

Paracetamol and its metabolites in children and adults with spinal muscular atrophy – a population pharmacokinetic model

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Abstract

Aims: The aim of the study was to investigate whether differences in paracetamol pharmacokinetics (PK) between spinal muscular atrophy (SMA) patients and healthy controls (HC) could be attributed to specific clinical covariates.

Methods: Nonlinear mixed-effects modelling (NONMEM 7.4) was used to develop a population PK model, explore covariates for paracetamol and its metabolites and perform simulations.

Results: With body weight as allometric scaling in the model, SMA disease resulted in a 58% (95% confidence interval [CI]: 20%–130%) increase in the volume of distribution for paracetamol and its metabolites compared to healthy controls. Decreased plasma myoglobin and plasma bilirubin concentrations, seen in SMA patients, resulted in a higher paracetamol leftover clearance (SMA, median: 13.30 L/h/70 kg, 95% CI: 9.14–18.29%; HC, median: 4.05 L/h/70 kg, 95% CI: 3.38–8.83%) and a shift from slower sulfate formation clearance (SMA, median: 8.78 L/h/70 kg, 95% CI: 7.22–

Qiaolin Zhao and Marie Mostue Naume contributed equally and should be considered shared first authorship.

The authors confirm that the Principal Investigator for this paper is Mette Cathrine Ørngreen and that she had direct clinical responsibility for patients.

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9.61%; HC, median: 9.30 L/h/70 kg, 95% CI: 8.42–10.15%) and faster oxidative metabolites elimination clearance (SMA, median: 3.74 L/h/70 kg, 95% CI: 3.31–4.72%; HC, median: 3.25 L/h/70 kg, 95% CI: 2.87–3.92%). Simulations revealed that in SMA patients, higher bodyweight was associated with increased exposure to paracetamol and its metabolites.

Conclusions: The differences in PK between SMA patients and healthy controls could be explained by body weight and the disease itself. SMA patients should be dosed cautiously, ensuring doses do not exceed the recommended body weight adjusted limit.

KEYWORDS

metabolites, paracetamol, pharmacokinetic, SMA

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder caused by mutations in the **survival motor neuron 1** (SMN1) gene, leading to reduced production of survival motor neuron (SMN) protein. This deficiency results in progressive degeneration of motor neurons in the spinal cord and brainstem, causing progressive muscular weakness, reduced mobility, and significantly decreased skeletal muscle mass.^{1–3} While SMA adults often demonstrate relative stability in motor function but experience gradual complications over time, children typically face severe motor impairment and rapid disease progression due to developmental vulnerabilities.⁴ Scoliosis is a common comorbidity in the patient group and SMA patients often undergo scoliosis surgery between the ages of 10 and 14 years. Furthermore, both children and adults with SMA are at increased risk of infections, especially pneumonia, due to compromised lung function, and malnutrition is a challenge in all age groups. **Paracetamol** is often used as an anti-pyretic treatment or analgesic treatment postoperatively in the patient group.

In therapeutic doses, paracetamol is almost exclusively metabolized by the liver and its metabolic pathway is widely known.^{5–8} The metabolic pathway is shown in Figure S1. Several case reports have described children and adults with SMA or other muscular wasting disorders developing acute liver failure after therapeutic doses of paracetamol.^{9–11} Based on these case reports, we recently investigated the pharmacokinetics (PK) of paracetamol in children and adults with SMA compared to healthy controls (HC).¹² We found that SMA patients had a significantly lower clearance of paracetamol compared to healthy controls (14.1 L/h vs. 21.5 L/h). We suspect that malnutrition and/or lower body weight may impact paracetamol PK. A case study reported that malnourished individuals have reduced antioxidant reserves and a shift towards oxidative metabolism, increasing N-acetyl-p-benzo quinonimine (**NAPQI**) formation and lowering neutralizing capacity, thereby increasing the risk of acetaminophen-induced hepatotoxicity.¹³ Several studies on paracetamol PK in paediatric patients have demonstrated a significant influence of body

What is already known about this subject

- The clearance of paracetamol in patients with spinal muscular atrophy is lower compared to healthy controls without body weight adjustment.

What this study adds

- The differences in pharmacokinetics between spinal muscular atrophy patients and healthy controls could be explained by body weight, and the disease itself (mainly influencing volume of distribution).

weight on PK parameters.^{14–16} Additionally, other studies have highlighted the role of body mass index (BMI) and fat mass with allometric scaling as a size descriptor or as a significant covariate in paracetamol PK.^{17–18} Myoglobin is a biomarker used to assess potential skeletal muscle damage in the clinic. Furthermore, other biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin are used in the clinic to assess the liver and bile function. During acute liver failure, the AST and ALT are increased significantly. Other studies have found bilirubin to be a significant covariate in paracetamol PK models,^{6,19,20} indicating that bilirubin levels may affect PK. Thus, we wanted to add these biomarkers to the PK model, to explore whether clinical biomarkers as potential covariates could explain paracetamol PK variability.

As a prolongation of the clinical trial, we wanted to conduct a sub-analysis to compare the body weight-corrected PK parameters of plasma paracetamol, paracetamol-glucuronide, paracetamol-sulfate and paracetamol-oxidative metabolites between SMA patients and healthy controls and to investigate potential covariates explaining PK differences after body weight adjustment.

2 | METHODS

2.1 | Study population and dosing

This study was approved by the ethics committee of Copenhagen in Denmark (H-18032928), the Danish medicine agency (EudraCT-number 2018-002295-40) and the Data Protection Agency (VD-2019-65). The study was performed in compliance with the Declaration of Helsinki. Informed written consent was provided by the participants or their guardians. Six adults with SMA, six children with SMA and 11 healthy controls were enrolled in this study. All subjects received oral paracetamol of 15 mg/kg every 6 h for 3 days, with a maximum dose of 1 g. Blood samples were collected hourly for 6–8 h on Days 1 and 3, starting with a baseline sample before treatment. Recruitment, inclusion and exclusion criteria, and analytical methods are described elsewhere.¹²

2.2 | Population pharmacokinetic analysis

A total of 294 plasma samples per component collected from enrolled SMA patients and healthy controls were used to build the population PK model. The volume of distribution (V_d) for all paracetamol metabolites cannot be identified, so we fixed them to 18% of the central V_d of paracetamol in plasma based on literature.²¹ Covariates were explored for their relationship to the parameters. Visual predictive check (VPC), the bootstrap resampling method,²² normalized prediction distribution errors (NPDE) and mirror plots were applied to assess the stability of the final model and investigate the accuracy of the model predictions. (For a detailed description of the model building process, see supplementary material 1: methods for model building.)

