

Population Pharmacokinetics of Paracetamol Across the Human Age-Range From (Pre)term Neonates, Infants, Children to Adults

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Abstract

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. Concentration-time data obtained in 220 neonates (post-natal age 1–76 days, gestational age 27–42 weeks), infants (0.11–1.33 yrs), children (2–7 yrs) and adults (19–34 yrs) were analyzed using NONMEM 7.2. In the covariate analysis, linear functions, power functions, and a power function with a bodyweight-dependent exponent were tested. 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 ($CL_i = CL_p \times (BW/70)^k$). 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. A pharmacokinetic model for paracetamol characterizing changes in pharmacokinetic parameters across the pediatric age-range was developed. Clearance was found to change in a 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.

Keywords

allometry, paracetamol, pharmacokinetics, clearance, pediatric

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 More recently, an intravenous formulation of paracetamol has become available, which was approved for use in term neonates, children and adults in Europe, even though the USFDA only approved its use for the treatment of acute pain and fever in adults and children aged 2 years and older. While intravenous paracetamol is now being used regularly as an analgesic in neonates, children and adults,^{2,3} in the last few years, intravenous paracetamol in a dose as high as 60 mg/kg has also been proposed as an off-label treatment of patent ductus arteriosus in preterm neonates.^{4–6}

To derive evidence based dosing guidelines for intravenous paracetamol across age ranges including preterm neonates, term neonates, and infants, information is needed on its pharmacokinetics. In the past, different pharmacokinetic models have been reported for paracetamol or its prodrug propacetamol after oral, rectal or intravenous administration in neonates, infants and/or children.^{7–12} These models have however not yet been used to guide dosing in children of different ages, as the official label for pediatric intravenous paracetamol has not changed since these publications. This may be explained by the fact that all these studies used a bodyweight based $\frac{3}{4}$ allometric function combined with an age-based maturation

function to describe changes in paracetamol clearance across the pediatric age range.^{7–12} These complex models may have reduced predictive value, because they use both bodyweight and age on the same parameter (ie, clearance) while these covariates are correlated.^{13,14} There is therefore a need for validated pediatric models that can be used to guide dosing, particularly in the youngest age range including preterm and term neonates.

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In this study, we aimed to develop and validate a pediatric population pharmacokinetic model for paracetamol on the basis of pharmacokinetic data from eight previously published paracetamol studies in preterm and term neonates, infants, children and adults.^{9,15–21} In the covariate analysis, linear functions, power functions, and a power function with a bodyweight dependent exponent^{22–25} were tested to capture changes in the different pharmacokinetic parameters across the pediatric age range. The results of the model were used to simulate dose scenarios in all pediatric subpopulations given a similar target exposure across age.²⁶

Methods

Subjects of the Original Studies

A total of 220 subjects from eight previously published studies^{9,15–21} 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). No data were available from children between 8 and 19 years of age. Detailed information on the studies is given below and summarized in Table 1.

Neonates^{9,15,16}

Study 1: Single dose intravenous propacetamol in neonates¹⁵. 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. 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 g propacetamol (500 mg paracetamol) powder-containing vial diluted in 50 mL normal saline. Propacetamol was administered for minor, painful procedures (ie, insertion of peripheral arterial, venous, or central venous line, chest tube placement) or as adjuvant therapy when receiving opioids.

Study 2: Repeated dose intravenous propacetamol in neonates¹⁶. 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. 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. Propacetamol was prescribed based on a standardized pain evaluation and analgesic algorithm after surgery or during specific medical conditions.

Study 3: Repeated dose intravenous paracetamol in neonates⁹. Sixty preterm and term neonates aged 1–28 days and weighing 0.6–4.8 kg, who received repeated

dose intravenous paracetamol, were included. 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 extremely preterm preterm (<32 weeks postmenstrual age), preterm (32–36 weeks postmenstrual age) and term neonates (>36 weeks postmenstrual age), respectively. Indications for paracetamol administration were medical (traumatic delivery, necrotizing enterocolitis, prostaglandin E2 administration, fever) or surgical (eg, cardiac, thoracic, abdominal). Samples were collected in the first 48 hours after loading dose with a non-uniform non-sparse sampling scheme with a median (range) number of samples per individual of 7 (2–11).

