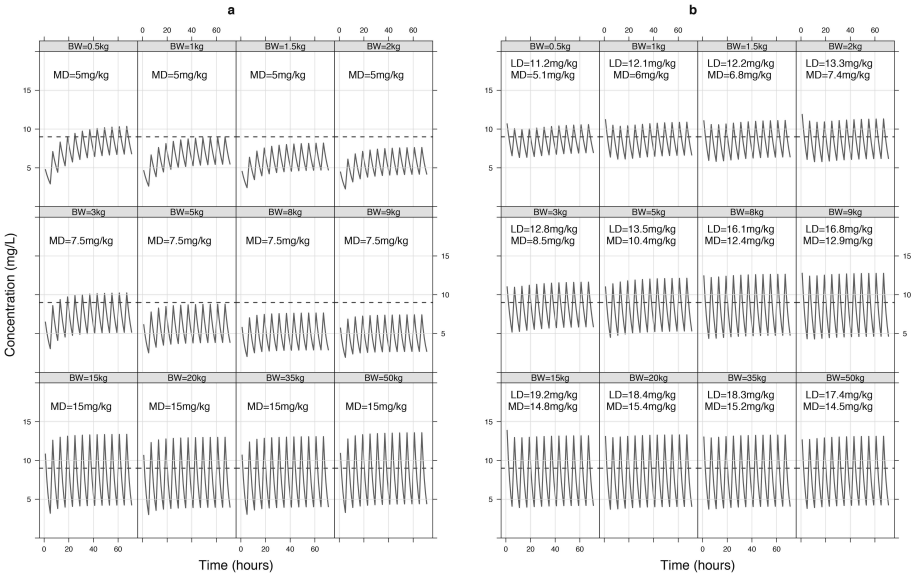

Figure 6-3 Simulated paracetamol concentration profiles of intravenously administered paracetamol 4 times daily based on a traditional regimen as described in section Methods (panel a) and a final model optimized regimen (panel b, Table 6-3) for neonates with a body weight between 0.5 - 3 kg (upper row), neonates and infants weighing between 3 – 10 kg (middle row) and children with a weight between 10 - 50 kg (lower row).

Solid curves are paracetamol concentration profiles; horizontal dotted line is the target average paracetamol concentration (9 mg/L) used for the final model optimized regimen (panel b) which was calculated from the average steady state concentration obtained upon the traditional dosing regimen in individuals weighing 15, 20, 35, 50 kg (panel a); MD is the maintenance dose per kilogram; LD is the loading dose per kilogram.

Intravenous paracetamol is not licensed for children younger than 2 years of age in the United States. Although intravenous paracetamol is licensed in the EU for children of all age ranges except prematurely born neonates, there is a large debate on the labelled dose for term neonates and children weighing less than 10 kg while doses for preterm neonates are based on expert opinion only [29]. In our study, we used the final model that was derived on the basis of eight different datasets across the entire human lifespan to simulate concentrations both upon a traditional dosing regimen and a model-based dosing regimen. For the traditional dosing regimen, 3 different maintenance doses were used 6 hourly, i.e. 5 mg/kg, 7.5 mg/kg and 15 mg/kg for neonates with a body weight between 0.5 - 3 kg, 3 – 10 kg and children with weight 10 - 50 kg, respectively. For the last two categories these doses are based on the official label, whereas the dose for preterm neonates is based on the Dutch Children's Formulary [29]. For the model-based dosing regimen a target paracetamol concentration was needed. Since the target therapeutic average paracetamol concentration for neonates is not known and the 6-hourly 15 mg/kg dose is widely accepted for children weighing more than 10 kg, we took the average paracetamol concentration reached in this dose group (i.e. 9 mg/L) as the target concentration for the model-based dosing regimen. On the basis of the 9 mg/L concentration as the target concentration, loading doses and maintenance doses of intravenous paracetamol were optimized based on clearance and volume of distribution as estimated using the final model (**Table 6-3**). Simulation results confirmed that 15 mg/kg maintenance doses is sufficient for children with weight 10 - 50 kg (**Figure 6-3 a** and **b**). However, 7.5 mg/kg was not enough to reach 9 mg/L average paracetamol concentration in neonates or infants weighing 5, 8 or 9kg, while 5 mg/kg proved too low of a dose for a prematurely born neonate weighing 1, 1.5 or 2 kg (**Figure 6-3 a**). Therefore bodyweight adjusted doses were proposed for these two categories as presented in **Table 6-3**, which proved to be in accordance with previous calls for adjustment of the labelled dose in infants and neonates. Palmer *et al*. recommended 10 mg/kg 6 hourly for preterm neonates with postmenstrual age (PMA) of 28-32 weeks, 12.5 mg/kg 6 hourly for neonates with PMA of 32-36 weeks and 15 mg/kg 6 hourly for neonates with PMA more than 36 weeks [33]. Allegaert *et al*. suggested a dosing regimen of 10 mg/kg every 6 hours within the age range 32–44 weeks postmenstrual age (PMA) [7]. Although final dose recommendations should consider not only the pharmacokinetics but also