TABLE 1 Demographic data for healthy controls and SMA patients who received paracetamol.

| Characteristic | Median [range] | | |
|-------------------------------------|----------------|---------------|-------------------------|
| | HC | SMA | P-value (Wilcoxon test) |
| Sample size | 11 | 12 | |
| Age (years) | 25 [20–36] | 17 [6–37] | 0.06 |
| Gender (male/female) | 6/5 | 7/5 | 1.00 |
| Body weight (kg) | 78[51–103] | 30.5[22–57] | <0.05 |
| Alanine aminotransferase (U/L) | 25 [9–60] | 18 [7–98] | <0.05 |
| Aspartate aminotransferase (U/L) | 23 [10–35] | 20[14–147] | 0.65 |
| International normalized ratio | 1.1 [0.8–1.3] | 1.1 [0.9–1.3] | 0.32 |
| Potassium (mmol/L) | 3.9 [3.2–4.6] | 3.8 [2.9–4.3] | <0.05 |
| Sodium (mmol/L) | 140 [136–144] | 140 [134–144] | 0.65 |
| Creatinine (μ mol/L) | 79 [44–102] | 9 [4–17] | <0.05 |
| Glomerular filtration rate (mL/min) | 87->90 | 87->90 | NA |
| Urea (mmol/L) | 3.9 [2.2–9.1] | 3.2 [1.9–5.1] | <0.05 |
| Alkaline phosphatase (U/L) | 56 [38–73] | 98 [43–209] | <0.05 |
| Lactic dehydrogenase (U/L) | 151 [95–175] | 160 [103–298] | <0.05 |
| Bilirubin (μ mol/L) | 7 [3–15] | 4 [2–25] | <0.05 |
| Creatine kinase (U/L) | 122 [43–278] | 61 [12–521] | <0.05 |
| Myoglobin (ng/mL) | 34 [17–74] | 17 [14–54] | <0.05 |

HC, healthy controls; SMA, spinal muscular atrophy.

2.3 | PK comparison between SMA patients and healthy controls

Post-hoc analysis was performed to compare individual PK parameters between SMA patients and healthy controls. Median values and confidence intervals were summarized.

2.4 | Simulation

Simulations were performed to visualize the effect of changes in covariates which turned out to be significant in the covariate model. For each simulation scenario, we simulated 1000 subjects, varied one covariate but kept the other covariates to the median.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/2024.

3 | RESULTS

3.1 | Patients

The demographic data of all 23 subjects are shown in Table 1. The median age of SMA patients and healthy controls was 17 (6–37) and 25 (20–36), respectively. There were seven males and five females in

the SMA patient group, and six males and five females in the HC group. The median body weight of the SMA and HC groups was 30.5 (22–57) kg and 78.0 (51–103) kg ($P < 0.05$), respectively. The baseline measurement of median myoglobin (normal range: 15–75 ng/mL) was lower in SMA patients compared to healthy controls (17 [14–54] ng/mL and 34 [17–74] ng/mL, respectively, [$P < 0.05$]). Median bilirubin (normal range: 0–30 ng/mL) in SMA was also lower compared to healthy controls (4 [2–25] ng/mL and 7 [3–15] ng/mL, respectively, [$P < 0.05$]).

3.2 | Base model

Baseline samples were below the lower limit of quantification (LLOQ) in 18 out of 23 patients (78.3%) for paracetamol, 13 out of 23 (56.5%) for glucuronide, 18 out of 23 (78.3%) for sulfate, 20 out of 23 (87.0%) for cysteine and 21 out of 23 (91.3%) for mercapturic acid. When building the base model, we fixed baseline concentrations to their actual values to focus on post-baseline PK variability. This approach assumes no baseline variability, potentially limiting the model's ability to capture it. For all 294 samples taken during treatment, there were only three cysteine samples (1.1%) and four mercapturic acid samples (1.5%) below the LLOQ. These samples were censored.

A one-compartment per compound model with first-order absorption, lag time and body weight allometric scaling best described

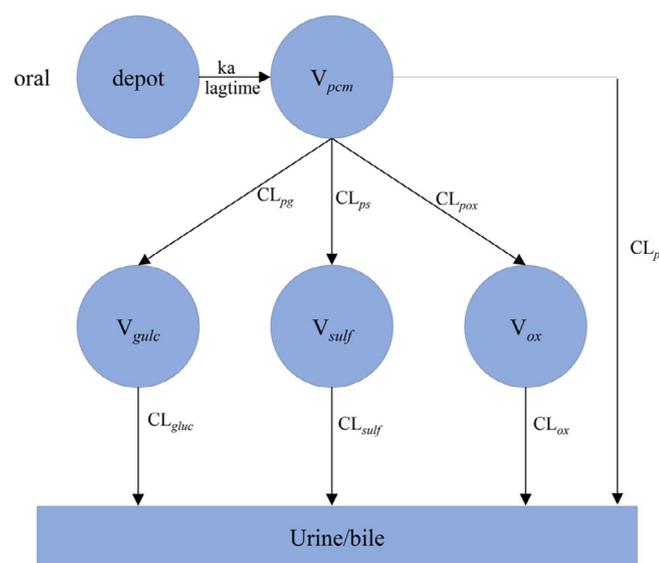


FIGURE 1 Schematic illustration of the structural pharmacokinetic model for paracetamol and its metabolites in plasma. All formation and renal clearances were modelled as first-order processes. CL_{pg} , CL_{ps} , CL_{pox} represent, respectively, formation (hepatic) clearances for paracetamol-glucuronide, paracetamol-sulfate and paracetamol-oxidative metabolites. CL_p , CL_{gluc} , CL_{sulf} , CL_{ox} represent, respectively, leftover clearance for paracetamol, elimination clearances of paracetamol-glucuronide, paracetamol-sulfate and paracetamol-oxidative metabolites. V_{pcm} , V_{gluc} , V_{sulf} , V_{ox} represent, respectively, volumes of distribution for paracetamol, paracetamol-glucuronide, paracetamol-sulfate and paracetamol-oxidative metabolites.

the paracetamol and its metabolites in this population (Figure 1). The allometric theory-based exponent (EXP) was fixed at 0.75 for clearance (CL) parameters and 1 for V_d . The estimation of the exponent on allometric scaling did not improve the model fit. Using fat free mass (FFM) as an allometric scaling factor resulted in a less optimal model performance compared to using body weight. Between subject variability (BSV) was included on the absorption rate constant (K_a), V_d for paracetamol (V_{pcm}/F), paracetamol leftover clearance (CL_p/F), glucuronide formation clearance (CL_{pg}/F), sulfate formation clearance (CL_{ps}/F) and oxidative metabolite elimination clearance (CL_{ox}/F).