Infants^{17,20}

Study 4: Repeated dose intravenous propacetamol and rectal paracetamol in infants¹⁷. 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 (12 subjects) or 20 mg/kg paracetamol rectally (14 subjects) every 6 hours. Propacetamol or paracetamol was administered for analgesia after craniofacial surgery.

Study 5: Repeated dose rectal acetaminophen in infants²⁰. Nineteen rectally dosed infants, aged 0.67–1.25 years and weighing 7.9–12.2 kg, were included. These infants received approximately 2 hours before anticipated extubation a loading dose of acetaminophen (40 mg/kg) that was administered rectally. Two hours after arrival in the pediatric surgical ICU, 20-mg/kg acetaminophen was administered rectally at 6, 12, and 18 hours.

Children

Study 6: Repeated dose rectal acetaminophen in children²¹. Twenty-nine children, aged 2–7 years and weighing 14–33 kg, were administered with acetaminophen for analgesia after adenotonsillectomy. Patients received a loading dose of 40 mg/kg rectally which was followed by a maintenance doses of 30 mg/kg rectally for every 8 hours. The loading dose and maintenance doses were calculated based on following weight class 14–16, 17–18, 19–21, 22–23, 24–26, 27–28, 29–31, and 32–33 kg, resulting in corresponding loading doses of 600, 700, 800, 900, 1000, 1100, 1200, or 1300 mg and corresponding maintenance dose of 450, 525, 600, 675, 750, 825, 900, or 975 mg, respectively.

Adults^{18,19}

Study 7: Intravenous infusion of propacetamol in healthy male adults¹⁸. Data from twelve healthy male

Table 1. Summary of Studies Included in this Analysis

Study	Population	N	PNA	Weight	Dosing regimen	Indication	Sampling times	Reference
1	Preterm and term neonates	30	1 day (PMA 27–40 wks)	0.5–4 kg	Propacetamol SD, 20 mg/kg or 40 mg/kg i.v. bolus infusion	Analgesia for painful procedures (ie insertion of peripheral arterial, venous or central venous line, chest tube placement)	0.5, 1, 1.5, 2, 3, 4, 10h	15
2	Preterm and term neonates	18	1–76 days (PMA 29–43 wks)	0.8–4 kg	Propacetamol LD 40 mg/kg i.v. + MD 20 mg/kg i.v. every 6, 8, or 12 h	Analgesia after surgery or during specific medical conditions	0.5, 1, 1.5, 2, 3, 4, 10h	16
3	Preterm and term neonates	60	1–28 days (PMA 27–42 wks)	0.6–4.3 kg	Paracetamol LD 20 mg/kg i.v. + MD 5, 7.5, or 10 mg/kg i.v. every 6 h	Medical or surgical indication	Unified sampling during first 48 h	9
4	Infants	26	0.11–1.33 yrs	7.5–12.2 kg	Paracetamol MD 20 mg/kg rectal or propacetamol 40 mg/kg i.v. every 6 h	Analgesia for extubation after craniofacial surgery	0.25, 1, 6, 12, 1, 16, 18, 24.5, 26, 27h	17
5	Infants	19	0.67–1.25 yrs	7.9–12.2 kg	Paracetamol LD 40 mg/kg rectal + MD 20 mg/kg rectal every 6 h	Analgesia for extubation after craniofacial surgery	0.5, 1, 1.5, 5, 8, 11, 14, 17, 20h	20
6	Children	29	2–7 yrs	14–33 kg	Paracetamol LD 40 mg/kg rectal + MD 30 mg/kg rectal every 8 h	Analgesia after adenotonsillectomy	1.5, 2, 3, 4, 6 h	21
7	Male adults	12	21–25 yrs	63–83 kg	Propacetamol SD 1 g i.v.	Clinical trial in healthy volunteers	0.25, 0.33, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24h	18
8	Adults	26	19–34 yrs	49.2–94 kg	Paracetamol LD 2 g i.v. + MD 1 g i.v. every 6 h	Clinical trial in healthy volunteers	0.25, 0.5, 1, 1.1, 2, 3, 4, 6, 6.25, 6.5, 7, 7.1, 8, 9, 10, 12, 12.25, 18, 18.25, 24, 24.25, 24.5, 25, 25.5, 26, 27, 28, 30, 32, 34, 36, 48 h	19

