Population Pharmacokinetic Modeling of Acetaminophen and Metabolites in Children After Cardiac Surgery With Cardiopulmonary Bypass

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Abstract

Children undergoing cardiac surgery often receive acetaminophen (paracetamol) as part of their postoperative pain treatment. To date, there is no information on the pharmacokinetics (PK) of acetaminophen in this special population, even though differences, as a result of altered hemodynamics and/or use of cardiopulmonary bypass, may be anticipated. Therefore, the aim of this study was to investigate the PK of intravenous acetaminophen in children after cardiac surgery with cardiopulmonary bypass. In the study, both children with and without Down syndrome were included. A population PK analysis, using NONMEM 7.2, was performed based on 161 concentrations of acetaminophen, acetaminophen sulfate, acetaminophen glucuronide, and oxidative metabolites from 17 children with Down syndrome and 13 children without Down syndrome of a previously published study (median age, 177 days [range, 92–944], body weight, 6.1 kg [4.0–12.9]). All children received 3 intravenous acetaminophen doses of 7.5 mg/kg (<10 kg) or 15 mg/kg (≥10 kg) at 8–hour intervals after cardiac surgery. For acetaminophen and its metabolites, 1-compartment models were identified. Clearance of acetaminophen and metabolites increased linearly with body weight. Acetaminophen clearance in a typical child of 6.1 kg is 0.96 L/h and volume of distribution 7.96 L. Down syndrome did not statistically significantly impact any of the PK parameters for acetaminophen, nor did any other remaining covariate. When comparing the PK parameters of acetaminophen in children after cardiac surgery with cardiopulmonary bypass with those from children of the same age following noncardiac surgery reported in the literature, clearance of acetaminophen was lower and volume of distribution higher.

Congenital heart disease accounts for almost one-third of all congenital defects.[1] In many institutions around the world, children routinely receive acetaminophen (paracetamol) as part of their postoperative pain treatment.[2]

Acetaminophen is metabolized in the liver by various metabolic pathways.[3] In adults, acetaminophen is mainly metabolized to acetaminophen glucuronide (55%) and acetaminophen sulfate (30%).[4–6] To a small extent, acetaminophen is excreted unchanged in urine (2%–5%). Metabolism by cytochrome P450 accounts for 5% to 10% of the elimination, which is mediated primarily by cytochrome P450 2E1 to form the toxic metabolite N-acetyl–p-benzoquinone inine (NAPQI).[4–8] Under normal conditions, NAPQI is immediately neutralized by conjugation with gluthatione.[9] After formation of acetaminophen glutathione, both acetaminophen cysteine and acetaminophen mercapturate are formed. However, at high dosages, gluthatione will be depleted and NAPQI can result in hepatocellular necrosis.[9]

Several studies have reported on the pharmacokinetics (PK) of acetaminophen in infants and children.[10,11]

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However, there are no reports on the PK of acetaminophen in children after cardiac surgery with cardiopulmonary bypass. There are several reasons why children may have different PK after cardiac surgery compared to noncardiac surgery.[12,13] This can be ascribed not only to the altered hemodynamic situation of those children with cardiac anomalies, but also to the perioperative use of cardiopulmonary bypass, which has profound effects on the PK because of hemodilution, hemodynamic changes, hypothermia, systemic inflammatory response syndrome, and sequestration of drugs in the cardiopulmonary bypass system.[13,14] Additionally, as nearly half of children with Down syndrome have a congenital heart defect,[15] they represent a relatively large subgroup in the population of children undergoing cardiac surgery. While differences in acetaminophen metabolism in adolescents and adults with and without Down syndrome have been suggested,[16] this has not been studied in children.

Therefore, the aim of this study is to investigate the PK of acetaminophen and its metabolites in children after cardiac surgery with cardiopulmonary bypass. For this purpose, in blood samples from a previously published study on morphine PK and pharmacodynamics after cardiac surgery in children with and without Down syndrome[17] acetaminophen concentrations were measured and data analyzed in relation to acetaminophen dosing information.