3.3 | Covariate model

SMA disease as a categorical covariate was selected as a significant covariate on V_{pcm}/F ($\Delta OFV = 11.5$). Myoglobin was included on CL_p/F (with negative correlation, $\Delta OFV = 18.5$), and bilirubin was included on CL_{ps}/F (with positive correlation, $\Delta OFV = 7.3$) and CL_{ox}/F (with negative correlation, $\Delta OFV = 7.3$). With all the significant covariates in the model, BSV for V_d decreased from 36.5% to 28.8%. BSV for other parameters did not decrease, but proportional error for paracetamol, glucuronide, sulfate and combined oxidative metabolites decreased from 0.283 to 0.280, 0.185 to 0.183, 0.223 to 0.218, and 0.174 to 0.168, respectively. BMI and FFM failed to become significant covariates. Parameter estimates for the final model of paracetamol and its metabolites in healthy controls and SMA patients are shown in Table 2.

3.4 | Model evaluation

The goodness-of-fit plots of the final model demonstrated population predictions, and individual predictions were evenly distributed around the unity line when compared with observed concentrations. Additionally, the conditional weighted residuals are evenly distributed over time (Figures S2–S5).

3.5 | Model validation

The VPC plots for paracetamol and its metabolites revealed strong concordance between observed plasma concentrations over time following dose with the model-based simulations (Figure S6). Median bootstrap estimates were close to estimates from the final model fit, and bootstrap 95% confidence intervals demonstrated reasonably good precision for parameters (Table 2). Five out of 500 runs with terminated minimization were skipped when calculating bootstrap results.

Mirror plots demonstrated that the model effectively characterized the variance and covariance structures, allowing parameters to accurately replicate findings from the original study (Figure S7).

NPDE results are shown in Figure S8 and Table S1. The mean values of paracetamol and its metabolites were close to zero. While

TABLE 2 Parameter estimates for the final model of paracetamol and its metabolites in healthy controls and SMA patients (the volume of distribution for all the metabolites was fixed to 0.18 of paracetamol; the exponent of body weight allometric scaling was fixed at 0.75 for clearance parameters and 1 for volume of distribution).

| Parameter | Base model | Final model | Bootstrap of the final model | |
|---|------------|-------------|------------------------------|-----------------|
| | | | Median | 95% CI |
| t_{lag} (h) (FIX) | 0.153 | 0.153 | 0.153 | 0.153–0.153 |
| k_a (1/h) | 3.29 | 2.84 | 2.44 | 1.43–5.64 |
| CL_p/F (L/h/70 kg) | 8.07 | 8.16 | 6.90 | 2.15–11.57 |
| CL_{pg}/F (L/h/70 kg) | 6.27 | 6.37 | 6.61 | 4.86–8.46 |
| CL_{gluc}/F (L/h/70 kg) | 5.56 | 5.69 | 5.73 | 4.78–7.17 |
| CL_{ps}/F (L/h/70 kg) | 8.34 | 8.43 | 9.00 | 7.25–11.80 |
| CL_{sulf}/F (L/h/70 kg) | 20.4 | 20.4 | 20.95 | 18.61–27.00 |
| CL_{pox}/F (L/h/70 kg) | 0.21 | 0.20 | 0.21 | 0.170–0.26 |
| CL_{ox}/F (L/h/70 kg) | 3.79 | 3.72 | 3.65 | 2.94–4.80 |
| V_{pcm}/F (L/70 kg) | 83.7 | 63.5 | 61.67 | 43.44–81.07 |
| V_{glu}/F (L/70 kg) | 15.1 | 11.43 | 11.1 | 7.82–14.60 |
| V_{sulf}/F (L/70 kg) | 15.1 | 11.43 | 11.1 | 7.82–14.60 |
| V_{ox}/F (L/70 kg) | 15.1 | 11.43 | 11.1 | 7.82–14.60 |
| BSV (%) | | | | |
| CL_p/F | 86.6% | 86.2% | 120.03% | 77.87%–340.06% |
| CL_{pg}/F | 28.6% | 30.1% | 28.05% | 12.56%–40.77% |
| CL_{ps}/F | 19.5% | 25.5% | 25.63% | 9.06%–44.56% |
| V_{pcm}/F | 35.4% | 28.3% | 27.55% | 8.7%–40.95% |
| K_a | 145.6% | 147% | 242.91% | 130.91%–1091.7% |
| CL_{ox}/F | 24.8% | 26.4% | 24.85% | 13.52%–32.66% |
| Covariate effect on CL_p/F | | | | |
| <i>Myoglobin</i> (mean 25 ng/mL) | | −1.10 | −1.14 | −3.07–0.49 |
| Covariate effect on CL_{ps}/F | | | | |
| <i>Bilirubin</i> (mean 6 μ mol/L) | | 0.18 | 0.16 | −0.02–0.39 |
| Covariate effect on CL_{ox}/F | | | | |
| <i>Bilirubin</i> (mean 6 μ mol/L) | | −0.177 | −0.176 | −0.45–0.03 |
| Covariate effect on V_{pcm}/F | | | | |
| <i>Disease</i> | | 1.58 | 1.62 | 1.20–2.30 |
| Residual variability | | | | |
| Proportional | | | | |
| Paracetamol | 0.28 | 0.28 | 0.28 | 0.23–0.33 |
| Paracetamol-glucuronide | 0.19 | 0.18 | 0.18 | 0.16–0.20 |
| Paracetamol-sulfate | 0.22 | 0.22 | 0.22 | 0.18–0.24 |
| Paracetamol-oxidative pathway metabolites | 0.17 | 0.17 | 0.16 | 0.13–0.20 |