the pharmacodynamics and safety of paracetamol in neonates and infants, we think that our model is a first step towards an evidence based dosing in children of all ages including preterm and term neonates. In addition, our model can also be used to derive adjusted pediatric doses by use of **Table 6-3** in which another target concentration (higher or lower than 9 mg/L) can easily be filled in, for instance when another therapeutic target concentration for a specific age category would be identified.

6.5. Conclusion

A pharmacokinetic model for paracetamol characterising changes in pharmacokinetic parameters across the entire human lifespan was developed in which clearance was found to change in a highly nonlinear manner with bodyweight. The results may provide insight in the exact relation between weight and clearance and as such provide a guide for individualised dosing in children varying between preterm neonates and adults. Once the therapeutic target concentration is known, corresponding appropriate doses can be easily calculated based on this model.

6.6. Acknowledgements

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Appendix

6.7.1 Notes for Figure 6-S1 and Figure 6-S2

The results obtained in this study were internally validated using advanced methods, which is highly important in particular for paediatric studies where datasets are often sparse and variability due to age is large [4]. From the population predicted versus observed diagnostic plots (**Figure 6-S1**), it can be concluded that the model had adequate predictive value for each of the four different age groups, indicating that the model accounted for the changes in pharmacokinetics across the entire age span from preterm neonates to adults. In addition, simulation based NPDE validation results proved the model without significant deficiency or model misspecification (**Figure 6-S2**).