Methods

Patients, Study Design, and Drug Dosing
In this population PK study, blood samples on acetaminophen and metabolite concentrations were analyzed from a previously published prospective observational clinical study on analgesia and sedation in 38 children with and without Down syndrome who underwent cardiac surgery with cardiopulmonary bypass.[17] The study design has been described in detail elsewhere[17] and is summarized here as relevant for this analysis. The study was conducted at the Department of Anesthesia and Intensive Care Medicine of Our Lady's Children's Hospital, Dublin, Ireland, following approval by the ethical board of the hospital. Written informed consent for the study was obtained from parents preoperatively. Its primary aim was to compare the PK and pharmacodynamics of morphine and midazolam in children with and without Down syndrome after cardiac surgery with cardiopulmonary bypass, while intravenous acetaminophen was also administered to most of the patients. In the initial study, inclusion criteria for patients both with and without Down syndrome were age 3 to 36 months and cardiac surgery with cardiopulmonary bypass for atrial septal defect, ventricular septal defect, atrioventricular septal defect or

Table 1. Characteristics of 30 Children Included in the Current Analysis

Variable	Children With Down Syndrome (n = 17)	Children Without Down Syndrome (n = 13)	P Value
Male	7 (41)	6 (46)	.79
Gestational age, weeks	39 [28–42]	39.3 [35.5–41.0]	.16
Age at surgery, days	175 [105–944]	175 [92–300]	.19
Weight at surgery, kg	6.1 [4.2–12.9]	5.7 [4.0–8.2]	.18
Procedure			<.001
AVSD	13 (76.5)	1 (7.7)	
VSD	4 (23.5)	5 (38.5)	
TOF	0 (0)	7 (53.9)	
RACHS score			<.001
2	4 (23.5)	12 (92.3)	
3	13 (76.5)	1 (7.7)	
CPB time, min	111 [51–168]	106 [61–105]	.89
Aortic cross-clamp time, min	74.5 [27–118]	66 [36–110]	.98

Values are presented as median [range] or N (%) unless specified otherwise. ASD, atrial septal defect; AVSD, atrioventricular septal defect; CPB, cardiopulmonary bypass; RACHS, risk adjustment for congenital heart surgery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

tetralogy of Fallot repair. An additional inclusion criterion for the Down syndrome group was a diagnosis of trisomy 21.

Postoperatively, intravenous acetaminophen, administered as an infusion over 15 minutes, was given 3 times in a dose of 7.5 mg/kg (<10 kg) or 15 mg/kg (≥10 kg) at 8-hour intervals according to the postoperative pain protocol. Scavenge blood samples from the subgroup receiving intravenous acetaminophen in the postoperative setting were used for the current study (n = 17 with Down syndrome; n = 13 without Down syndrome). Figure S1 provides plots of the spread in sampling times relative to the first paracetamol dose (Figure S1A) and relative to time after the most recent dose (Figure S1B). The number of samples in which acetaminophen and metabolite concentrations were measured ranged from 3 to 9 per patient. The PK model was based on 161 acetaminophen, 161 acetaminophen sulfate, 161 acetaminophen glucuronide, 161 acetaminophen cysteine, and 153 acetaminophen mercapturate concentrations. The clinical characteristics of the included patients (N = 30) are shown in Table 1.

Analytical Assay
Blood samples were centrifuged, and plasma was stored at –80°C for 2 years. Concentrations of acetaminophen and its metabolites, glucuronide, sulphate, gluthathione, cysteine, and mercapturate, were determined by ultra-performance liquid chromatography and tandem mass spectrometry at the hospital pharmacy, Erasmus Medical Centre Rotterdam, The Netherlands.[3]

The assays were linear over 0.020 to 25.0 mg/L, 0.047 to 47.0 mg/L, and 0.043 to 43.0 mg/L for acetaminophen, acetaminophen glucuronide, and

acetaminophen sulfate, respectively, and over 0.022 to 43.0 mg/L, 0.020 to 10.0 mg/L, and 0.010 to 15 mg/L for acetaminophen gluthation, acetaminophen cysteine, and acetaminophen mercapturate. The lower limit of the ranges represents the lower limits of quantification (LLOQ). Intra- and interassay accuracies ranged from 93.6% to 130.9%. Intra- and interassay imprecision did not exceed 15%.[3]

Population PK Analysis and Internal Validation

Acetaminophen and metabolite concentrations were analyzed using nonlinear mixed-effect modeling software NONMEM version 7.2 (ICON Development Solutions, Ellicott City, Maryland) using the first-order estimation method with the interaction option and subroutine ADVAN13, TOL4. Pirana (version 2.9.2), R (version 3.3.0), and PsN® version (version 4.4.8) software were used to process the runs and evaluate and visualize the data.