Abbreviations: BSV, between-subject variability; CL_p/F , CL_{pg}/F , CL_{ps}/F , CL_{pox}/F , represent, paracetamol leftover clearance, paracetamol-glucuronide formation (hepatic) clearance, paracetamol-sulfate formation (hepatic) clearance and paracetamol-oxidative metabolites formation (hepatic) clearance, respectively; CL_{gluc}/F , CL_{sulf}/F and CL_{ox}/F , represent, elimination clearance (from body to others) for paracetamol-glucuronide, paracetamol-sulfate, and paracetamol-oxidative metabolites, respectively; K_a , absorption rate constant; t_{lag} , lagtime (lag time was fixed to 0.153 in the model building); V_{pcm}/F , volume of distribution for paracetamol; V_{glu}/F , volume of distribution for paracetamol-glucuronide; V_{sulf}/F , volume of distribution for paracetamol-sulfate; V_{ox}/F , volume of distribution for paracetamol-oxidative metabolites.

the Fisher variance test suggested that simulation variance was significantly different from 1 for glucuronide and oxidative metabolites, the Shapiro–Wilk test indicated slight deviations from normality for

paracetamol and sulfate. These deviations were minor and did not compromise the model's overall validity. Therefore, the model remains the most robust representation of the available data.

3.6 | PK comparison between SMA patients and healthy controls

The SMA patients had 58% higher V_d than the healthy controls (with a positive factor of 1.58), and disease did not affect CL. However, myoglobin and bilirubin, which were different in SMA patients compared to the healthy controls, influenced the CL of paracetamol and its metabolites (Table 2).

Furthermore, we did a post hoc analysis to compare the V_d and CL between SMA patients and healthy controls. The results in Table 3 show median values of individual PK parameters, including CL, V_d , AUC ratio and total CL between SMA patients and healthy controls. We found SMA patients exhibited a higher CL_p/F compared to healthy controls (SMA, median: 13.30 L/h/70 kg, 95% confidence interval [CI]: 9.14–18.29%; HC, median: 4.05 L/h/70 kg, 95% CI: 3.38–8.83%). Similarly, SMA patients demonstrated lower CL_{ps}/F (SMA, median: 8.78 L/h/70 kg, 95% CI: 7.22–9.61%; HC, median: 9.30 L/h/70 kg, 95% CI: 8.42–10.15%) but higher CL_{ox}/F (SMA, median: 3.74 L/h/70 kg, 95% CI: 3.31–4.72%; HC, median: 3.25 L/h/70 kg, 95% CI: 2.87–3.92%). The fractions of formation clearance of paracetamol and its metabolites in SMA patients and healthy controls are also shown in Table 3 and Figure S9.

3.7 | Simulations

The first simulation was performed to compare differences in exposure for paracetamol and its metabolites in SMA patients with different body weights but the same myoglobin and bilirubin values. The results indicated that SMA patients with higher body weight exhibited increased paracetamol and metabolite exposure, mainly because paracetamol exposure increases proportionally with the dose amount at therapeutic doses (Figure 2 and Table S2).

The second simulation was performed to visualize the myoglobin effect on paracetamol and its metabolites exposure in SMA patients. The results indicated that an increase in myoglobin levels was associated with a gradual increase in exposure of paracetamol and paracetamol metabolites. This relationship was primarily attributed to the inverse correlation between myoglobin levels and CL_p/F , as higher myoglobin levels are linked to reduced clearance, leading to greater drug accumulation in the body (Figure 3 and Table S3).

The third simulation was performed to visualize the bilirubin effect on paracetamol and its metabolites exposure in both SMA patients and healthy controls. The results indicated that an increase in bilirubin levels was associated with a gradual rise in paracetamol and metabolite exposure, as well as a prolonged half-life of oxidative metabolites. We did not see that lower myoglobin and bilirubin values in SMA patients caused higher exposure to paracetamol oxidative metabolites, which tended to be lower instead (Figure 4 and Table S3).

TABLE 3 Overview of median values and 95% CIs of individual parameter estimations for SMA patients compared to healthy controls.

| | HC Median, 95% CI | SMA Median, 95% CI |
|--|-----------------------|------------------------|
| CL_p/F (L/h/70 kg) | 4.05, (3.38, 8.83) | 13.30, (9.14, 18.29) |
| CL_{pg}/F (L/h/70 kg) | 6.33, (5.07, 8.58) | 6.58, (5.66, 7.28) |
| CL_{gluc}/F (L/h/70 kg) | 5.69, (5.69, 5.69) | 5.69, (5.69, 5.69) |
| CL_{ps}/F (L/h/70 kg) | 9.30, (8.42, 10.15) | 8.78, (7.22, 9.61) |
| CL_{sulf}/F (L/h/70 kg) | 20.40, (20.40, 20.40) | 20.40, (20.40, 20.40) |
| CL_{pox}/F (L/h/70 kg) | 0.20, (0.20, 0.20) | 0.20, (0.20, 0.20) |
| CL_{ox}/F (L/h/70 kg) | 3.25, (2.87, 3.92) | 3.74, (3.31, 4.72) |
| V_{pcm}/F for paracetamol (L/70 kg) | 73.40, (53.00, 79.18) | 94.90, (89.26, 116.16) |
| V_{glu}/F for glucuronide (L/70 kg) | 13.21, (9.54, 14.25) | 17.08, (16.07, 20.91) |
| V_{sul}/F for sulfate (L/70 kg) | 13.21, (9.54, 14.25) | 17.08, (16.07, 20.91) |
| V_{ox}/F for oxidative metabolites (L/70 kg) | 13.21, (9.54, 14.25) | 17.08, (16.07, 20.91) |
| AUC (0–24 h) ratio of glucuronide to paracetamol | 0.44, (0.30, 0.75) | 0.45, (0.31, 0.82) |
| AUC (0–24 h) ratio of sulfate to paracetamol | 0.12(0.10, 0.14) | 0.11, (0.09, 0.15) |
| AUC (0–24 h) ratio of oxidative metabolites to paracetamol | 0.02, (0, 0.05) | 0.02, (0, 0.03) |
| Total CL (L/h/70 kg) | 20.30, (18.56, 26.28) | 29.50, (23.44, 34.17) |
| Fraction of paracetamol leftover CL | 0.27 | 0.47 |
| Fraction of paracetamol glucuronide formation CL | 0.3 | 0.23 |
| Fraction of paracetamol sulfate formation CL | 0.42 | 0.29 |
| Fraction of paracetamol oxidative metabolites formation CL | 0.01 | 0.01 |

