A novel maturation equation for hepatic clearance across preterm, term neonates, children, and adults: application to paracetamol and its metabolite

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Abstract

A preterm and term neonate to adult (PTNA) maturation equation was introduced recently to describe the glomerular filtration rate maturation from birth to adulthood for neonates of varying gestational age. This study aims to evaluate the newly developed PTNA equation against common maturation approaches like allometric scaling (AS0.75), the AS0.75 plus postmenstrual age (PMA)-based E_{max} (AS0.75 + PMA) equation, and the bodyweight dependent exponent equation (BDE) for the maturation of three hepatic pathways of paracetamol (PCM) from preterm and term neonates up to adults. A population pharmacokinetic analysis was conducted with pooled plasma and urine data of PCM, PCM-glucuronide (PCM-GLU), PCM-sulfate (PCM-SULF), and PCM-oxidative metabolites (PCM-OXI) (number of observations:6428) from 298 subjects, including preterm and term neonates, infants, children, and adults. PTNA, AS0.75, AS0.75 + PMA, and BDE were evaluated separately to describe the formation clearance of each PCM metabolite. Results indicated that the PTNA equation best described the formation clearance of PCM-GLU, outperforming the BDE and AS0.75 + PMA equations in both statistical and graphical evaluation metrics and inter-individual variability reduction. For PCM-SULF and PCM-OXI, the PTNA equation also had the best performance, but the improvements were smaller. The final model described the PK of PCM and its metabolites adequately among subpopulations as indicated by diagnostic plots. In conclusion, the PTNA maturation equation best describes the maturation of all hepatic elimination pathways of PCM. It can, as such, be potentially applied to other drugs and pathways when data from both preterm and term neonates and older children are part of the PK analysis.

Keywords

glucuronidation, maturation, oxidation, paracetamol, preterm neonates, sulfation

Introduction

Describing the maturation of clearance (CL) from children to adulthood in population pharmacokinetic (popPK) modeling relies on identifying the most influential covariates accounting for the between-subject variability, which can evolve with age. Specifically,

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within the heterogeneous population of preterm and term neonates in their first weeks and months of life, the degree of prematurity, often represented by covariates such as gestational age (GA), birthweight and/or postmenstrual age (PMA), and postnatal age (PNA) are important factors to predict CL.[1,2] As PNA increases, the impact of prematurity gradually gives way to postnatal maturity, and PNA is still required for accurate prediction of CL across this heterogeneous neonatal population. However, for older children, the impact of PNA on the PK diminishes, with bodyweight typically accounting for the majority of between-subject variability.[3–5] Consequently, describing the maturation of a given pathway in a population spanning preterm and term neonates to older infants, children, and adults presents the challenge of continuously quantifying the dynamic contributions of covariates across age.

There are several well-known empirical equations to describe clearance (CL) maturation from birth to adulthood, including the simple allometric scaling equation (AS0.75) with a fixed exponent of 0.75 using current body weight (CW) and the bodyweight-dependent exponent (BDE) equation that allows this exponent on CW to vary with weight.[6,7] Another type of equation uses the combination of CW and the sigmoid E_{max} equation of postmenstrual age PMA (AS0.75 + PMA equation), depicting gradual CL maturation in early life, which eventually leads to a mature adult clearance at a later age.[8]

Recently, a preterm and term neonate to adult (PTNA) maturation equation was published.[3] It describes the maturation of glomerular filtration rate (GFR) in both preterm and term neonates from birth to adulthood. This equation incorporates CW, birthweight, and a sigmoidal E_{max} equation based on PNA and GA. It allows the continuous description of the decreasing impact of prematurity and PNA at early ages and increasing impact of bodyweight in older children. Additionally, it allows for the description of the combined impact of prematurity and PNA on maturation by accounting for the effect of prematurity on the postnatal maturation.

Paracetamol (PCM), one of the most used analgesic and antipyretic drugs around the world,[9] is hepatically metabolized into PCM-glucuronide (PCM-GLU), PCM-sulfate (PCM-SULF), and the oxidative metabolites, that is, PCM-cysteine and mercapturate (PCM-OXI). Throughout childhood, the contribution of each metabolic pathway changes considerably, with sulfation dominating in neonates and the contribution of glucuronidation progressively increasing.[10–13] Many pharmacokinetic (PK) analyses of PCM in children have been published.[6,7,14–21] However, no attempts have been made to examine the maturation of PCM hepatic pathways across a wide age range, including preterm and term neonates beyond the first months of age. Given the aforementioned properties of the PTNA equation, we explored using this equation to describe the maturation of the three hepatic pathways involved in PCM metabolism.

This study aims to evaluate the common maturation covariate equations like AS0.75, the BDE and the AS0.75 + PMA equation, and the newly developed PTNA equation for the description of the development of PCM hepatic elimination pathways, that is, glucuronidation, sulfation, and oxidation, from pre(term) neonates up to adults.

Methods

Datasets

This analysis comprised pooled datasets with plasma and urine concentration–time data of PCM and its metabolites (PCM-GLU, PCM-SULF, PCM-cysteine, and mercapturate) after intravenous and/or rectal PCM or propacetamol from 298 subjects, including neonates,[7,17,18,22,23] infants,[19] children,[24] and adults.[21] Table 1 summarizes the demographic information for neonates,[7,17,18,23,22] while Table 2 presents the summary of data from infants,[19] children,[24] and adults.[21] GA information is exclusively available for datasets in Table 1 (less than 137 days of PNA). A uniform GA assumption of 40 weeks was made for infants and adults. Plasma metabolite concentration–time data were available in four datasets, including three neonatal datasets[7,23,22] and one adult dataset.[21]Three datasets[7,17,22] from neonates provided urine concentration–time data for both PCM and its metabolites. All studies' protocols have been approved by the ethics committees and more details can be found in the original papers.

Neonates

Dataset 1[22] consisted of plasma and urinary concentration–time data of PCM and its metabolites from 60 preterm neonates (GA $\leq$32 weeks, PNA between 0 and 10 days), who were included at the level three Neonatal Intensive Care Units (NICU) of the Erasmus Medical Center—Sophia Children's Hospital in Rotterdam and Isala Clinics in Zwolle, the Netherlands, between October 2010 and October 2013 (MEC-2009-250, National Trial Register 2290). The neonates were randomized to receive one dose of 10, 15, or 20 mg/kg PCM intravenously. After that, blood samples were scheduled to be collected at different time points (20, 60, 240, 540 min or 15, 30, 120, 360, and 720 min after the start of the infusion). Urine samples were scheduled to be collected from the diaper over a continuous period of a maximum of 12 h after PCM administration.