Concentrations were expressed in acetaminophen equivalents (mg/mL) via conversion based on molecular weights (acetaminophen = 151.165 g/mol; acetaminophen glucuronide = 349.271 g/mol; acetaminophen sulphate = 231.222 g/mol; acetaminophen cysteine = 254.304 g/mol; acetaminophen mercapturate = 296.341 g/mol).[18–22] For acetaminophen, acetaminophen glucuronide, acetaminophen sulphate, and acetaminophen cysteine, 3 samples (1.08 %) were below LLOQ; and for acetaminophen mercapturate, 8 samples (4.88 %) were below LLOQ. These samples were excluded from the analysis. All acetaminophen glutathione concentrations were below LLOQ, and this metabolite was therefore not included in the model.

The model-building process was performed in a stepwise manner: (1) the structural model, (2) the statistical model, (3) the covariate model, and (4) model evaluation.[23] Discrimination between submodels was made by the likelihood ratio test using the objective function value (OFV) (ie, –2 log likelihood), where a decrease in OFV of 7.8 points ($P < .005$ based on an assumed χ^2 distribution) was considered as statistically significant, between nested models with 1 degree of freedom. Furthermore, basic goodness-of-fit plots were evaluated, as well as precision of the parameter estimates and the condition number.

Structural and Statistical Model. One- and 2-compartment PK models for acetaminophen and its metabolites were tested. To investigate a possible delay in metabolite formation, addition of transit compartments was tested. As acetaminophen cysteine and acetaminophen mercapturate are gluthation-derived metabolites formed from the toxic NAPQI metabolite, the sum of both metabolite concentrations

was modeled in 1 compartment, assuming the same distribution volume for both metabolites.[24]

For the metabolite model to be identifiable, it was assumed that the ratio of formation clearance of acetaminophen sulfate and acetaminophen glucuronide is the same in children between 3 and 9 years of age—namely, a fraction of 0.49 and 0.36 of total elimination acetaminophen clearance[25]—and that the oxidative metabolites and the unchanged clearance of acetaminophen are the same as in healthy adults, namely, 0.10 and 0.05 of the total acetaminophen clearance.[4–6,26]

Interindividual variability on the model parameters was assumed to be log-normally distributed and tested on all parameters. For the intraindividual variability and residual unexplained variability, a proportional, additive, and combined error model were tested.

Covariate Model. To evaluate the impact of growth and maturation on PK processes, body weight and age were tested as covariates. Additionally, tested covariates included sex, Down syndrome, cardiopulmonary bypass, and risk adjustment for congenital heart surgery (which quantifies the risk for in-hospital mortality for pediatric patients undergoing cardiac surgery, with a value of 1 indicating the lowest risk and 6 the highest[27]). Continuous covariates were entered into the model using a linear or power equation (Equation 1).

$$Pi = \theta_1^* \left(\frac{COV_i}{COV_{median}} \right)^{\theta_3} + \theta_2 \qquad (1)$$

In the equation, Pi represents the individual parameter estimates, θ_1 and θ_2 represent the typical parameter estimates for the covariate relationship, and COV_i represents the covariate value for the individual, which is normalized by the median covariate value (COV_{median}) representing the median value of the covariate. θ_3 is an exponent fixed to 1 for a linear function or estimated for a power function. For the categorical covariates, such as Down syndrome and sex, the fractional change for one group compared to the other group was calculated.