Abbreviations: AUC, area under the curve; CI, confidence interval; CL, clearance; CL_p/F , CL_{pg}/F , CL_{ps}/F , CL_{pox}/F , represent, paracetamol leftover clearance, paracetamol-glucuronide formation (hepatic) clearance, paracetamol-sulfate formation (hepatic) clearance and paracetamol-oxidative metabolites formation (hepatic) clearance, respectively; CL_{gluc}/F , CL_{sulf}/F and CL_{ox}/F , represent, elimination clearance (from body to others) for paracetamol-glucuronide, paracetamol-sulfate, and paracetamol-oxidative metabolites, respectively; V_{pcm}/F , V_{glu}/F , V_{sul}/F and V_{ox}/F , represent, volume of distribution for paracetamol, glucuronide, sulfate and oxidative metabolites, respectively.

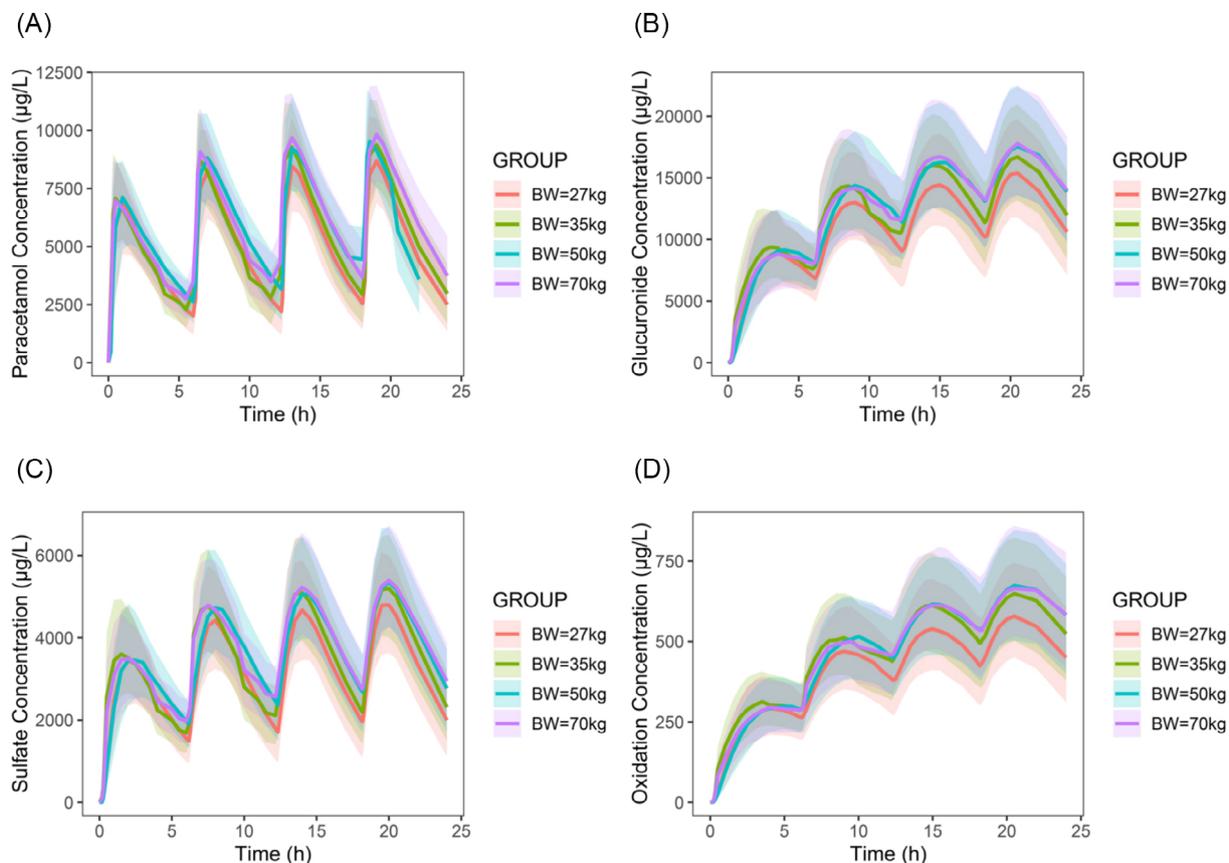


FIGURE 2 Model-based simulation of the concentrations over time for plasma paracetamol and its metabolites in SMA patients with different body weight in steady state with the dosage of 1000 mg. (A) Paracetamol concentration–time profile; (B) paracetamol–glucuronide concentration–time profile; (C) paracetamol–sulfate concentration–time profile; (D) paracetamol–oxidative metabolites concentration–time profile. Concentrations are presented as median (solid line) and 90% prediction interval (dashed line). HC, healthy controls; SMA, spinal muscular atrophy.

4 | DISCUSSION

In this paracetamol population PK model, body weight was incorporated as an allometric scaling factor and was found to significantly improve the model fit. Alternative covariates, including FFM and BMI, were also tested to explore whether these might further refine the model by accounting for unique aspects of body composition in the SMA population. However, neither FFM nor BMI improved the model performance beyond what was achieved with body weight alone. This may indicate that body weight sufficiently captures size-related variability in this patient group. This is most likely because paracetamol is hydrophilic and widely distributed in total body water, which is generally well correlated with body weight. Thus, FFM and BMI did not add additional predictive power.