Table 1. Demographic Information for Included Datasets for Neonates

	Dataset 1 [22]	Dataset 2 [23]	Dataset 3 [7]	Dataset 4 [18]	Dataset 5 [17]	Total
Demographic information						
No. patients	60	88	35	30	22	235
Birthweight (g)	952 (462-1550)	1010 (540-1920)	2980 (523-4370)	2040 (531-4160)	3080 (558-3840)	1110 (462-4370)
Gestational age (weeks)	27.9 (24-31.1)	27.4 (24.4-31.9)	37 (23-41)	33.9 (26.9-39.9)	37.1 (23.4-40.4)	28.9 (23-41)
Current bodyweight (g)	952 (462-1550)	1110 (560-2190)	2800 (460-4200)	2000 (505-4000)	2980 (815-6300)	1190 (460-6300)
Postmenstrual age (weeks)	28.6 (24.9-31.7)	28.8 (24.7-39.4)	37.6 (23.1-41.6)	34 (27-40)	38.5 (29-60)	29.9 (23.1-60)
Postnatal age (days)	5.5 (0-10)	5.14 (0.06-78.8)	6 (1-26)	1 (1-1)	6.5 (1- 137)	5 (0-137)
Postnatal age (years)	0.0151 (0-0.0274)	0.0141 (0.000164-0.216)	0.0164 (0.00274-0.0712)	0.00274 (0.00274-0.00274)	0.0178 (0.00274-0.375)	0.0137 (0-0.375)
SEX, male (n) (%)	32 (53.33%)	37 (42.05%)	15 (42.86%)	15 (50%)	5 (22.73%)	104 (44.26%)
PNA at start of treatment(days)						
GA <28	6 (0-10)	7.08 (0.06-40.9)	10 (1-26)	1 (1-1)	22 (11-39)	7 (0-40.9)
GA 28-32	4 (0-7)	2.54 (0.06-78.8)	3 (2-5)	1 (1-1)	40 (3-77)	3 (0-78.8)
GA 32-37	-	-	6 (4-10)	1 (1-1)	2 (1-14)	1 (1-14)
GA ≥37	-	-	6 (2-12)	1 (1-1)	6.5 (3-137)	4 (1-137)
Dosing information, median (IQR)						
Weight-normalized dose (mg/kg)	15 (10-20)	9.27 (6.19-10.1)	15 (15-15)	15.3 (10.1-20)	10 (9.72-10.2)	9.83 (7.83-11.8)
Number of dose per ID (n)	1 (1-1)	21 (12-32)	6 (5-6)	1 (1-1)	12 (6-12)	13 (6-27)
Dose interval (h)	-	6.16 (5.78-8)	8 (8-9)	-	6 (6-6)	6.2 (5.93-8)
Treatment duration (days)	0.5 (0.385-0.51)	9 (4.59-18.9)	3 (2.83-3.02)	0.25 (0.188-0.417)	5 (3-5)	5.41 (3.02-10.7)
Number of plasma samples per ID						
Plasma PCM	4 (3-5)	5 (1-13)	8 (3-11)	7 (2-8)	9 (1-13)	7 (1-13)
Plasma PCM-glucuronide	4 (3-5)	5 (1-13)	8 (3-11)	-	-	5 (1-13)
Plasma PCM-sulfate	4 (3-5)	5.5 (1-13)	8 (3-11)	-	-	5 (1-13)
Plasma PCM-oxidative metabolites	4 (3-5)	6 (1-13)	8 (3-11)	-	-	5 (1-13)
Number of urine samples per ID						
Urine PCM	1 (1-1)	-	11 (2-16)	-	11 (1-12)	11 (1-16)
Urine PCM-glucuronide	1 (1-1)	-	11 (2-16)	-	11 (1-12)	11 (1-16)
Urine PCM-sulfate	1 (1-1)	-	11 (2-16)	-	11 (1-12)	11 (1-16)
Urine PCM-oxidative metabolites	1 (1-1)	-	11 (2-16)	-	-	11 (1-16)

GA, gestational age; IQR, Interquartile range; PNA, postnatal age.
Data are shown as median (range) unless indicated.

Table 2. Demographic Information for Included Datasets for Infants, Children, and Adults

	Dataset 6 [19]	Dataset 7 [24]	Dataset 8 [21]	Total
Demographic information				
No. patients	26	29	8	63
Birthweight (g)	3420 (3420-3570)	3420 (3420-3570)	3490 (3420-3570)	3420 (3420-3570)
Gestational age (weeks)	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)
Current bodyweight (g)	10,200 (7500-12,200)	19,000 (14,000-33,000)	69,600 (53,400-91,700)	15,000 (7500-91,700)
Postmenstrual age (weeks)	92.1 (45.7-109)	249 (144-405)	2180 (979-2650)	196 (45.7-2650)
Postnatal age (days)	365 (40.2-485)	1460 (730-2560)	15,000 (6570-18,200)	1100 (40.2-18,200)
Postnatal age (years)	1 (0.11-1.33)	4 (2-7)	41 (18-50)	3 (0.11-50)
SEX, male (n) (%)	9 (34.62%)	11 (37.93%)	4 (50%)	104 (44.26%)
Dosing information, median (IQR)				
Weight-normalized dose (mg/kg)	20.7 (20.6-21.1)	31.6 (31.6-31.6)	16.1 (12.5-18.1)	20.4 (16.6-20.9)
Number of dose per ID (n)	4 (4-4)	1 (1-1)	5 (4-5)	4 (4-4)
Dose interval (h)	5.99 (5.85-6.17)	-	5.42 (0.183-8.99)	5.94 (5.29-6.22)
Treatment duration (days)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Number of plasma samples per ID				
PCM	8 (3-10)	4 (1-5)	14 (12-15)	8 (1-15)
PCM-glucuronide	-	-	15 (12-15)	15 (12-15)
PCM-sulfate	-	-	15 (12-15)	15 (12-15)
PCM-oxidative metabolites	-	-	14 (12-15)	14 (12-15)
PCM-oxidative metabolites	-	-	14 (12-15)	14 (12-15)

IQR, Interquartile range; PNA, postnatal age.
Data are shown as median (range) unless indicated.

Dataset 2[23] consisted of plasma PCM and metabolite concentration–time data from 88 neonates (GA ≤32 weeks, PNA between 0 and 79 days) who were included in the drug dosage improvement in neonates (DINO) study (NL47409.078.14, MEC-2014-067, and NCT02421068) between September 2014 and July 2017. Multiple intravenous PCM doses, according to Wang et al[6] were given and could vary according to the clinical situation or treating physician, resulting in a median dose of 9.3 mg/kg PCM (interquartile range [IQR]:6.2-10.1). Blood samples were scavenged from routine care or strategically drawn to determine PCM and metabolite concentrations. No urine samples were collected.

Dataset 3[7] consisted of plasma and urinary PCM and metabolite concentration–time data from 35 preterm and term neonates (GA 23-41 weeks, PNA 1-26 days) with an indwelling arterial line and a clinical indication for intravenous analgesia who were admitted to intensive care units at the Children's National Health System (Washington, DC) (NCT01328808). Included neonates were either given five 15 mg/kg doses of *intravenous* PCM at 12-h intervals (<28 weeks' GA) or seven 15-mg/kg doses at 8-h intervals (>28 weeks' GA). Plasma samples were collected over 24 h following the first and final PCM doses. The urine samples were collected at 3- to 4-h intervals over the 24 h following the first and final PCM doses.

Dataset 4[18] consisted of plasma PCM concentration data from 30 preterm and term neonates (GA 27-40 weeks and PNA 1 day) in University Hospital, Gasthuisberg, Leuven, Belgium. They were given a single dose of propacetamol on the first day of life when they had minor, painful procedures or as an additional treatment for opioids. Fifteen patients received 20 mg propacetamol (i.e., 10 mg PCM)/kg intravenously, and the remaining 15 received a 40 mg (i.e., 20 mg PCM)/kg dose of propacetamol. Blood samples (0.2 mL) were taken from an arterial line 30, 60, 90, 120, 180, 240, and 600 min after the start of intravenous administration.

Dataset 5[17] consisted of plasma PCM concentrations and urinary PCM and metabolites data from 22 preterm and term neonates (GA 23-40 weeks and PNA 1-137 days) in the NICU of the University Hospital, Gasthuisberg, Leuven, Belgium. They were given multiple doses of propacetamol based on a standardized evaluation of pain and an analgesic algorithm according to a variety of surgical or medical interventions. A loading dose of 30 mg/kg propacetamol (i.e., 15 mg/kg PCM), followed by 20 mg/kg propacetamol (i.e., 10 mg/kg PCM) every 6 h in infants with a PMA age >36 weeks or every 8 h in infants with a PMA >36 weeks was administered. Collection of urine was started at the initiation of administration of the loading dose of propacetamol. It was achieved by either a urinary catheter, if already in place, or by a plastic collector. All urine was collected in 6- (PMA >36 weeks) or 8- (PMA <36 weeks) hourly aliquots. Besides collection of urine samples, blood samples were also collected every 3 h for

the first 12 h and at 6-h intervals thereafter in some of these neonates for the measurement of PCM.