PNA, postnatal age; PMA, postmenstrual age; wks, weeks; yrs, years; SD, single dose; LD, loading dose; MD, maintenance dose; i.v., intravenous.

volunteers aged 21–25 years and weighing 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 g of propacetamol HCL (=500 mg paracetamol) intravenously at a constant infusion rate over 15 minutes.

Study 8: Intravenous infusion of paracetamol in healthy adults¹⁹. 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 g of paracetamol (Perfalgan), followed by four additional 15 minutes infusions of 1 g paracetamol each, at 6 hours intervals.

Pharmacokinetic Modeling

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) using the first-order conditional estimation method with the interaction (FOCEI). Pirana²⁷ 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 ($P < .05$ assuming a Chi-square distribution). Next to evaluation of the OFV for statistical significance, the goodness-of-fit plots (observed vs. individual predicted concentrations and vs. population predicted concentrations, and conditional weighted residuals vs. time and vs. population prediction concentrations) of all data and data stratified per age category were evaluated. Beside the OFV and goodness-of-fit plots, 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 when selecting the structural model. For intravenously administered propacetamol (72 subjects), 1 unit propacetamol dose was converted to 0.5 unit of paracetamol as dosing input for the pharmacokinetic analysis.

Structural model. One, two, and three compartment models were tested. 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 CL between central compartment and two peripheral compartments (Q2, Q3), was superior over a one compartment model given the criteria as described under Model building. 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.

For the pharmacokinetic data from studies in which propacetamol (an intravenous prodrug of paracetamol) was used, we tested a pseudo deposit compartment for propacetamol and its first order hydrolysis rate in order to describe the process of conversion from propacetamol to paracetamol.²⁰ As the half-life of the hydrolysis rate turned out to be very short (<0.0001 hour), this pseudo deposit compartment was not implemented in the final model.

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

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

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.

Absolute bioavailability was constrained between 0 and 1, as it represents the ratio between the amount of drug reaching the systemic circulation and the amount of drug administered.²⁸ Therefore, the interindividual variability in bioavailability could not be parameterized as described in Eq. (1) and was parameterized in a model proposed by Karlsson et al²⁸ 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 was expressed as:

$$\log C_{ij} = \log C_{pred,ij} + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2) \quad (3)$$

where C_{ij} is the value of the observed paracetamol concentration of i th individual at time j , is the value of the predicted paracetamol concentration of the i th individual at time j , and $C_{pred,ij}$ is a random variable for this

observation from a normal distribution with mean zero and variance σ^2 .

Covariate model. Covariates (bodyweight, age) were plotted independently versus the individual post hoc parameter estimates and the conditional weighted residuals to evaluate potential relationships. In addition, gestational age and postmenstrual age were evaluated for neonates. Potential covariates were separately implemented into the model using 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) model²² and is shown in Eq. (4), where it is applied to paracetamol CL.

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

In Eq. (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.²²

The significance of a covariate for a parameter in the model was statistically evaluated by the use of the OFV. In the forward inclusion a P value $<.005$ was considered as statistically significant while a more stringent P value $<.001$ was used in the backward deletion. When two or more covariates were found to significantly improve the model, the covariate that reduces the OFV the most was retained in the model. Then the influence of the remaining covariates was tested in the covariate-adjusted model for significance. The final covariate model was selected on the basis of the criteria in this section covariate analysis, provided that improvements as a result of inclusion of the covariate in the model were observed as described under Model Building. Finally, the model was accepted when the results of the model validation were adequate (see under Model validation).