A data-driven covariate analysis was performed. Potential covariates were entered separately into the model and considered statistically significant when OFV decreased with at least 7.8 points ($P < .005$). When more than one significant covariate was identified, the covariate causing the largest drop in OFV was retained in the model and additional covariates had to reduce this OFV with the use of the same criteria to be retained in the model. In addition, it was evaluated whether the interindividual variability of the parameter was reduced upon inclusion of the covariate and the observations in the plot of eta versus covariate would be randomly spread around zero.
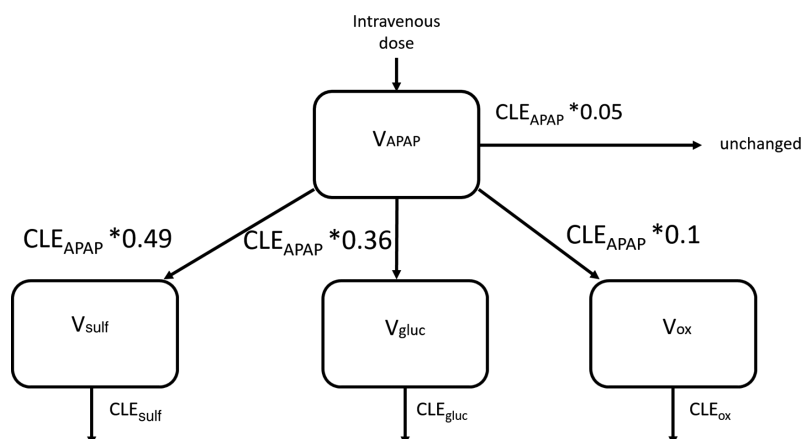
Figure 1. Schematic overview of the population pharmacokinetic model of acetaminophen (APAP) and its metabolites acetaminophen sulfate (sulf), acetaminophen glucuronide (gluc), and the combined oxidative cysteine and mercapturate metabolites (ox). V indicates distribution volume for the respective compounds, and CLE indicates the elimination clearance of the respective compound. Formation clearance of the metabolites and unchanged elimination clearance were calculated as fixed fractions of the elimination clearance of acetaminophen.

Internal Validation

A normalized prediction distribution error (NPDE) analysis was performed to evaluate the accuracy of the predictions of the median trend and variability in concentrations of acetaminophen, acetaminophen sulfate, acetaminophen glucuronide, and oxidative metabolites. In order to perform this analysis, the original data set was simulated 1000 times. Thereafter, each observed concentration was compared to the simulated concentrations by using the NPDE package in R.[28]

Comparison With Noncardiac Surgery

The results obtained in our study were compared to reported values for a similar population after noncardiac surgery. For this, the study by Prins et al[29] was used, as to the best of our knowledge this is the only compartmental PK study using a similar population after noncardiac surgery. This study included 26 patients between 6 months and 2 years of age after craniofacial surgery. To illustrate the implication of the differences in parameter values, PK profiles for acetaminophen were generated upon a single dose of 7.5 mg/kg intravenous infusion (administration in 15 minutes) in a typical patient (body weight, 6.1 kg) after cardiac and noncardiac surgery.

Results

Population PK Analysis

Structural and Statistical Model. A 1-compartment model for acetaminophen and a 1-compartment model for acetaminophen sulfate, acetaminophen glucuronide, and the oxidative metabolites best fitted the data (Figure 1). Two-compartment models for the distribution of acetaminophen and its metabolites did not statistically significantly improve the model fit. Interindividual variability could be identified for all

parameters. A proportional error model best described residual variability for each of the compounds.

Covariate Model

In the covariate analysis, body weight was identified as a significant covariate. It was included in a linear relationship (Equation 1) on the total elimination clearance of acetaminophen (CLE_{APAP}) and its metabolites (CLE_{sulph}, CLE_{gluc}, CLE_{ox}). Including body weight in an exponential instead of linear relationship on elimination clearance of acetaminophen and its metabolites did not further improve the model. As formation of the metabolites is described as a fraction of the elimination clearance of acetaminophen, the linear relationship with body weight is perpetuated in these parameters (see Methods). For volume of distribution of acetaminophen, there was a trend toward a positive correlation with body weight; however, this relationship did not reach statistical significance probably because it relied mostly on the presence of 3 individuals with body weights outside the body weight range of the other individuals (Figure S2). In addition, body weight in a linear function on volume of distribution of the oxidative metabolites significantly decreased OFV. However, this covariate was not implemented, as the parameter value could not be estimated accurately (relative standard error [RSE], 161%) (Figure S2). No trends between body weight and volume of distribution were seen for acetaminophen sulfate and acetaminophen glucuronide. Differences between patients with or without Down syndrome were not observed at the various stages throughout the covariate analysis. Inclusion of any of the remaining covariates did not statistically significantly improve the model fit. All parameter estimates of the final model are shown in Table 2. From this table it is apparent that the parameter values could be accurately estimated (RSE generally ≤50%).