Infants

Dataset 6[19] consisted of plasma PCM concentrations from 26 infants (aged 0.11-1.33 years and weighing 7.5-12.2 kg) after major craniofacial surgery performed at the pediatric surgical intensive care unit (PSICU) of the Erasmus MC – Sophia Children's hospital between September 2004 and February 2005. During surgery, all infants received a rectal loading dose of 40 mg/kg PCM 2 h before anticipated extubation. After surgery, all patients were extubated, admitted to PSICU, and were randomized to receive either a 15 min infusion of 40 mg/kg propacetamol (i.e., 20 mg/kg PCM) intravenously (12 subjects) or 20 mg/kg PCM rectally (14 subjects) every 6 h. Blood samples of 1 mL were taken from the arterial catheter at 15 min, 1 h, and 6 h after the first dose, at 5 min, 4 h, and 6 h after the third dose, and at 30 min, 2 h, and 3 h after the fourth dose.

Children

Dataset 7[24] consisted of plasma PCM concentrations from 29 children (aged 2-7 years and weighing 14-33 kg) with PCM for analgesia after adenotonsillectomy during the period from July 2000 to November 2001. Patients received a loading dose of 40 mg/kg rectally PCM and a maintenance dose of 30 mg/kg rectally every 8 h. Blood samples (1.0 mL) for PCM were taken through a peripheral intravenous cannula at the start and the end of surgery and 1, 2, and 3 h postoperatively.

Adults

Dataset 8[21] consisted of plasma PCM and its metabolites data from eight healthy patients (aged 18-50 years and weighing 53.4-91.7 kg) undergoing oral and maxillofacial surgery at St. Antonius Hospital in The Netherlands (ClinicalTrials.gov study ID NCT01764555; EudraCT number 2012-000956- 32). All patients received 2000 mg of PCM intravenously (two doses of 1000 mg each, consecutively delivered over 20 min) before induction of anesthesia. Blood samples were collected at T = 0, 2.5, 7.5, 15, 30, and 45 min, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h after the end of the 2000 mg infusion. After 8 h of blood sampling, the standard postoperative pain protocol was initiated (i.e., 1000 mg of intravenous PCM every 6 h). One last blood sample was taken 24 h after the end of the 2000 mg PCM infusion, and other PCM doses were given according to the standard protocol.

Model Development

The popPK analysis was performed with the nonlinear mixed effects modeling software NONMEM version 7.5.1. (ICON Development Solutions, Ellicott City, MD) aided with Perl-speaks-NONMEM (PsN) (version 5.2.6, Uppsala University, Uppsala, Sweden). R (version 4.4.1; R Core Team) was used to visualize the outputs and evaluate the models. Population parameters were estimated using the first-order conditional estimation with interaction (FOCEI) method and the ADVAN6 subroutine. The number of significant digits required for convergence (NSIG), predicted values (TOL), and the objective function (SIGL) were set to 2, 6, and 6, respectively. Parameter precision was obtained with the R covariance matrix.

For intravenously administered propacetamol, one unit propacetamol was converted to 0.5 units of PCM as dosing input for the PK analysis.[17] All metabolite concentrations were expressed in PCM equivalents (mg/L) via conversion based on molecular weights. PCM-mercapturate and PCM-cysteine concentrations were summed up to represent the metabolites formed in the oxidation pathway (PCM-OXI). Urine concentrations and urine volumes for PCM and metabolite urine samples were included in the NONMEM input dataset so that NONMEM could scale appropriately to urinary amounts. The concentrations of PCM and all metabolites were logarithmically transformed.

Base Model

A two-compartment linear model was used to describe the disposition of PCM, and one-compartment models for each metabolite.[23] To describe the process of rectal absorption for individuals (dataset 6[19] and 7[24]) who were given PCM 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. These parameters were fixed at the values from the model by Wang et al,[6] as the datasets in which rectal dosages were given (datasets 6[19] and 7[24]) were previously modeled in their study. Total PCM clearance was assumed to be equal to the sum of formation CL of PCM-GLU, PCM-SULF and PCM-OXI, and renal excretion of the unchanged mother compound.[23] The metabolites were assumed to be solely renally excreted unchanged.[25]

In the base model, the AS0.75 equation was implemented for the formation CL of each metabolite to capture all data from all individuals ranging from preterm neonates to adults. Regarding volume of distribution, for PCM, the central volume of distribution and inter-compartment CL were estimated and scaled with current bodyweight using power functions with estimated exponents. The volumes of distribution of the metabolites were assumed to be an estimated fraction, constant throughout life, of the central volume of distribution of PCM (Equation 1). This assumption assured the structural identifiability of the formation

CL of the metabolites in adults when no urine samples were available.

$$V_m = \theta_{f,volume} \times V_{c,PCM} \quad (1)$$

where V_m is the distribution volume for the metabolite and $V_{c,PCM}$ is the central volume of distribution of PCM, and $\theta_{f,volume}$ is the estimated fraction of the volume for the metabolites compared to $V_{c,PCM}$.

Regarding renal elimination clearance of PCM and metabolites, we assumed that the renal elimination clearance of unchanged PCM and its metabolites was an estimated fraction of GFR which allowed it to be lower or higher than GFR (Equation 2). The GFR values for each patient were calculated using the equation developed in a previous study (Equation 3).[3]

$$C\,L_r = \theta_{f,renalCL} \times GFR \quad (2)$$

$$GFR\ (L/h) = 1.26 \times \frac{Bwb}{1.75} + \frac{\left(8.98 \times \left(\frac{CW}{1.75}\right)^{0.738} - 1.26 \times \frac{Bwb}{1.75}\right) \times PNA^{1.03}}{\left(\frac{GA}{34}^{-3.61} \times 34\right)^{1.03} + PNA^{1.03}} \quad (3)$$

where CL_r is the renal CL for the unchanged PCM and its metabolites and $\theta_{f,renalCL}$ is the estimated fraction of the renal CL for the aforementioned compounds compared to the GFR. Bwb is the birthweight in kilos, GA the gestational age in weeks, PNA is the PNA in days, and CW is the current weight in kilos.

Evaluation of Different Maturation Equations for the Formation Clearance of Metabolites

To evaluate the different maturation equations, we tested whether the three maturational equations (i.e., BDE,[6] AS0.75 + PMA,[8] and PTNA[3]) would lead to an improvement over the base model in which the formation CL was described using allometric scaling (AS0.75). The evaluation was conducted in a stepwise way. In step 1 we replaced the AS0.75 equation with BDE, AS0.75 + PMA equation and the PTNA maturation equation separately for each pathway. The model with the largest objective function values (OFV) reduction from the base model was selected, with a chosen maturation equation for that pathway. In step 2, we kept the covariate equation chosen from step 1 and tested the maturation models for the remaining two pathways separately. The model with the lowest OFV in step 2 was chosen for step 3 where different equations were tested for the remaining pathway. Except for OFV, we also evaluated GOF plots (split for different covariates), plots of individual ETA values versus covariate values (ETA plots vs GA, PNA, CW, etc.), and the reduction in inter-individual variability (IIV) on the parameter of interest. The description of the four maturation equations is given below.

AS0.75 Equation

$$C\,L_i = CL_p \times \left(\frac{CW_i}{1.75}\right)^{0.75} \quad (4)$$

where the CLi is clearance in the i-th individual with current weight CW_i in kilos; CL_p is the typical clearance in an individual with a current weight of 1.75 kg. The exponent of current weight on clearance was fixed at 0.75.