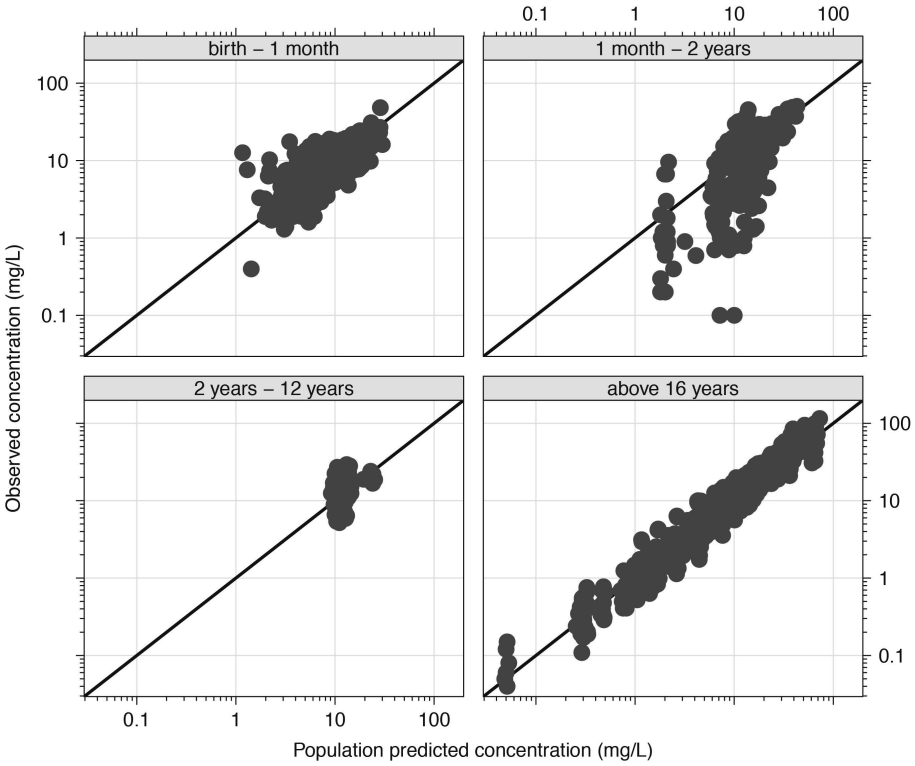

Figure 6-S1: Observed versus population predicted paracetamol concentrations stratified for four different age groups

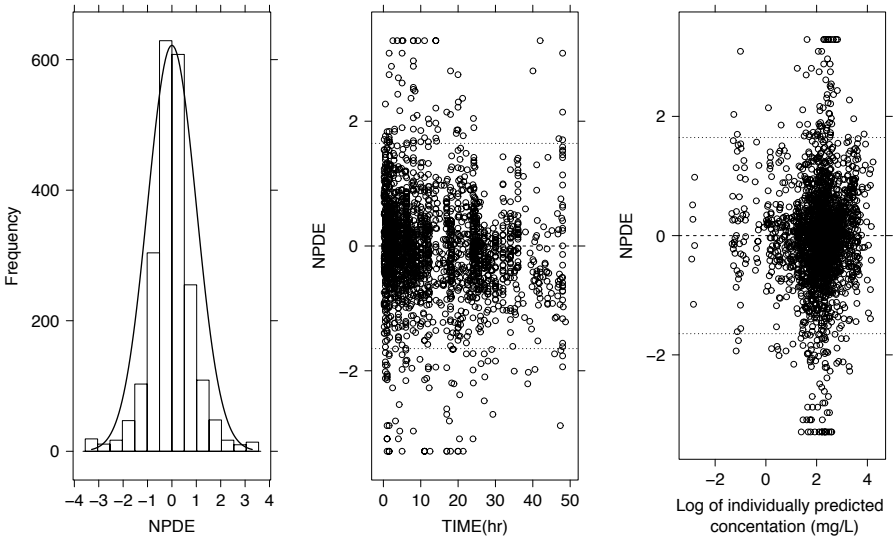

Figure 6-S2: Results of the Normalized Prediction Distribution Error (NPDE) validation with a histogram showing the NPDE distribution of paracetamol concentrations with a solid line indicating a normal distribution (left), distribution of NPDE versus time (middle) and distribution of NPDE versus the log of the paracetamol concentration (right).

6.7.2 Notes for Table 6-S1 and Figure 6-S3

Supplemental **Table 6-S1** summarizes previously published functions to describe changes in paracetamol clearance in various age ranges across whole age span [1-3]. From the age of 1.8 years onwards typically an allometric function with an exponent of 0.75 suffices to describe the change in clearance. However when including neonates [1,2], advanced functions and multiple covariates bodyweight and age (postconceptional age or postnatal age) are needed to describe the variation in clearance (**Table 6-S1**). In **Figure 6-S3**, we plotted the model predicted clearances from the three previously published models [1-3] and from our model, against the individual bodyweights of all our individuals. The model-predicted paracetamol clearances from these three models were derived by applying the respective maturation functions (**Table 6-S1**) to the individual data from our analysis. The predictions for these models were limited to the age range of the original studies (**Table 6-S1**) in order to prevent unintended extrapolations of these models. **Figure 6-S3** shows that the predictions of these four models were in reasonable agreement with each other, such despite the fact that different functions and covariates were used. While Zuppa *et al.*[2] did not study neonates and had mainly access to children of 7 kg onwards without

reporting bodyweight and Mohammed *et al*.[3] studied children from 1.8 years onwards, Anderson *et al*. did have a large number of preterm and term neonates in the dataset [1]. For the neonatal range, the performance of the latter model [1] seemed in good agreement with the current model, such despite the fact that the models varied largely in functions and number of covariates (**Table 6-S1**). From neonates to infants of about 20 kg years, it seems that the models by Zuppa *et al*.[2], by Anderson *et al*.[1] and by Mohammed *et al*.[3] slightly overestimated clearance compared to the values in our study. Finally, none of these analyses had adult data included even though predictions up to 30 kg were fairly similar to the predictions of our model which did have access to adult data.