According to the post-hoc analysis, SMA patients were associated with higher V_d for paracetamol and its metabolites compared to healthy controls, assuming identical body weight. An increased CL_p/F was also observed in the SMA patients. This is interesting, as in the already published paper with actual PK parameters without body weight correction, the V_{pcm}/F was significantly lower in SMA patients due to their lower body weight compared to the healthy controls.¹² Furthermore, we also found significant differences between the SMA

patients and healthy controls in all three metabolic pathways, with the SMA patients having a slower metabolism of paracetamol.¹² However, after body weight adjustment, only CL_p/F and V_d were significant and relatively high adjusted for body weight compared to healthy controls. The higher V_d of paracetamol in SMA patients could be explained by several factors. The most important may be their altered body composition.^{23–26} Patients with SMA have decreased skeletal muscle mass, and paracetamol distributes into various tissues beyond muscle, including the liver and other organs. It is possible that in SMA patients, there are differences in how paracetamol is distributed into these non-muscular tissues compared to healthy controls, leading to a higher V_{pcm}/F . Furthermore, around 20%–25% of paracetamol is bound to plasma proteins²⁷ and any alterations in plasma protein binding, such as changes in protein levels or affinity, can affect the V_{pcm}/F . Moreover, SMA may compromise gastrointestinal motility and change emptying time^{28,29} and the reduced motility may alter the rate and extent of absorption of an exogenous compound.³⁰ This possible change in the bioavailability may change the apparent V_d and systemic clearance because the bioavailability was included in the PK model parameters as a denominator in this study. To gain a deeper understanding of the higher V_{pcm}/F in SMA patients and the difference between body composition and bioavailability, it

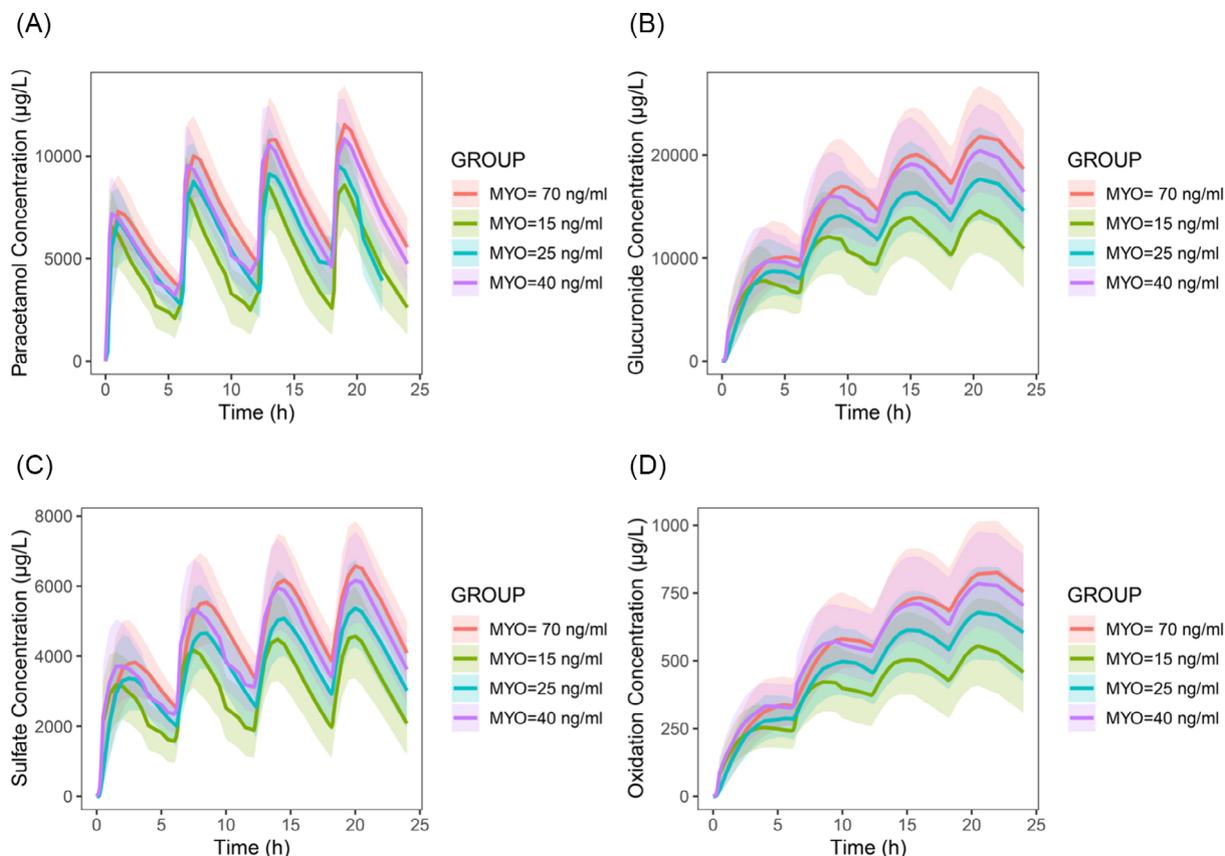


FIGURE 3 Model-based simulation of plasma paracetamol and its metabolites in 70 kg SMA patients with different myoglobin in steady state with the dosage of 1000 mg. (A) Paracetamol concentration–time profile; (B) paracetamol-glucuronide concentration–time profile; (C) paracetamol-sulfate concentration–time profile; (D) paracetamol-oxidative metabolites concentration–time profile. Solid line representing median value and dashed line representing 90% prediction interval. HC, healthy controls; SMA, spinal muscular atrophy; MYO, myoglobin.

would be essential to study the PK of intravenously administered paracetamol.