Table 2. Population Pharmacokinetic Parameters of the Final Pharmacokinetic Model for Acetaminophen and Its Metabolites in Children After Cardiac Surgery With Cardiopulmonary Bypass

Parameter	Final Model (RSE%) [Shrinkage %]
Acetaminophen	
V_{APAP} (L)	7.96 (10)
$CLE_{APAP} = \theta_1 * (BW/6.1) + \theta_2$	
θ_1 (L/h)	1.50 (27)
θ_2 (L/h)	−0.54 (61)
Acetaminophen sulfate	
V_{sulf} (L)	0.68 (29)
$CLE_{sulf} = \theta_3 * (BW/6.1) + \theta_4$	
θ_3 (L/h)	0.65 (19)
θ_4 (L/h)	−0.24 (35)
Acetaminophen glucuronide	
V_{gluc} (L)	1.69 (29)
$CLE_{gluc} = \theta_5 * (BW/6.1) + \theta_6$	
θ_5 (L/h)	1.41 (21)
θ_6 (L/h)	−0.53 (50)
Oxidative metabolites	
V_{ox} (L)	0.042 (18)
$CLE_{ox} = \theta_7 * (BW/6.1) + \theta_8$	
Θ_7 (L/h)	40.86 (25)
Θ_8 (L/h)	−1.26 (28)
Interindividual variability [ω^2]	
V_{APAP}	0.189 (27) [11]
CLE_{APAP}	0.185 (27) [6]
V_{sulf}	0.726 (52) [12]
CLE_{sulf}	0.189 (32) [6]
V_{gluc}	0.927 (50) [15]
CLE_{gluc}	0.129 (39) [13]
V_{ox}	0.600 (49) [9]
CLE_{ox}	0.552 (32) [9]
Residual variability [σ^2]	
Proportional error for acetaminophen	0.146 (29) [9]
Proportional error for acetaminophen sulfate	0.0507 (15) [16]
Proportional error for acetaminophen glucuronide	0.0813 (14) [15]
Proportional error for oxidative metabolites	0.0494 (12) [16]

See also Figure 1.
BW, body weight; $CLE_{APAP} = CLf_{sulf} + CLf_{gluc} + CLf_{ox} + Clf_{APAP\ unchanged}$, where CLf_{sulf} is formation clearance of acetaminophen sulphate, CLf_{gluc} is formation clearance of acetaminophen glucuronide, and CLf_{ox} is formation clearance of oxidative metabolites; CLE_{gluc}, elimination clearance of acetaminophen glucuronide; CLE_{ox}, elimination clearance oxidative metabolites; CLE_{sulph}, elimination clearance of acetaminophen sulfate; V_{gluc}, central volume of distribution acetaminophen glucuronide; V_{ox}, central volume of distribution oxidative metabolites; V_{pcm}, central volume of distribution of acetaminophen; V_{sulf}, central volume of distribution acetaminophen sulfate

Moreover, the residual variability was generally well below 15%.

Figure 2 presents the plots of observed versus population-predicted concentrations of acetaminophen and its metabolites. These plots show no bias around the line of unity, indicating that the model accurately describes concentrations over the concentration range (Figure 2A): this is the same for children with and without Down syndrome. Similarly, the conditional weighted residuals over time after dose are unbiased for both subpopulations (Figure 2B), indicating that concentrations predictions are accurate over the entire time range.

Internal Model Validation
The NPDE distribution for acetaminophen and metabolites are depicted in Figure S3. The histograms of the NPDE follow a normal distribution. No trend is observed in the NPDE vs time and the NPDE vs predicted concentrations, confirming that the model adequately quantifies both the median trend and the variability in the observed concentrations.

Comparison With Noncardiac Surgery
For the typical child of 6.1 kg in our study, total elimination clearance and distribution volume of acetaminophen are 0.96 L/h and 7.96 L, respectively (Table 2). Prins et al[29] reported a clearance value of 1.04 L/h and 2-compartment distribution with volumes of 0.69 L and 3.80 L of the central and peripheral compartments, respectively, in the same typical child (6.1 kg) after noncardiac surgery. Figure 3 shows the population-predicted acetaminophen concentrations after a single intravenous dose of 7.5 mg/kg of acetaminophen over 15 minutes in this typical individual after both types of surgery. The maximum concentration (C_{max}) value for acetaminophen was 84% lower after cardiac surgery compared to after noncardiac surgery. In addition, maximum concentration shows a different shape of peak for the cardiac vs noncardiac surgery group, due to the use of a 2-compartment model to describe PK of acetaminophen in the noncardiac surgery group. In addition, because the clearance of acetaminophen was lower after cardiac surgery compared to noncardiac surgery, the trough level at 8 hours was more than a factor 50 higher in this typical patient, compared to a typical patient after noncardiac surgery.