BDE Equation

$$C\,L_i = CL_p \times \left(\frac{CW_i}{1.75}\right)^{k} \quad (5)$$

$$k = k_0 - \frac{k_{max} \times CW_i^{Hill}}{k_{50}^{Hill} + CW_i^{Hill}} \quad (6)$$

where the CL_i is clearance in the i-th individual with current weight CW_i in kilos; CL_p is the typical clearance in an individual with a current weight of 1.75 kg; k is the exponent; k_0 is the value of the exponent at a theoretical current weight of 0 kg; k_{max} is the maximum decrease of the exponent; k_{50} is the current weight at which a 50% decrease in the maximum decrease of exponent value is attained, and the Hill coefficient determining the steepness of sigmoidal decline in the exponent. The $k_0 - k_{max}$ value was fixed at 0.75, meaning that the exponent k will eventually reach 0.75.

AS0.75 + PMA Equation

$$C\,L_i = CLp_{max} \times \left(\frac{CW_i}{1.75}\right)^{0.75} \times \left(\frac{PMA_i^{Hill}}{PMA_{50}^{Hill} + PMA_i^{Hill}}\right) \quad (7)$$

where the CL_i is clearance in the i-th individual with current weight CW_i in kilos and PMA_i in weeks; CLp_{max} is the maximum clearance scaled with a current weight of 1.75 kg with an exponent fixed at 0.75; PMA_{50} is the PMA at which a 50% of the maximum clearance is attained, and the Hill coefficient determining the steepness of sigmoidal increase of the PMA-based maturation.

PTNA Equation

$$C\,L_i = CLp_{birth} \times \left(\frac{Bwb_i}{1.75}\right)^{\theta_{BWb}} + \frac{\left(CLp_{max} \times \left(\frac{CW_i}{1.75}\right)^{0.738} - CLp_{birth} \times \left(\frac{Bwb_i}{1.75}\right)^{\theta_{BWb}}\right) \times PNA_i^{Hill}}{\left(\frac{GA_i}{34}^{GA_{PNA_{50}}} \times PNA_{50}\right)^{Hill} + PNA_i^{Hill}} \quad (8)$$

This equation was previously used to describe the maturation of GFR in preterm and term neonates from birth to adulthood,[3] was applied in the current study with parameters re-estimated for each pathway of PCM. In this equation, CL_i is clearance in the i-th individual with current weight CW_i in kilos and PNA_i in days, Bwb_i in kilos, and GA_i in weeks; CLp_{birth} is the CL at birth scaled with birthweight (Bwb) of 1.75 kg with an exponent of θ_{BWb}, CLp_{max} is the maximum CL scaled with a CW of 1.75 kg with an exponent of 0.738 (fixed parameter to increase the stability of the model); PNA_{50} is the PNA at which 50% of the maximum CL is attained, scaled for gestational age (GA), $GA_{PNA_{50}}$ is the impact of GA on PNA_{50}, the Hill coefficient determines the steepness of sigmoidal increase.

Stochastic Model

Between subject variability (BSV) was implemented on structural parameters where required assuming log-normal distribution. For the residual error, an additive error model for log-transformed concentrations was used.[6,23]

Model Refinement

After the best maturation equation for each pathway was determined, the model was checked for misspecification and refined if necessary.

Model Evaluation

Goodness of Fit (GOF) plots split for GA and PNA and dataset were used for model evaluation. A bootstrap analysis (n = 200) stratified on datasets was performed to assess the stability of the final model and parameter estimates. A normalized prediction distribution error (NPDEs) analysis was performed based on 1000 simulations to evaluate the predictive ability of the final model. Each observed concentration was compared to the range of simulated concentrations using the NPDE package in R, in output stratified for each compound and biological matrix of the measurement.[26]

Model Simulation

To illustrate the maturation of the total PCM CL and the CL of each elimination pathway, the population estimates of the final model were used to simulate the CL of PCM and the formation CL of glucuronidation, sulfation, oxidation, and renal elimination CL of unchanged PCM in four typical individuals from birth to 18 years old, born with a GA of 26, 30, 35, and 40 weeks, corresponding to birthweights of 850, 1350, 2450, and 3500 g, respectively.

Results

Evaluation of Different Maturation Equations for the Formation Clearance of Metabolites

Compared to the base model with AS0.75 implemented, replacing the formation CL of PCM-GLU with the other three maturations equations BDE, AS0.75 + PMA, and PTNA reduced the OFVs most compared to the other pathways, regardless of the maturation equations. The PTNA equation led to the highest drop in OFV compared to the BDE and AS0.75 + PMA models (ΔOFV = −415, −345, and −325, respectively). Besides that, the PTNA function corrected the trends in ETA on PCM-GLU formation CL with PNA and GA, which were obvious when applying the other maturation equations (Figure 1). Additionally, it reduced IIV on PCM-GLU formation CL from 115% to 55%, which was lower than the BDE equation and AS0.75 + PMA equation (69% and 61%, respectively). Figure S1 shows the model predictions of absolute clearance across age of the AS0.75, BDE and AS0.75 + PMA equations for PCM-GLU compared to the prediction of the PTNA equation. The difference between PTNA and the other equations was the smallest during the period where the data was the most abundant (preterm neonates within first month of age), but can be more than 10-fold different (AS0.75) and around 3-fold different at some ages for the other maturation equations.

In the second step, the formation CL of PCM-SULF was described using the PTNA equation, which resulted in the lowest OFV. The reduction of OFV values was −100, −78, and −62 for the PTNA, BDE, and AS0.75 + PMA equations, respectively. In the equation, the effect of GA on the postnatal maturation ($GA_{PNA_{50}}$, Equation 88) was insignificant and was removed from the equation (ΔOFV = +2.67, $P > .05$). Compared to the other maturational models, this model improved the ETA versus GA plot and slightly improved the ETA versus PNA plot (Figure 1). IIV was reduced from

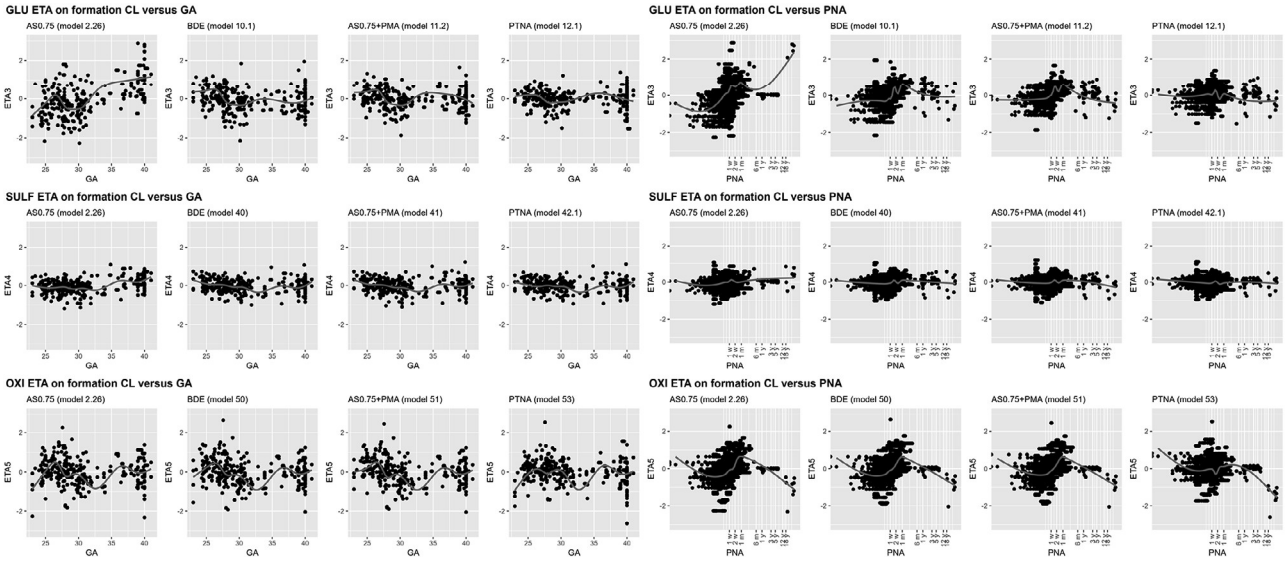

Figure 1. ETA plots of formation clearance (CL) of paracetamol glucuronide (GLU), paracetamol sulfate (SULF) and paracetamol oxidative metabolites (OXI). AS0.75 is allometric scaling equation; BDE is the bodyweight dependent exponent equation; AS0.75 + PMA equation is the allometric equation with sigmoidal E_{max} model based on postmenstrual age (PMA); PTNA is the preterm and term neonate to adult maturation equation; PNA is the postnatal age; GA is the gestational age.