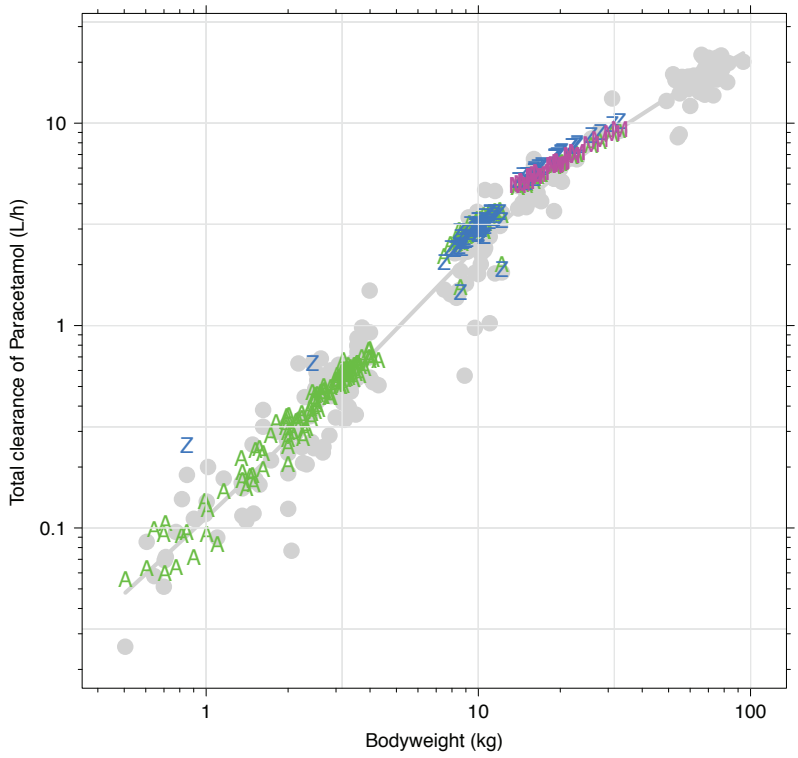

Figure 6-S3: Graphical comparison of predictions of paracetamol clearance versus bodyweight between the final model of the current analysis (gray circles and gray line) and three previously reported models (colored letters) in log-log scale. Gray circles: post hoc individual clearances estimated from the current model; Gray line: final model predicted clearance as defined by $(CL_i = CL_p \bullet (BW/70)^k$ with $k = k_0 - k_{max}\ BW^\gamma / (k50^\gamma + BW^\gamma)$, see Table 6-2 for parameter estimates); Green'A': predicted clearance with model from Anderson *et al*.[1]; Blue'Z': predicted clearance with model from Zuppa *et al*.[2]; Pink'M': predicted clearance with model from Mohammed *et al*.[3]

Table 6-S1: Paracetamol clearance across the human age span: comparison between previously published reports and current study

Year	Author	Weight	Age-span	Covariate model for clearance
2005	Anderson *et al.*[1]	0.5 – 55 kg	postconception age 27 weeks -14 years	$CL = 16.3\times(BW/70)^{0.75}\times(1-0.885\times\exp(-PCA\text{ in weeks}\times Ln(2)/26.6)$
2011	Zuppa *et al.*[2]	not reported	29 days - less than 18 years	$CL = 18.4\times(BW/70)^{0.75}\times(1-0.678\times\exp(-PNA\text{ in weeks}\times Ln(2)/41)$
2012	Mohammed *et al.*[3]	13.7 - 56 kg	1.8 - 15 years	$CL = 16.51\times(BW/70)^{0.75}$
	This study	0.5 – 94 kg	postconception age 27 weeks - 34 years	$CL=17.6\times(BW/70)^{k}$; $k= 1.204 – 0.454\times BW^{1.4} / (12.2^{1.4} + BW^{1.4})$ §