Model Validation

The model was validated internally using five criteria that were recently proposed for pediatric population model evaluation.²⁹ (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,³⁰ (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)³¹ is calculated based on 2,000 simulations of the entire dataset and is evaluated visually for bias and precision.³¹

Simulations on the basis of the final model

Based on the final model paracetamol concentration-time profiles were simulated with NONMEM for children with a 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, that is, a standard of care dosing regimen and a model-based dosing regimen.

The standard of care dosing regimen for prematurely born neonates and children was based on the Dutch Children's Formulary [5 mg/kg every 6 hours (group 1 with weight 0.5, 1, 1.5, and 2 kg)]³² 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 15 mg/kg every 6 hours (group 3 with weight 15, 20, 35, and 50 kg).

In the model-based dosing regimen, recommended doses were derived for children of all bodyweights on the basis of a loading dose and a maintenance dose every 6 hours. For this model based dosing regimen, an average target concentration was needed. Since the target therapeutic average paracetamol concentration for neonates is unknown 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 (ie, 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 CL and volume of distribution as estimated using the final model.

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 eight paracetamol studies was summarized in Table 1.

Table 2 presents the results of the final model. The results demonstrated that a three-compartment structural model for distribution and elimination of paracetamol was

Table 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/h \times 70 kg)	17.6	3.2%	17.5	2.8%
k	$=k_0 - k_{max} BW^\gamma / (k_{50}^\gamma + BW^\gamma)$			
k_{max}	0.45	5.4%	0.44	5.7%
$k_0 - k_{max}^\S$	0.75 FIX	—	—	—
k_{50} (kg)	12.2	27.2%	28.3	202.9%
γ	1.4 FIX	—	—	—
V1	$=TVV1 \times (BW/70)$			
TVV1 (L/70 kg)	25.1	11.2%	24.4	16.1%
Q2	$=TVQ2 \times (BW/70)$			
TVQ2 (L/h \times 70 kg)	96.8	12.6%	103.7	19.5%
V2	$=TVV2 \times (BW/70)$			
TVV2 (L/70 kg)	36.1	5.5%	36.8	7.3%
Q3	$=TVQ3 \times (BW/70)$			
TVQ3 (L/h \times 70 kg)	1.4	9.8%	1.4	8.1%
V3	$=TVV3 \times (BW/70)$			
TVV3 (L/70 kg)	21.6	12.8%	22.2	13.9%
Ka (1/h)	0.25	13.8%	0.29	25.9%
Tlag (h)	0.4	5.7 %	0.4	6.4%
F	0.96	8%	0.9	11.7%
Random effect (%)				
ω CL	35.4%	9.1%	34.6%	17.6%
ω V1	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); \S $k_0 - k_{max}$ was parameterized as a fixed effect parameter (THETA) in NONMEM.

superior over a two-compartment model, based on the improvement of the goodness of fit plots and a decrease in OFV value ($P < .0001$). 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/h) with an interindividual variability of 86.7%.

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 2). For CL, a power function in which the exponent k varied with bodyweight in a sigmoidal function (BDE model, Eq. 4) proved superior over a linear or a power function with a fixed exponent k ($P < .05$) according to the criteria stated in section Methods. 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 2). The corresponding age to the bodyweight of 12.2 kg (k_{50}) proved 2 years in this study. The minimum exponent ($k_0 - k_{max}$) that is applicable to the adult range only was fixed to 0.75, since this value for the exponent was identified 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 2).

Figure 1 (left panel) shows that on the basis of this BDE model, the change in individual paracetamol CL over bodyweight of all individuals of this analysis was very well captured. As η -shrinkage was low (12.8%), the reliability of the individual CL values in the subjects can be considered high.³⁰ 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 S1). Concerning the evaluation of the implementation of the covariate model for CL in the final model by the bodyweight-dependent