In the covariate analysis, we found that myoglobin was a significant covariate, and lower myoglobin was inversely correlated to CL_p/F . The simulation results showed that an increase in myoglobin levels was associated with a gradual increase in exposure of paracetamol and its metabolites. However, we need to pay attention to the fact that myoglobin levels are influenced by both age and disease, and these two factors may also contribute as potential confounders to the observed differences. Myoglobin is a protein stored in the skeletal muscle and facilitates oxygen diffusion from the haemoglobin molecule and is not necessarily a direct marker of skeletal muscle mass.³¹ In patients with SMA, myoglobin levels are elevated during childhood, indicating muscle damage. However, as these patients reach adulthood, myoglobin levels tend to decrease and normalize. This normalization is most likely due to the significant muscle waste and life-long inactivity of the muscles. In the paracetamol metabolic pathway, glutathione (GSH) plays a critical role in detoxifying the toxic intermediate NAPQI. It has been suggested that skeletal muscle has a remarkable GSH-synthesizing ability and high activity of GSH-dependent enzymes.³² Thus, we speculate that the low skeletal muscle mass, and the lower myoglobin levels, indirectly weakens the detoxifying

process in the oxidative metabolic pathway. Specifically, with low skeletal muscle mass, there may be less GSH available to metabolize paracetamol, leading to accumulation and compensatory increasing CL_p/F . Moreover, CL_p/F can consist of unchanged paracetamol but also possibly paracetamol not being metabolized through the known pathways. Even though the paracetamol metabolic pathway is widely reported, we do not know if another (toxic) pathway could also potentially be involved in this typical population. The increased CL_p/F may be attributable to another increasing route. Accordingly, as mentioned in the introduction, there are some cases in the literature reporting acute liver failure after intake of standard doses of paracetamol in SMA patients.^{9–11} Similarly, one adult SMA patient in our study had elevated liver biomarkers after 2 days of paracetamol intake with body weight-corrected doses, which was reported by our team.¹² Thus, we need to be cautious about the risk of potential hepatotoxicity of standard doses of paracetamol in patients with SMA.

Furthermore, according to the covariate analysis, the study found that a decrease in bilirubin could decrease CL_{ps}/F and increase CL_{ox}/F . The simulation showed that an increase in bilirubin levels was associated with a gradual rise in paracetamol and metabolite exposure, as well as a prolonged half-life of oxidative metabolites. However, similar to myoglobin, potential confounders such as co-medication should

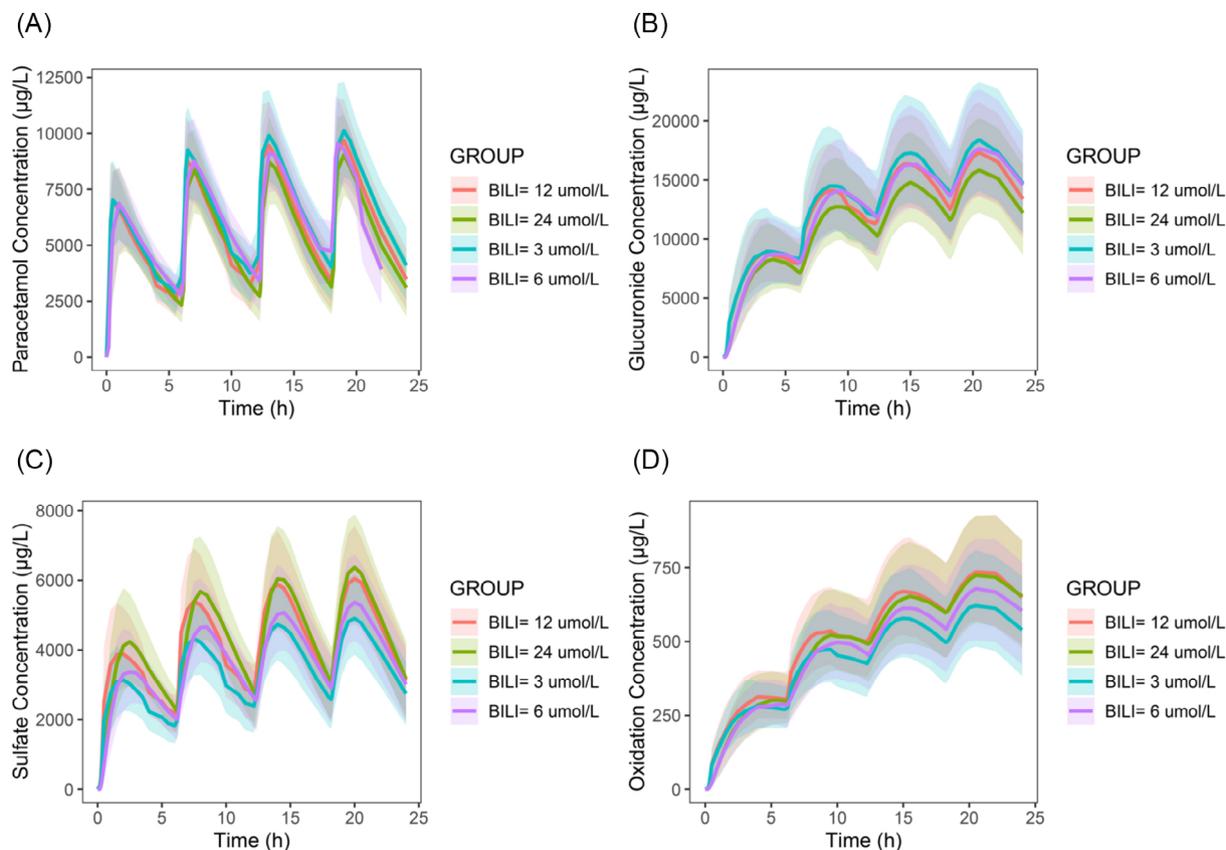


FIGURE 4 Model-based simulation of plasma paracetamol and its metabolites in 70 kg SMA patients with different bilirubin in steady state with the dosage of 1000 mg. (A) Paracetamol concentration–time profile; (B) paracetamol-glucuronide concentration–time profile; (C) paracetamol-sulfate concentration–time profile; (D) paracetamol-oxidative metabolites concentration–time profile. Solid line representing median value and dashed line representing 90% prediction interval. HC, healthy controls; SMA, spinal muscular atrophy; BILI, bilirubin.

not be overlooked, as some co-administered drugs may impose an additional metabolic burden on the liver. Bilirubin is formed of haeme from haemoglobin released from myoglobin, and thus might increase during circumstances of muscle breakdown due to the breakdown of muscle tissue and red blood cells. Furthermore, bilirubin is an indicator of liver and bile function, and elevation of bilirubin is often seen in chronic liver diseases and during drug-induced toxicity.³³ Since the bilirubin values were within the normal range and low in both the SMA patients and healthy controls, we still do not know the clinical implication of bilirubin as a significant covariate in our study. In clinical practice, paracetamol is often used as a co-medication together with other medications that may cause subtle hepatic differences, such as decreased liver enzyme activity, that do not cause overt liver dysfunction but still impact bilirubin metabolism. Another potential physiological reason could be the fact that both paracetamol and bilirubin undergo substantial clearance via glucuronidation,³⁴ and bilirubin is therefore expected to be correlated with paracetamol PK parameters. In several paracetamol population PK studies performed in neonates, bilirubin was also found as a significant covariate on paracetamol clearance and researchers suggested that bilirubin could be a significant covariate due to the fact that both bilirubin and paracetamol are cleared by glucuronoxylan transferase.^{6,19,20} While the

covariate analysis provided interesting insights into the impact of bilirubin on paracetamol PK, further studies are needed to elucidate the clear biological relevance of this result.