CL= paracetamol clearance; BW=bodyweight; PCA=postconception age; PNA=postnatal age
§ see table 2 for parameter estimates

6.7.3 NONMEM codes

```
$SUBROUTINES ADVAN5 TRANS1
;-------------------------------------------------------------------------------
$MODEL
NCOMPARTMENTS=4
COMP=(DEPOT) ;RECTAL DOSE
COMP=(CENTRAL DEFDOSE DEFOBS) ;CENTRAL PLASMA COMPARTMENT
COMP=(PERIPH1) ;PERIPHERAL COMPARTMENT1
COMP=(PERIPH2) ;PERIPHERAL COMPARTMENT2
;-------------------------------------------------------------------------------
$PK
KDEC  = THETA(10)              ; DECREASE OF EXPONENT
KMAX  = THETA(11)+KDEC         ; MAXIMUM EXPONENT
KHAL  = THETA(12)              ; K50
GAMMA = THETA(13)              ; GAMMA
KBDE  = KMAX-KDEC*(BW**GAMMA)/(KHAL**GAMMA+BW**GAMMA)

TVCL  = THETA(1)*(BW/70)**KBDE
CL    = TVCL*EXP(ETA(1))
TVVC  = THETA(2)*(BW/70)
VC    = TVVC*EXP(ETA(2))
```

```
Q2    = THETA(3)*(BW/70)
TVVP1 = THETA(4)*(BW/70)
VP1   = TVVP1*EXP(ETA(3))
Q3    = THETA(5)*(BW/70)
TVVP2 = THETA(6)*(BW/70)
VP2   = TVVP2*EXP(ETA(4))

KA   = THETA(7)*EXP(ETA(5))
ALAG1 = THETA(8)
TVF1 = THETA(9)

F1=EXP(LOG(TVF1/(1-TVF1))+ETA(6))/(1+EXP(LOG(TVF1/(1-TVF1))+ETA(6)))

;-------------------------------------------------------------------------------
ET1 = ETA(1)
ET2 = ETA(2)
ET3 = ETA(3)
ET4 = ETA(4)
ET5 = ETA(5)
ET6 = ETA(6)
;-------------------------------------------------------------------------------
S2=VC
;-------------------------------------------------------------------------------

K12 = KA
K23 = Q2/VC
K32 = Q2/VP1
K24 = Q3/VC
K42 = Q3/VP2
K20 = CL/VC

;-------------------------------------------------------------------------------
$ERROR
IPRED=LOG(0.000001)
IF (F.GT.0) IPRED = LOG(F)
Y = IPRED + EPS(1)
```

```
; Y = IPRED + SQRT(THETA(10)**2+THETA(11)**2/F**2)*ERR(1)
;-------------------------------------------------------------------------------
$THETA
(0.01, 5,    )  ;TH1 CL
(2,   10,    )  ;TH2 VC
(0.01, 70,    ) ;TH3 Q2
(0.1,  30,   )  ;TH4 VP1
(0.01, 2,    )  ;TH5 Q3
(0.1,  30,   )  ;TH6 VP2
(0.01, 0.13, )  ;TH7 KA
(0.01, 0.2,  )  ;TH8 ALAG
(0.01, 0.93, 1)  ;TH9 F1

(0.1,  0.4,  1)  ;TH10 KDEC
0.75 FIX  ;TH11 KMAX-KDEC OR KMIN
(0.05, 3.5,  )  ;TH12 K50
1.4 FIX ;TH13 GAMMA
;-------------------------------------------------------------------------------
$OMEGA
0.12   ;CL
0.12   ;VC
0 FIX  ;VP1
0 FIX  ;VP2
0.11   ;KA
0.2    ;F1
;-------------------------------------------------------------------------------
$SIGMA
0.1
;-------------------------------------------------------------------------------
$EST NOABORT SIGDIG=3 PRINT=15 MAXEVAL=9999 METHOD=1 INTERACTION
POSTHOC
$COV COMP PRINT=E
```

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