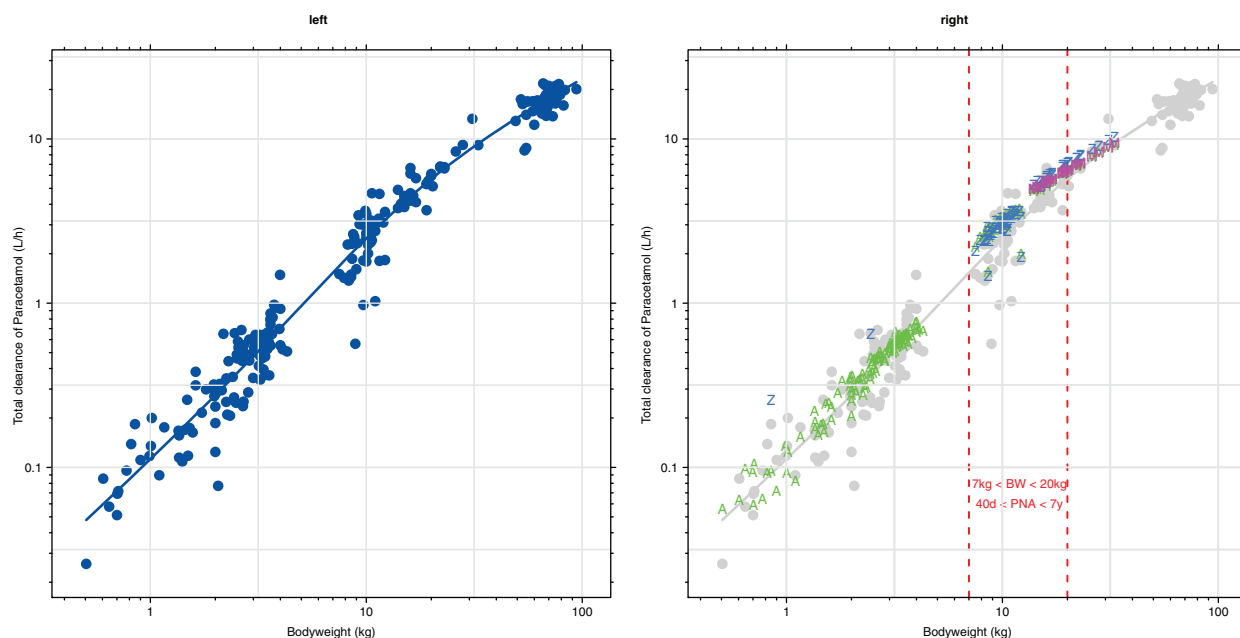


Figure 1. Paracetamol clearance (filled circle) against bodyweight of all individuals in this study (left panel) and paracetamol clearance (filled circle) against bodyweight of all individuals in this study in comparison with the results of three previously reported models (letters) (right panel) in log-log scale. Solid line: model predicted paracetamol clearance as defined by $CL_i = CL_p \times (BW/70)^k$ with $k = k_0 - k_{max} \frac{BW^\gamma}{(k_{50}^\gamma + BW^\gamma)}$ with parameters as shown in Table 2. Dashed vertical lines: boundary lines of a range in bodyweight between 7 and 20 kg, which corresponds to a range in postnatal age (PNA) between 40 days and 7 years in our study dataset. “A”: predicted clearance with model from Anderson et al¹⁰; “Z”: predicted clearance with model from Zuppa et al¹¹; “M”: predicted clearance with model from Mohammed et al.¹²

exponent (BDE) model, Supplemental Figure S2 shows that there were no remaining trends in the post hoc eta of CL versus bodyweight, postnatal age (PNA), postmenstrual age (PMA), and gestational age (GA) plots. As the data of PMA and GA were only available in neonates, corresponding plots were limited to 50 weeks in the x-axes. 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 , $P < .001$) 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 S3). In addition, the results of the bootstrap validation of the final model are listed in Table 2.

Simulations on the basis of the final model for both a standard of care dosing regimen and a model-based dosing regimen are presented in Figure 2. For the standard of care dosing regimen, 3 different maintenance doses were used 6 hourly, that is, 5, 7.5, and 15 mg/kg for neonates with a body weight between 0.5–3, 3–10, and children with weight 10–50 kg, respectively, according to the official label and the Dutch Childrens Formularium.³² The simulations upon the standard of care dosing regimen in group 3 (Figure 2a, bottom row, 10–50 kg) show that on average a concentration of 9 mg/L was attained (Figure 2a, dotted reference line). For the other groups, a variety of

average concentrations was attained upon this traditional mg/kg dosing regimen (Figure 2a, upper two rows).