45% to 37% from the model with AS0.75 to the PTNA model.

Regarding PCM-OXI, similarly to the PCM-SULF, the PTNA maturation equation resulted in the largest OFV reduction compared to the BDE and AS0.75 + PMA equation (−90, −20, and −16, respectively), and it significantly improved the ETA versus GA plot and ETA versus PNA plot (Figure 1). The reduction of IIV was 79% to 73% when compared to the AS0.75 model. The model selection process for the formation clearance of the metabolites with values of OFV and IIV on formation CL is shown in Table S1.

Model Refinement

Improvement of the Description of Renal Elimination Clearance of PCM-SULF. After carefully examining the GOF plots split by GA and PNA, we noticed a slight misfit of PCM-SULF concentrations with increasing GA and PNA. Combined with the indications from the ETA plots versus GA and PNA, this was most likely attributed to the underprediction of the renal elimination CL of PCM-SULF, which increased with GA and PNA. As the renal elimination of PCM-SULF was reported also to involve renal secretion,[27] we included an equation to describe the renal secretion that matures with GA and PNA, using the structure of the PTNA maturation equation (Equation 8), and added this to the GFR fraction equation (Table 3). Then, the PTNA equation used to describe the maturation of secretion CL was simplified by fixing the CLp_{birth} to 0 and Hill to 1, which did not significantly influence the fit (ΔOFV = +0.9, df = −2, $P > .05$). The addition of renal secretion reduced OFV by 88 points (df = 3), with IIV of the fraction of renal sulfate CL compared to GFR slightly changing from 50% to 40%. By introducing this additional equation, the renal CL of PCM-SULF changed from 31% of GFR from birth to 163% in adulthood, and the trends in split GOF plots and ETA plots for PCM-SULF were resolved.

Misspecifications of PCM-GLU in the adult dataset were observed in the GOF plots and ETA versus PNA plots. These trends were attributed to the underestimation of the renal CL of PCM-GLU in adulthood. Considering the reported renal CL of PCM-GLU close to or exceeding GFR in adults,[28–30] a correction factor was added to the renal CL of PCM-GLU in adult data. This addition reduced the OFV of 7 points ($P < .01$) and improved the GOF plots. This addition led to the renal CL of PCM-GLU increasing from 44% in neonates and children to 74% of the GFR in adults.

Final Model. Figure 2 schematically represents the final model structure. Table 3 shows the final estimates of the model. The goodness-of-fit plots of plasma and urine samples (Figures S2 and S3) indicate that the final model describes the plasma concentrations and excreted amounts of PCM and its metabolites adequately, except for a slight underprediction of PCM-OXI in the adult data.

Model Evaluation. No structural trends were observed in NPDEs when plotted against time after dose (TAD) and individual predicted concentrations, even though

Table 3. Parameter Estimates of the Final Model

Parameters	Estimates (RSE%)	IIV (RSE %) [Shrinkage %]	Bootstrap median (95 % CI)
Paracetamol			
$Vp(L) = TV_{vp} \times \frac{BW_c}{1080}^{\theta_{BWc}}$	-	-	-
TV_{vp}	1.01 (2.8%)	27.38 (6) [19.7]	1.01 (0.962-1.07)
θ_{BWc}	0.978 (2%)	-	0.974 (0.938-1.02)
$Vpp(L) = TV_{vpp} \times \frac{BW_c}{1080}^{\theta_{BWc}}$	-	-	-
TV_{vpp}	0.2707 (9.8%)	-	0.268 (0.218-0.337)
θ_{BWc}	0 FIXED	-	0 (0-0)
$Q(L/h) = TV_Q \times \frac{BW_c}{1080}^{\theta_{BWc}}$	-	-	-
TV_Q	0.0892 (23%)	-	0.085 (0.0529-0.119)
θ_{BWc}	2.212 (26%)	-	2.14 (1.1-2.51)
Ka ($\frac{1}{h}$)	0.275 FIXED[a]	64.43 (13) [64.6]	0.275 (0.275-0.275)
Tlag (h)	0.0103 FIXED[a]	-	0.0103 (0.0103-0.0103)
F	0.96 FIXED[a]	0 FIXED	0.96 (0.96-0.96)
Formation CL			
PCM-GLU	-	-	-
$CL_{formation,\ GLU}\ (Lh) = TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}} + \frac{(TV_{CL_{max}} \times \frac{BW_c}{1750}^{\theta_{BWc}} - TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}}) \times PNA^{Hill}}{(\frac{GA}{34}^{\theta_{GAPNA50}} \times TV_{PNA_{50}})^{Hill} + PNA^{Hill}}$			
$TV_{CL_{birth}}$	0.00796 (18%)	55.99 (6.6) [24.1]	0.00774 (0.00323-0.0113)
θ_{BWb}	1.515 (16%)	-	1.44 (0.676-2.06)
$TV_{CL_{max}}$	0.3378 (15%)	-	0.338 (0.257-0.429)
θ_{BWc}	0.738 FIXED	-	0.738 (0.738-0.738)
$TV_{PNA_{50}}$	62.67 (23%)	-	61.7 (37.1-112)
$\theta_{GAPNA50}$	−4.625 (14%)	-	−4.75 (−6.38 to 1.71)
Hill	1.553 (8.9%)	-	1.57 (1.19-2.1)
PCM-SULF	-	-	-
$CL_{formation,\ SULF}\ (L/h) = TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}} + \frac{(TV_{CL_{max}} \times \frac{BW_c}{1750}^{\theta_{BWc}} - TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}}) \times PNA^{Hill}}{(\frac{GA}{34}^{\theta_{GAPNA50}} \times TV_{PNA_{50}})^{Hill} + PNA^{Hill}}$			
$TV_{CL_{birth}}$	0.1854 (4.2%)	36.1 (5.9) [18.8]	0.186 (0.174-0.202)
θ_{BWb}	1.173 (5%)	-	1.16 (1.04-1.28)
$TV_{CL_{max}}$	0.3787 (11%)	-	0.393 (0.288-0.496)
θ_{BWc}	0.738 FIXED	-	0.738 (0.738-0.738)
$TV_{PNA_{50}}$	25.92 (24%)	-	25.2 (13.5-53.2)
$\theta_{GAPNA50}$	0 FIXED	-	0 (0-0)
Hill	1.955 (23%)	-	2.04 (1.31-19.7)
PCM-OXI	-	-	-
$CL_{formation,\ OXI}\ (L/h) = TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}} + \frac{(TV_{CL_{max}} \times \frac{BW_c}{1750}^{\theta_{BWc}} - TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}}) \times PNA^{Hill}}{(\frac{GA}{34}^{\theta_{GAPNA50}} \times TV_{PNA_{50}})^{Hill} + PNA^{Hill}}$			
$TV_{CL_{birth}}$	0.02047 (13%)	70.49 (5.9) [25.6]	0.0201 (0.0155-0.0268)
θ_{BWb}	0.978 (17%)	-	0.973 (0.591-1.22)
$TV_{CL_{max}}$	0.06377 (12%)	-	0.0618 (0.0456-0.0826)
θ_{BWc}	0.738 FIXED	-	0.738 (0.738-0.738)
$TV_{PNA_{50}}$	10.47 (12%)	-	10.2 (7.01-12.8)
$\theta_{GAPNA50}$	0 FIXED	-	0 (0-0)
Hill	2.972 (17%)	-	3.17 (2.48-20)