Discussion
The present study investigated the PK of acetaminophen and its metabolites in children after cardiac surgery with cardiopulmonary bypass, using a population PK modeling approach. Contrary to a previous report,[16] no differences in PK parameters were observed between children with or without Down syndrome; therefore, these data were combined.

Although the study sample size may be considered limited, the advantage of population PK modeling is that all concentration-time data are analyzed together, thereby enhancing the statistical power.[12,29] Indeed, the RSEs of the parameter estimates obtained in this analysis show that these values could be obtained with acceptable precision given the available data.
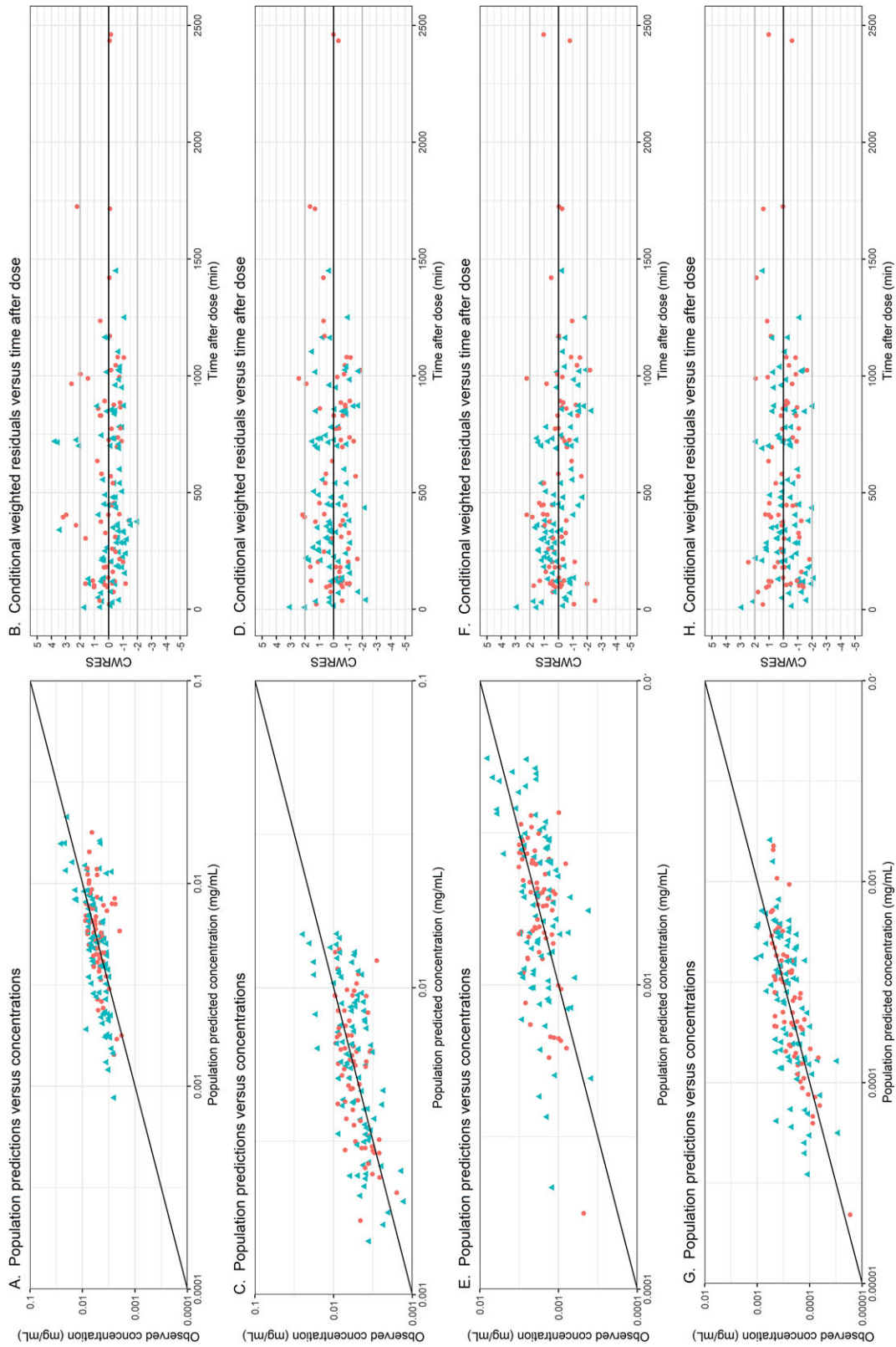
Figure 2. Observed vs population-predicted concentrations and conditional weighted residuals (CWRES) versus time after dose graphs of acetaminophen (A, B), acetaminophen-sulphate (C, D), acetaminophen-glucuronide (E, F) and the oxidative metabolites (G, H) in the final model for children with (blue triangle) and without (red circle) Down syndrome.
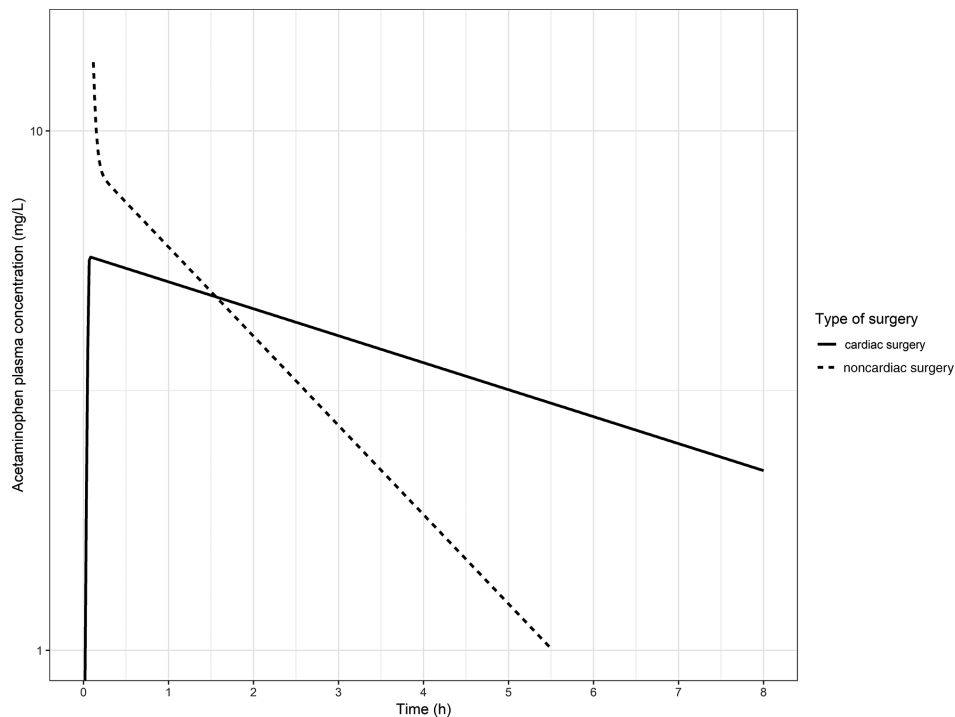
Figure 3. Acetaminophen concentrations over time in a typical child of 6.1 kg upon a single intravenous dose of 7.5 mg/kg after cardiac surgery (solid black line) and noncardiac surgery (dotted black line).