Table 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 2b). Figure 2b shows the simulated concentrations in all individuals upon this model-based dosing regimen. This figure illustrates that the target concentration of 9 mg/L is achieved at all weights when using the dosing table depicted in Table 3.

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 showed that, developmental changes in CL 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 CL was adequately implemented, as changes in CL with bodyweight were captured in an optimal way (Figure 1, left panel). This model was confirmed by advanced internal validation procedures that have been proposed

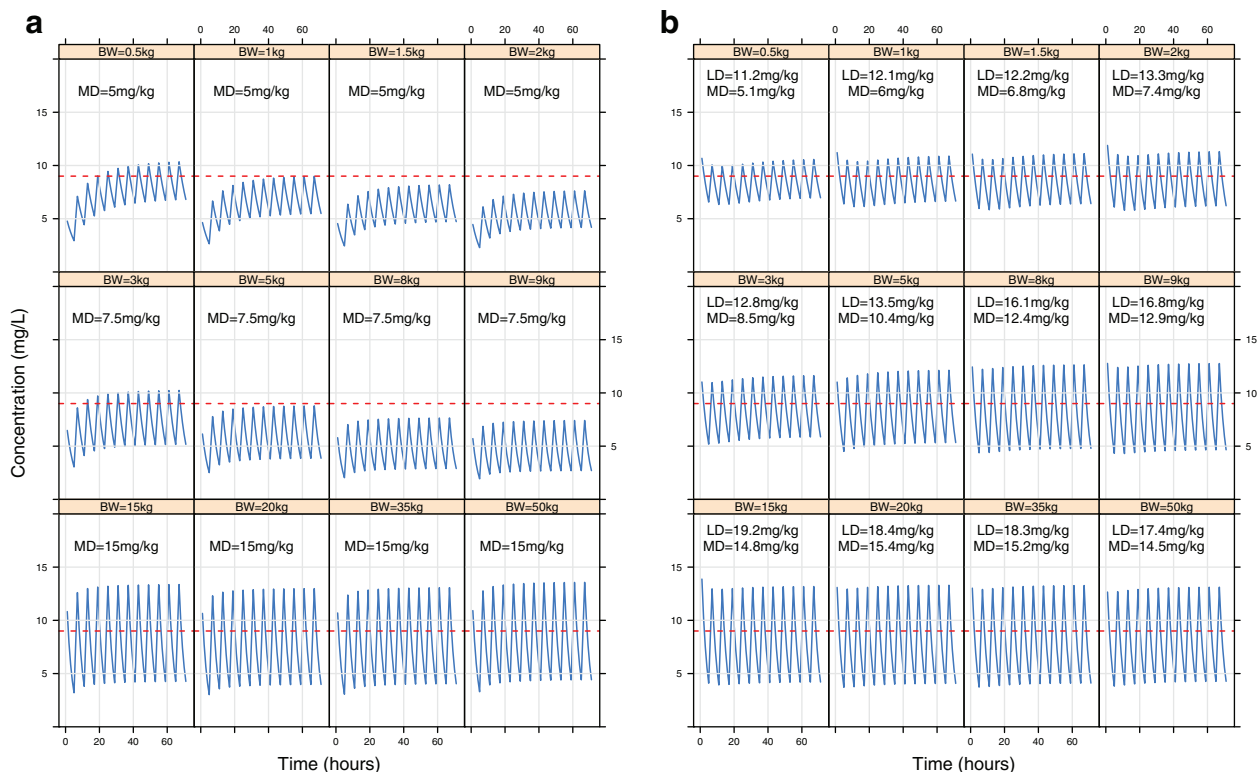


Figure 2. Simulated paracetamol concentration profiles of intravenously administered paracetamol 4 times daily based on a standard of care regimen as described in section Methods (panel a) and a final model optimized regimen (panel b, Table 3) for neonates with a body weight between 0.5 and 3 kg (upper row), neonates and infants weighing between 3 and 10 kg (middle row) and children with a weight between 10 and 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 standard of care 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.