(*Continued*)

Table 3. (Continued)

Parameters	Estimates (RSE%)	IIV (RSE %) [Shrinkage %]	Bootstrap median (95 % CI)
Renal elimination			
PCM	-	-	-
$CL_{r,\ PCM}$ (L/h) = $f_{PCM} \times GFR$	-	-	-
f_{PCM}	0.08486 (9.7%)	78.2 (10) [50.5]	0.0852 (0.073-0.0959)
PCM-GLU	-	-	-
$CL_{r,GLU}$ (L/h) = $f_{GLU} \times GFR \times f_{GLU,\ adult}$	-	-	-
f_{GLU}	0.4475 (6.5%)	40.89 (12) [48.2]	0.438 (0.401-0.491)
$f_{GLU,\ adult}$	1.663 (18%)	-	1.65 (1.37-2.09)
PCM-SULF	-	-	-
$CL_{r,SULF}$ (L/h) = $f_{SULF} \times GFR + CL_{secretion,\ SULF}$			
$CL_{secretion,\ SULF} = TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}} + \frac{(TV_{CL_{max}} \times \frac{BW_c}{1750}^{\theta_{BWc}} - TV_{CL_{birth}} \times \frac{BW_b}{1750}^{\theta_{BWb}}) \times PNA^{Hill}}{(\frac{GA}{34}^{\theta_{GAPNA50}} \times TV_{PNA_{50}})^{Hill} + PNA^{Hill}}$			
f_{SULF}	0.3059 (12%)	41.5 (7.4) [34.8]	0.308 (0.24-0.381)
$TV_{CL_{birth}}$	0 FIXED	-	0 (0-0)
θ_{BWb}	0 FIXED	-	0 (0-0)
$TV_{CL_{max}}$	11.92 (20%)	-	12 (10.1-13.8)
θ_{BWc}	0.738 FIXED	-	0.738 (0.738-0.738)
$TV_{PNA_{50}}$	80.03 (28%)	-	81.1 (58.8-118)
$\theta_{GAPNA50}$	−5.849 (11%)	-	−5.85 (−7.39 to 4.7)
Hill	1 FIXED	-	1 (1-1)
PCM-OXI	-	-	-
$CL_{r,\ OXI}$ (L/h) = $f_{OXI} \times GFR$	-	-	-
f_{OXI}	0.7393 (6.8%)	42.38 (10) [48.6]	0.728 (0.643-0.808)
Volume of distribution			
VG (L) = $f_{VG} \times VP$			
VS (L) = $f_{VS} \times VP$			
VO (L) = $f_{VO} \times VP$			
f_{VG}	0.3299 (6.8%)	-	0.327 (0.288-0.379)
f_{VS}	0.3476 (3.8%)	-	0.351 (0.316-0.386)
f_{VO}	0.7048 (6.9%)	-	0.697 (0.605-0.803)
Other parameters			
Correction factor for urine volume	3.068 (8%)	0 FIXED	2.99 (2.32-4.2)
Residual error (variance)			
Exponential error for plasma PCM	0.0706 (2.2%)	[10.6]	0.069 (0.056-0.088)
Exponential error for plasma GLU	0.2602 (2.8%)	[10.8]	0.258 (0.176-0.366)
Exponential error for plasma SULF	0.08214 (2.9%)	[13]	0.083 (0.066-0.1)
Exponential error for plasma OXI	0.1558 (2.8%)	[12.3]	0.156 (0.134-0.181)
Exponential error for urine PCM	0.6132 (3.4%)	[6.7]	0.610 (0.477-0.808)
Exponential error for urine GLU	0.5661 (3.6%)	[5]	0.57 (0.465-0.669)
Exponential error for urine SULF	0.9305 (3.2%)	[1.1]	0.944 (0.712-1.21)
Exponential error for urine OXI	0.8032 (4%)	[3.5]	0.789 (0.632-0.988)

BWb, birthweight; BWc, current bodyweight; CLrP, CLrG, CLrS, and CLrO are the renal clearance of PCM and its respective metabolites; PCM, GLU, SULF, and OXI represents paracetamol, paracetamol-glucuronide, paracetamol-sulfate, and the combined oxidative metabolites (paracetamol-cysteine and paracetamol-mercapturate), respectively; Qp is the inter-compartmental clearance of PCM; VP, VG, VS, and VO are the distribution volumes of the central compartment of PCM, PCM-glucuronide, PCM-sulfate, and the combined oxidative metabolites, respectively; VPP is distribution volume of the peripheral compartment of PCM.

[a] Parameters fixed according the model estimates from Wang et al (2014).[6]

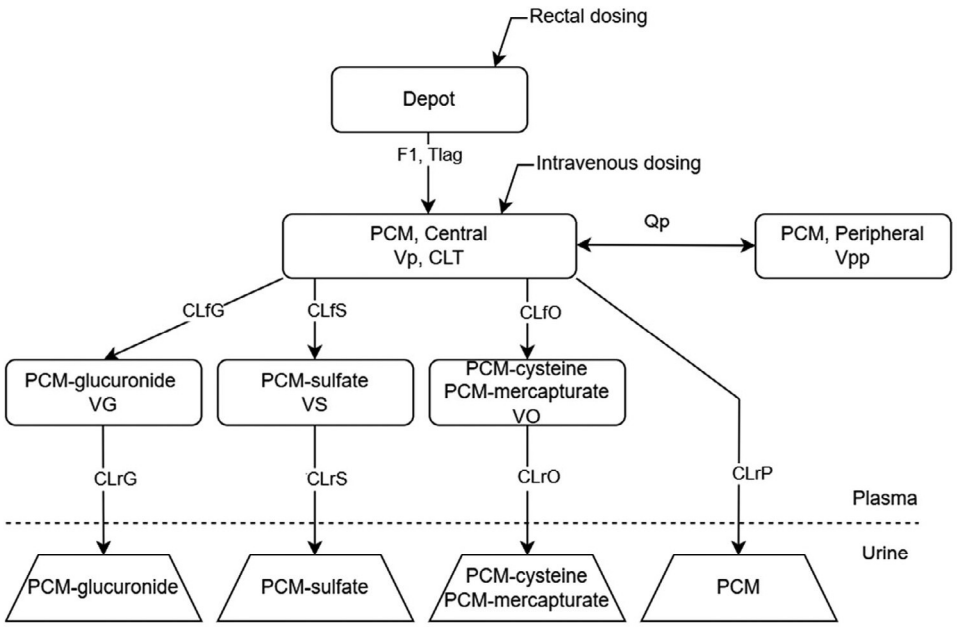

Figure 2. Schematic illustration of the final model of paracetamol (PCM) and its metabolites. CLfG, CLfS, CLfO are the formation clearance of PCM-glucuronide, PCM-sulfate, and the combined oxidative metabolites (PCM-cysteine and PCM-mercapturate), respectively; CLrP, CLrG, CLrS, and CLrO are the renal clearance of PCM and its respective metabolites; CLT is the total PCM clearance and is the sum of CLfG, CLfS, CLfO and CLrP; F1 is the rectal bioavailability; Qp is the inter-compartmental clearance of PCM; Tlag is the lag time in rectal absorption; VP, VG, VS, and VO are the distribution volumes of the central compartment of PCM, PCM-glucuronide, PCM-sulfate and the combined oxidative metabolites, respectively; VPP is the distribution volume of the peripheral compartment of PCM.