Furthermore, extensive model validation showed that the model not only describes the obtained data well (Figure 2) but also predicts the data well (Figure S3).

In our study, the clearance of acetaminophen and metabolites was found to increase with body weight, which was found to be a better descriptor of the impact of maturational changes than age, which is in line with other studies.[30] However, it is important to mention that the model was developed based on data from children aged between 3 months and 3 years, with a body weight ranging between 4.0 and 12.9 kg. As many developmental changes occur in children younger and older than this age range, extrapolation outside this age range is not justified as the linear function in this covariate relationship is only appropriate in the studied age range.[30]

Due to differences in parameterization and covariate relationships, direct comparisons between literature values are difficult; however, comparisons between parameter values for typical individuals are possible. A previous study on the PK of acetaminophen after noncardiac surgery[29] reported for a child weighing 6.1 kg a clearance value of 1.04 L/h, which is higher in comparison with our estimate in post-cardiopulmonary bypass cases (0.96 L/h). In our analysis, we identified a 1-compartment model, while in patients after noncardiac surgery 2 compartments were identified. Although our analysis included observed concentrations shortly after dosing (Figure S1), it is possible that this was

not sufficient to identify 2 compartments. Alternatively, differences in the impact of the 2 surgery types on patients' physiology may cause true differences in the distribution of acetaminophen. Either way, the combined central and peripheral volume of distribution after noncardiac surgery (4.49 L for a 6.1-kg child) was lower in comparison with the total volume of distribution found in our analysis in children after cardiac surgery (7.96 L for a 6.1-kg child). The differences in clearance and volume of distribution may be attributed to the influence of cardiopulmonary bypass causing hemodynamic changes and fluid shifts, while the occurrence of inflammation or systemic inflammatory response syndrome may also impact metabolic capacity.[12,13]