particularly for pediatric studies where datasets are often sparse and variability is large.²⁹ Most importantly, Figure S2 shows that the model can be applied for individuals with a given bodyweight, age, PMA, or PNA because the Empirical Bayes Estimates (EBE) based post hoc interindividual variability of CL had no trend against either bodyweight or age (including PNA, PMA, and GA) (Figure S2), confirming that an appropriate final model has been reached.³³ These results demonstrate that the influence of bodyweight on CL as described by the highly non-linear BDE function also captures the influence of age (PNA, PMA, or GA) into account. However, caution is needed for this BDE function in case of data from obese individuals. There were no obese individuals in our datasets, therefore our model may not be valid for obese children.

We compared our model with previously reported models for paracetamol CL in children as listed in Table 4. The model reported by Zuppa et al¹¹ mainly studied children of 7kg onwards without reporting bodyweight range. The model reported by Mohammed et al¹² studied children from 1.8 years onwards and the model reported by Anderson et al also had access to data from a large

number of preterm and term neonates.¹⁰ The model-predicted paracetamol CL from these three models were derived by applying the respective maturation functions (Table 4) to the individual data in our analysis. The predictions were limited to the age range of the original studies (Table 4) in order to prevent unintended extrapolations of three literature models. In Figure 1 (right panel), we plotted the model predicted CL from the three previously published models¹⁰⁻¹² and from our model, against the individual bodyweights of all our individuals. This figure shows that the predictions of these four models were in reasonable agreement with each other, although different functions and covariates were used. For the neonatal range, the performance of the Anderson's model¹⁰ seemed in good agreement with the current model, even though the two models varied largely in functions and number of covariates (Table 4). For individuals aged between 40 days and 7 years with corresponding body weight between 7kg and 20kg (Figure 1 right panel), it seems that the models by Zuppa et al,¹¹ by Anderson et al,¹⁰ and by Mohammed et al¹² slightly overestimated CL compared to the estimates obtained in our study.

Table 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

BW (kg)	CL (L/h)	V (L)	t 1/2 (h)	Target Cavg (mg/L)	MD (mg)	MD/kg (mg/kg)	SoCMD/kg (mg/kg)	Target reached?	% DIFF MD/kg	L/M Ratio	LD (mg)	LD/kg (mg/kg)
0.5	0.047	0.18	2.6	9	2.5	5.1	5	Partly	+2%	2.2	5.6	11.2
1	0.11	0.36	2.2	9	6.0	6.0	5	No	+20%	2	12.1	12.1
1.5	0.19	0.54	2.0	9	10.2	6.8	5	No	+36%	1.8	18.3	12.2
2	0.27	0.72	1.8	9	14.8	7.4	5	No	+48%	1.8	26.7	13.3
3	0.47	1.08	1.6	9	25.5	8.5	7.5	Partly	+13%	1.5	38.3	12.8
5	0.96	1.79	1.3	9	51.8	10.4	7.5	No	+39%	1.3	67.3	13.5
8	1.8	2.87	1.1	9	99.1	12.4	7.5	No	+65%	1.3	128.9	16.1
9	2.1	3.23	1.0	9	116.2	12.9	7.5	No	+72%	1.3	151.0	16.8
15	4.1	5.38	0.9	9	221.9	14.8	15	Yes	-1%	1.3	288.4	19.2
20	5.7	7.17	0.9	9	307.2	15.4	15	Yes	+3%	1.2	368.7	18.4
35	9.9	12.55	0.9	9	533.0	15.2	15	Yes	+1%	1.2	639.6	18.3
50	13.4	17.93	0.9	9	724.8	14.5	15	Yes	-3%	1.2	869.8	17.4

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 standard of care dosing regimen is given.