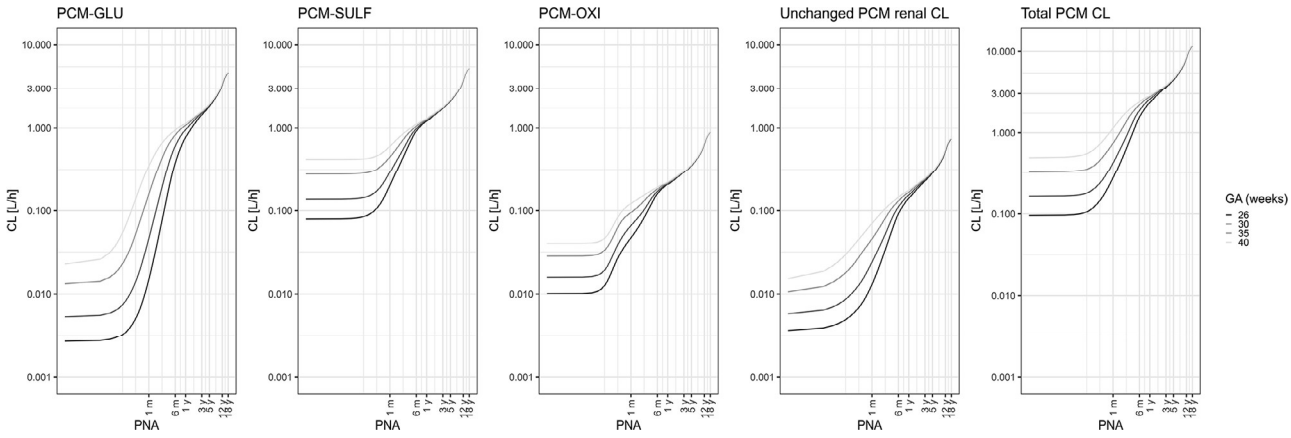

Figure 3. Absolute clearance values for total paracetamol clearance and the four elimination pathways of paracetamol versus postnatal age (PNA) for different gestational age (GA) according to the final model. PCM, PCM-GLU, PCM-SULF, and PCM-OXI represents paracetamol, paracetamol-glucuronide, paracetamol-sulfate, and the combined oxidative metabolites (paracetamol-cysteine and paracetamol-mercapturate), respectively.

an overprediction of the variability was seen (Figure S4).

Model Simulation. Figures 3 and 4 show the maturation of total PCM CL and the formation CL of the four pathways from birth to 18 years for individuals born with GA of 26, 30, 35, and 40 weeks. Generally, CL increases with GA and PNA and bodyweight. At first there is a large difference between individuals with different GA. The differences diminish with increasing PNA, until a point when all GA neonates reach full age-related maturation and only bodyweight has an impact on CL. It was predicted that 97% of the age-related maturation is reached at PNA of 587, 153, 34 and 993 days for PCM-GLU (for a median GA of 34 weeks), PCM-SULF, PCM-OXI, and renal clearance of PCM (for a median GA of 34 weeks).

Overall, PCM-GLU contributes only 2%-4% of total CL at birth but increases to 41% in adulthood. PCM-SULF accounts for around 80% of the total PCM CL

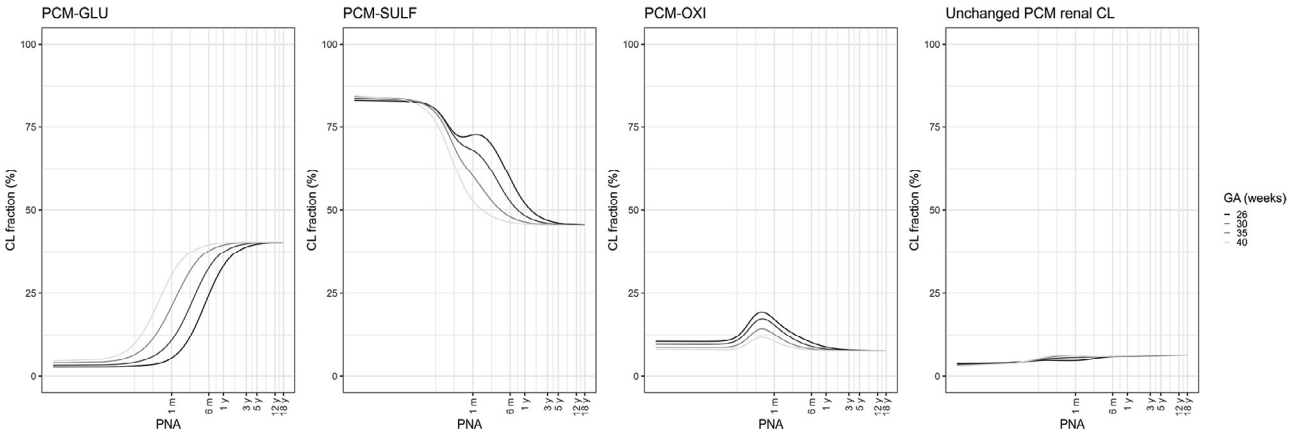

Figure 4. Fraction of total paracetamol clearance of the different elimination pathways of paracetamol versus postnatal age (PNA) for different gestational age (GA) according to the final model. PCM, PCM-GLU, PCM-SULF, and PCM-OXI represents paracetamol, paracetamol-glucuronide, paracetamol-sulfate, and the combined oxidative metabolites (paracetamol-cysteine and paracetamol-mercapturate), respectively.

at birth, is decreasing rapidly after birth, stabilizing at 45% in adulthood. Oxidation begins at around 8%-11% at birth, and after reaching its maximum at around 20 days of PNA, it decreases and eventually stabilizes at around 8% of the total PCM CL in adulthood. The relative proportions of glucuronidation, sulfation, oxidation, and renal clearance of unchanged PCM may vary for neonates with different GA at the same PNA. For instance, at 1 month of age, these fractions are 5%, 72%, 17%, and 4% for a 26-week preterm neonate, while for a 40-week term neonate, they are 30%, 52%, 10%, and 6%, respectively. In the latter case, the glucuronidation fraction already surpasses oxidation at 1 month of age.

Discussion

This study is the first attempt to describe the maturation of PCM hepatic elimination pathways from birth up to adulthood for both, preterm and term-born individuals. By integrating both plasma and urine samples of PCM and its metabolites across various age groups—from preterm and term neonates up to infants, children, and adults—our study was able to evaluate different maturational equations at different ages. Our findings highlight the superiority of the PTNA equation in describing the CL of glucuronidation, sulfation, and oxidation pathways of PCM in case of a combined preterm and term neonate, older children and adult dataset. The advantages of the PTNA equation allow a more accurate estimation of clearance (CL), which can facilitate better dosing strategies for pediatric populations with varying GA, particularly for preterm neonates reaching 1 month of age, a critical yet understudied period.

While other maturation equations have the advantage of being simple and easy to use, they lose flexibility in describing younger populations when multiple factors still impact CL. The AS0.75 overlooks the PNA-related maturation, resulting in an increasing trend in the ETA plot with increasing PNA (Figure 1, Figure S1). The BDE equation attempts to describe the fast maturation at an early age by estimating a different exponent on bodyweight, rather than a fixed 0.75, which did improve the model fit and the trend in ETA plots (Figure 1). However, solely relying on bodyweight as a covariate still neglects the differences in age including GA and PNA, where the predicted CL for older preterm neonates is identical to that of younger term neonates when they have the same bodyweight. Consequently, this function underpredicted CL for older preterm neonates and overpredicted CL for younger term neonates (negative trend of ETA vs GA and positive trend of ETA vs PNA in Figure 1). The AS0.75 + PMA equation assumes the same effect from the GA and PNA effect by using only PMA as a maturation factor, resulting in CL underprediction for lower GA with higher PNA, although to a lesser extent than the BDE equation (Figure 1).