SMA patients suffer from several comorbidities. A study reported that a total of 71.4% of SMA patients had comorbidities, ranging from one to three, including the central nervous system, gastrointestinal and genitourinary system.³⁵ The potential of many comorbidities makes it hard to standardize the first- and second-line use of analgesic drugs and other co-medications. Even though SMA patients are generally shielded from severe pain, their pain score appears to be comparable to that of people with osteoarthritis or chronic low back pain.^{36,37} However, pain perception and tolerance vary significantly between individuals which can pose a potential risk of overdose. As paracetamol is often used as a co-medication for analgesic treatment, and concomitant medications may potentially also affect liver function, it is difficult to conclude in clinical practice that paracetamol alone is the cause of liver failure. However, the patients included in the study did not use any co-medications known to affect liver function. Furthermore, we have suspected that these patients have compromised paracetamol metabolism when the body is stressed due to fever or surgery, as we know they are prone to hypoglycaemia and hyperketosis within 16 h of fasting, and thus

present as more vulnerable both in our clinic and in literature.³⁸ Moreover, there is a possibility that the patients may take supratherapeutic doses due to poor or partial analgesic response, and that underweight adults might take adult doses, despite weighing less than 40 kg,³⁹ increasing the risk of liver toxicity. However, the case reports mentioned in the introduction did not report other medications known to impair liver function, and the doses were not supratherapeutic. This study highlights the need for future research to better understand the interplay between paracetamol, co-medications and individual variability in liver function to inform safer therapeutic practices.

According to the published literature in paracetamol population PK analysis,^{5–8} the fraction of unchanged paracetamol is around 4%. However, our study has shown a high fraction of CL_p/F (the value for patients with SMA is 47% and for healthy controls is 23%). A potential major reason for the high CL_p/F fraction was the assumption that metabolites could share the same V_d and be equal to 18% of paracetamol V_d , which might compromise the estimation. Another minor reason would be that our model structure did not take into account biliary excretion, since small fractions of paracetamol and its metabolites are known to undergo biliary excretion in humans.⁴⁰

The parent–metabolite model built in this study has successfully illustrated the differences in paracetamol PK between patients with SMA and healthy controls after body weight correction. Furthermore, the model has explored significant physiologic covariates on paracetamol PK in different metabolic pathways and contributed to a deeper understanding of paracetamol PK in SMA patients. The paracetamol total clearance value in this study was consistent with that in many published paracetamol population PK studies,^{6,7,41,42} all being around 20 L/h/70 kg. V_{pcm}/F in our model was also close to many published paracetamol population PK models with estimates around 60 L/70 kg.^{6,7,14,15,41,42} However, BSV was particularly high for CL_p/F (105%) and K_a (147%) in our study compared with some published studies for CL_p/F (around 20–30%).^{6,16,42} This high BSV highlights that there is still a large unexplained variability in paracetamol absorption and elimination phases. We need to obtain more covariates, including genetic and demographic data, to further explain the variability.

A strength of this study is that all the paracetamol metabolites were included instead of only the parent drug, so that we could look deeper into different metabolic pathways, especially the toxic pathway. Furthermore, the inclusion of healthy controls enhances the model's robustness and informativeness by allowing us to study the effect of the disease while improving the precision and accuracy of parameter estimation, despite the limited sample size.

However, there are some limitations. When we built the model, due to lack of urine data, we failed to estimate V_d for the metabolites and the formation fraction. Therefore, we assumed that the V_d for all the metabolites was a fixed fraction (0.18) of that for paracetamol, which might lead to deviations from the assumed relationship. However, with this fixed relationship, the model had a good fit with the observed data during validation and evaluation. Thus, even though

simplifying the model, the assumption might capture the overall trend of the data. Another limitation is that the sample size was small. Except for the 11 healthy controls, there were only six SMA children and six SMA adults, and even if they were good representations of the SMA population, the small sample size together with known large interindividual variability in paracetamol disposition limit the generalizability of the findings. However, clinical trials in special populations, such as SMA patients and children, are limited by the population size and difficulties with inclusion. Therefore, it is not reasonable to expect the same sample size compared to ordinary adult studies. Additionally, PK samples in this study were extensively collected on Days 1 and 3, including measurements of both the parent drug and its metabolites (294 samples for every compound), resulting in a comprehensive dataset. Nevertheless, we assume that those drawbacks could be compensated by intensive sampling and advanced data techniques which were developed for non-linear mixed effect model in the population PK analysis.

In conclusion, we found a relatively higher V_{pcm}/F and CL_p/F in patients with SMA compared to healthy controls with body weight as allometric scaling in the model. Besides body weight, the differences in PK between SMA patients and healthy controls could be explained by the disease itself (mainly influencing volume of distribution) and was inversely correlated with myoglobin concentrations. We suggest SMA patients should be dosed cautiously with a maximum dose not exceeding the recommended dose based on body weight.

AUTHOR CONTRIBUTIONS

Q.Z. conducted model analysis, manuscript preparation and revising. M.M.N., C.E.H.H., P.B.J. and M.C.O. designed the study, collected the data and critically revised the manuscript. B.C.M.W. supervised Q.Z. through the model analysis. S.S.H.K. designed the drug pharmacokinetics blood sample collection timepoints. S.S.H.K., T.K., K.L.R., J.V., H.H., M.H.M., T.M.H., M.D., A.P.B. and M.C.O. designed and conducted the clinical trial. P.B.J. performed the laboratory plasma drug concentration analysis. All authors reviewed and approved the manuscript before submission.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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