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 standard of care dosing regimen; MD is the final model optimized maintenance dose = Target Cavg \times CL \times 6 h; MD/kg is the final model optimized maintenance dose per kilogram = MD/BW; SoCMD/kg is the maintenance dose per kilogram of the standard of care dosing regimen; Target Reached is the indication of whether the target concentration is reached with the standard of care dosing regimen; % DIFF MD/kg is the change of model based MD/kg from the SoCMD/kg in percentage = $100\% \times (\text{MD/kg} - \text{SoCMD/kg}) / \text{SoCMD/kg}$; 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 \times L/M Ratio; LD/kg is the final model optimized loading dose per kilogram.

The BDE function was originally developed on the basis of a very large and rich dataset from preterm neonates to adults on propofol.²² Later on, it was applied for scaling morphine across the entire human lifespan²³ and in the current study on paracetamol. Concerning the results from propofol, morphine, and paracetamol from the current study, 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). This similarity 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 semi-physiological function for glucuronidation in humans.” For a previously developed function for morphine glucuronidation from preterm neonates to 3-year-old children, this semi-physiological function concept recently was proposed and thereafter

evaluated using physiologically based modeling principles.^{34,35} In contrast with the similarity in ranges of exponent value (k) across three drugs, the current function for paracetamol differed from propofol and morphine by the k_{50} being 12. Two kilograms for paracetamol versus 3.78 and 4.01 kg for propofol and morphine, respectively, implying that paracetamol CL matures at a slower rate than glucuronidation of propofol and morphine. A possible explanation for this finding could be that paracetamol is not entirely metabolized through glucuronidation as sulphation plays an important role, particularly in neonates.¹¹ Therefore the current BDE model probably reflects a mixture of maturation processes with different rates for glucuronidation and sulfation.

Intravenous paracetamol is not licensed for use in children younger than 2 years of age in the United States.

Table 4. Paracetamol Clearance Across the Human Age Span: Comparison Between Previously Published Reports and the Current Study

Year	Author	Weight	Age-span	Covariate model for clearance
2005	Anderson et al ¹⁰	0.5–55 kg	PCA 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 ¹¹	Not reported	PNA 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 ¹²	13.7–56 kg	1.8–15 years	$CL = 16.51 \times (BW/70)^{0.75}$
	This study	0.5–94 kg	PCA 27 weeks—34 years	$CL = 17.6 \times (BW/70)^k$; $k = 1.204 - 0.454 \times BW^{1.4} / (12.2^{1.4} + BW^{1.4})^a$

CL, paracetamol clearance; BW, bodyweight; PCA, postconceptional age; PNA, postnatal age.

^aSee Table 2 for parameter estimates.

Although intravenous paracetamol is licensed in the EU for use in children of all age ranges except prematurely born neonates, there is a debate on the optimal dose for term neonates and children weighing less than 10 kg because higher doses than the label recommends are anticipated.³² Current doses for preterm neonates are based on expert opinion only.³² Simulation results from our study confirmed that 15 mg/kg maintenance doses are sufficient for children with a weight between 10 and 50 kg (Figure 2a and b). However, a dose of 7.5 mg/kg is not enough to reach 9 mg/L average paracetamol concentration in neonates or infants weighing 5, 8, or 9 kg. Besides, the maintenance dose of 5 mg/kg proved to be too low to reach the target concentration for a prematurely born neonate weighing 1, 1.5, or 2 kg (Figure 2a). Therefore, bodyweight adjusted doses were proposed for these two categories as presented in Table 3. These doses proved to be in accordance with previous calls for adjustment of the labeled dose in infants and neonates. Palmer et al³⁶ 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. Allegaert et al⁹ suggested a dosing regimen of 10 mg/kg every 6 hours within the age range 32–44 weeks PMA. Although final dose recommendations should consider not only the pharmacokinetics but also the pharmacodynamics and safety of paracetamol in neonates and infants, the current model can be the first step towards an evidence based dosing in children of all ages including preterm and term neonates. In addition, this BDE model can also be used to derive adjusted pediatric doses by use of Table 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.

Conclusions

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

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Declaration of Conflicting Interests

All authors declare no conflict of interest.

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Supporting Information

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