This study benefits from ample plasma and urine data for PCM and its metabolites from preterm and term neonates within the first 2 months of age, allowing a separate estimation of formation and elimination CL of the metabolites and therefore enabling us to effectively capture the maturation of different pathways during this critical period. At birth, glucuronidation CL showed minimum activity (below 0.01 L/h) until 30 weeks of GA (Figure 3), consistent with findings by Kawade et al[31] who reported no increase in UDP-glucuronosyltransferase (UGTs) activity toward bilirubin until 30 weeks of gestation, followed by accelerated maturation between 30 and 40 weeks of gestation. Prematurity impacts the postnatal maturation, as glucuronidation reaches only 12.5% of total PCM

clearance in 32-week neonates at 1 month of age, compared to 40-week neonates reaching the same level at only 9 days of age. This observation explains the seemingly contradictory results of the relative fraction of glucuronidation in the two previous PCM popPK studies.[7,23] The study by Cook et al,[7] in which mainly term neonates were studied, showed a fraction of 10%-20% of glucuronidation at the first month age, while Wu et al[23] showed a lower fraction (5%-15%) of glucuronidation in preterm neonates under 32 weeks of GA.

In contrast to the maturation of glucuronidation of PCM, there appeared to be no significant additional GA effect on the rate of postnatal maturation for both of its sulfation and oxidation pathways. This might be attributed to the early development of their activity during pregnancy, resulting in less interruption by preterm birth. Sulfation is mainly carried out by sulfotransferase (SULT) SULT1A1, 1A3/4, 2A1, and 1E1, which already show activity in the earliest periods of gestation.[32,33] Similarly, the oxidation pathway is primarily mediated by enzyme CYP2E1, which was clearly expressed in the developing human fetal liver as early as the beginning of the second trimester (13 to 26 weeks).[34]

A fixed gestational age (GA) of 40 weeks was assumed for data from infants, children, and adults due to the inability to obtain the GA of the included (adult and pediatric) subjects. This limitation has led to less confidence in the exact prediction of the maturation of preterm neonates after 2 months of age. Nonetheless, our final models showed that the time for the three pathways to reach half of the maximum maturation (PNA50) for the typical individual is 61, 25, and 10 days, respectively, for glucuronidation, sulfation, oxidation and, which were within the range of the available data. The slow maturation of glucuronidation is consistent with literature studies.[12,35] Additionally, studies have shown that the expression of CYP2E1 approaches adult values by approximately 90 days of PNA, which is close to the estimate of this study (50 days calculated as 99% of E_{max}).[34]

To ensure the identifiability of the formation CL, the fraction of metabolites' distribution volume to the volume of PCM was assumed to remain constant throughout life. This assumption can be partly supported by literature. In neonates, the volume of glucuronide and sulfate ranges from 25%- to 48% and 35% to 46% of the volume of PCM, respectively.[7,23] In healthy adults undergoing third molar dental extraction, these fractions were 32% and 31%.[36] Given the consistency of these fractions across different age groups, they were fixed accordingly in our study, with estimates of 34.2% and 34.8% for the fraction of the volume of PCM-GLU and PCM-SULF to that of PCM. However, information on the fraction of oxidative metabolites is limited. In neonates, the fraction of the volume of the oxidative metabolites is reported 111% of that of PCM,[7] but solid information for adults is lacking.

At the beginning, renal elimination CL of PCM and its metabolites were assumed to be constant fractions of GFR regardless of age. Based on this assumption, the estimated fraction of renal elimination CL of PCM, PCM-GLU, PCM-SULF, and PCM-OXI to that of GFR was 8 %, 44%, 31%, and 74%, respectively. This constant fraction assumption was considered valid during the neonatal period for PCM, PCM-GLU, and PCM-OXI, as the fit for both plasma and urine concentrations were satisfactory. For PCM, the constant fraction can be extended to children or adults, supported by the study from Prescott et al,[29] who found that renal clearance for PCM is significantly lower than GFR in healthy adult volunteers (11.9 mL/min), which is close to our estimates of around 12 mL/min. However, for PCM-GLU and PCM-SULF, studies by Morris et al[27] and Critchley et al[30] have shown that their renal CL are comparable to or even higher than GFR. Therefore, for PCM-SULF we added a separate maturation equation on top of the GFR to describe the renal elimination CL of PCM-SULF and therefore allowed the fraction to change with age. We assigned the increased fraction of renal elimination CL of PCM-SULF to be as a result of the maturation of secretion. This was based on a study in dogs,[37] which confirmed that PCM-SULF undergoes secretion, and the administration of probenecid can inhibit the assumed secretion of sulfate. We also added a correction factor to the renal clearance of PCM-GLU in adults, leading to the renal CL of PCM-GLU increasing from 44% in neonates and children to 74% of the GFR in adults. Still, there is few information for PCM-OXI.

Generally, the PK of PCM and its metabolites from birth up to adulthood, including preterm and term neonates was well characterized. However, some discrepancies remain for certain age groups, particularly for PCM-OXI in adulthood. This may be due to the model's assumptions regarding PCM-OXI, which could be oversimplified due to the limited available literature and may not be universally applicable. Additionally, the dataset is heavily skewed toward neonatal and infant data, with fewer observations from older children and adult and even less for PCM-OXI compared to other compounds. Still, the primary goal of this study is to describe the maturation of PCM maturation pathways by comparing the existing maturation equations in a dataset with preterm and term neonates (where GA, PNA, and birthweight are relevant covariates) together

with older children and adults (where bodyweight is the main covariate). The PTNA equation showed the best performances amid the tested equations, especially for glucuronidation but also the other pathways.

In summary, this study has demonstrated that the PTNA equation offers the best performances for modeling the elimination pathways of PCM. The benefit of using the PTNA equation increases with younger age, with the most significant improvements seen in children under 1 year old, as illustrated in Figure 1. Given its complexity, the PTNA equation requires a robust dataset that includes patients with a range of GA and PNA values, especially covering the period around half-maturation. This requirement may limit its widespread use. However, it remains a valuable alternative for capturing complex maturational patterns when simpler equations for populations consisting of both prematurely born and term-born neonates (i.e., AS0.75 and AS0.75 + PMA), as discussed previously, are insufficient.

In our study, PCM served as a proof-of-concept drug due to its abundance in PK data (both plasma and urine data) and extensively studied elimination pathways. To apply the PTNA equation to other compounds and elimination routes when extrapolating/describing CL from adults to a population consisting of both (pre)term neonates, it is advised to first evaluate simpler equations. The PTNA equation can be considered when previous popPK researches of the same compound provides evidence of birth impact on a certain pathway (e.g., birthweight/GA + PNA covariates equation is significantly better than PMA or CW covariates).

Conclusion

In this study, with PK data in preterm and term neonates, older infants, children, and adults, the newly developed PTNA maturation equation showed the best properties for describing the maturation of PCM hepatic elimination pathways across all groups. Given its ability to capture the maturation of CL for individuals with varying GA across the pediatric age range and to delineate both prenatal and postnatal maturation while also addressing the prolonged impact of prematurity, this equation deserves further study for other drugs and pathways.

Conflicts of Interest

Yunjiao Wu, Swantje Völler, Sebastiaan C. Goulooze, Karel Allegaert, Catherine M. T. Sherwin, Anne van Rongen, Daniëlla W. E. Roofthooft, Sinno H. P. Simons, Dick Tibboel, Robert B. Flint, John N. van den Anker, and Catherijne A. J. Knibbe have no conflicts of interest that are directly relevant to the content of this article.

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Data Availability Statement

Please contact the corresponding author. Upon request, data may be shared based on a case-by-case situation.

Patient Informed Consent

All studies 'protocols have been approved by the ethics committees and more details can be found in the original papers.

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