To allow for a further comparison of the differences in the PK of acetaminophen after cardiac and noncardiac surgery, Figure 3 displays PK profiles of a typical individual of 6.1 kg after both types of surgery. This figure shows that maximum concentration is lower after cardiac surgery compared to noncardiac surgery, while the through level at 8 hours is higher in patients after cardiac surgery. Whether these differences also result in different dose requirements depends on the relationship between exposure and efficacy and safety parameters in both populations. This is part of further investigations.

A strength of our analysis is the inclusion of both acetaminophen and its metabolites. However, as no study in noncardiac surgery patients investigated all metabolites, no comparison between cardiac and

noncardiac pediatric surgery patients can be made regarding the PK of the metabolites.

Interestingly, oxidation of acetaminophen has been suggested to be increased in adolescents and adults with Down syndrome,[16] which was not observed in the current (younger) patient population. In our model, all parameters were estimated with high accuracy and the same set of model parameters could be used to predict acetaminophen and metabolite concentrations without bias in both subpopulations. The previously observed findings could be artifacts resulting from a smaller sample size (4 individuals [mean age, 20.8 [range, 20–21] years) with Down syndrome and 4 individuals (25.4 [18–32]) without Down syndrome and from performing a noncompartmental analysis. In our study, we were not able to detect NAPQI and acetaminophen gluthatione, likely because NAPQI is immediately neutralized by conjugation to gluthathione. When conjugation occurs, downstream metabolites will not be formed and, consequently, cannot be measured. In the absence of the occurrence of NAPQI in the blood, no conclusions can be drawn on a possible difference in the saturation process of NAPQI between children with and without Down syndrome. As we studied acetaminophen in the therapeutic range and the above-mentioned process occurs only with higher doses, we do not expect that this phenomenon occurred. In addition, to the best of our knowledge there are no published reports linking Down syndrome with any differences in the risk of developing acetaminophen-related hepatotoxicity.

There are some limitations to our study. In the absence of recovery of all of the metabolites in urine, assumptions were necessary to quantify PK parameters of the metabolites. We chose to fix the fraction eliminated through each pathway based on published values,[25] as there is no reason to assume that contributions of the different metabolic pathways of acetaminophen are altered after cardiac surgery. This also means that the maturation identified on total paracetamol clearance is assumed to be the same for both metabolic pathways. Although model validation confirmed that the model can accurately describe concentrations of acetaminophen and its metabolites with the estimated model parameters, if the true fractions for each route deviate from the assumed fractions in children after cardiac surgery with cardiopulmonary bypass, the elimination clearance and distribution volume of the metabolites would change. This means that absolute values of the parameters related to the metabolites should be considered only in the context of the assumptions made. Our ability to investigate differences in acetaminophen PK between children with and without Down syndrome is not impacted by our assumptions,

as a fractional difference between the groups could still be tested as a covariate on all model parameters.

Conclusions

In conclusion, we report the PK of acetaminophen in infants undergoing cardiac surgery. Comparing the results with those reported in children with noncardiac surgery, clearance of acetaminophen is decreased while volume of distribution is increased in children after cardiac surgery with cardiopulmonary bypass. In this population, Down syndrome does not impact the PK of acetaminophen.

Author Contributions

P.M. analyzed data and wrote paper; A.J.V. conceived and designed the study, performed research, and wrote paper; K.A. wrote paper; B.C.P.K. wrote paper and analyzed blood samples; C.V.B. conceived and designed the study, performed research, and wrote paper; C.A.J.K. wrote paper; D.T. conceived and designed the study and wrote paper; E.H.J.K. supervised, analyzed data, and wrote paper.

Declaration of Conflicting Interests

The authors declare no conflict of interest.

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Data Sharing

For questions concerning data sharing, please contact A.J. Valkenburg (A.Valkenburg@erasmusmc.nl).

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Supporting Information

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