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ORIGINAL ARTICLE

# 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.

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 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.

### 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).

## 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.)

### 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

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

| | Median [range] | | |
|---|---|---|---|
| **Characteristic** | **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 (μmol/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 (μmol/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.

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 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 ($CL_{ox}/F$).

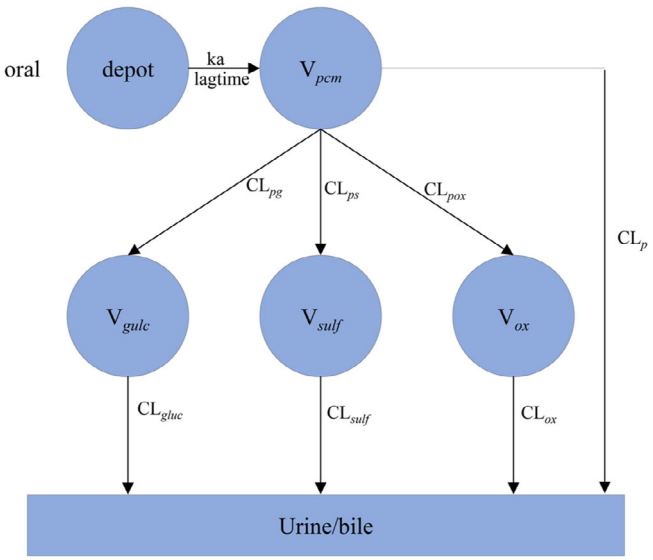


**FIGURE 1** Schematic illustration of the structural pharmacokinetic model for paracetamol and its metabolites in plasma. All formation and renal clearances were modelled as first-order processes. $CL_{pg}$, $CL_{ps}$, $CL_{pox}$ represent, respectively, formation (hepatic) clearances for paracetamol-glucuronide, 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.

## 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).

| | | | Bootstrap of the final model | |
|---|---|---|---|---|
| **Parameter** | **Base model** | **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 | | | | |
| *Myoglobin (mean 25 ng/mL)* | | −1.10 | −1.14 | −3.07–0.49 |
| Covariate effect on $CL_{ps}$ /F | | | | |
| *Bilirubin (mean 6 μmol/L)* | | 0.18 | 0.16 | −0.02–0.39 |
| Covariate effect on $CL_{ox}$/F | | | | |
| *Bilirubin (mean 6 μmol/L)* | | −0.177 | −0.176 | −0.45–0.03 |
| Covariate effect on $V_{pcm}$/F | | | | |
| *Disease* | | 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; Ka, absorption rate constant; tlag, 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.

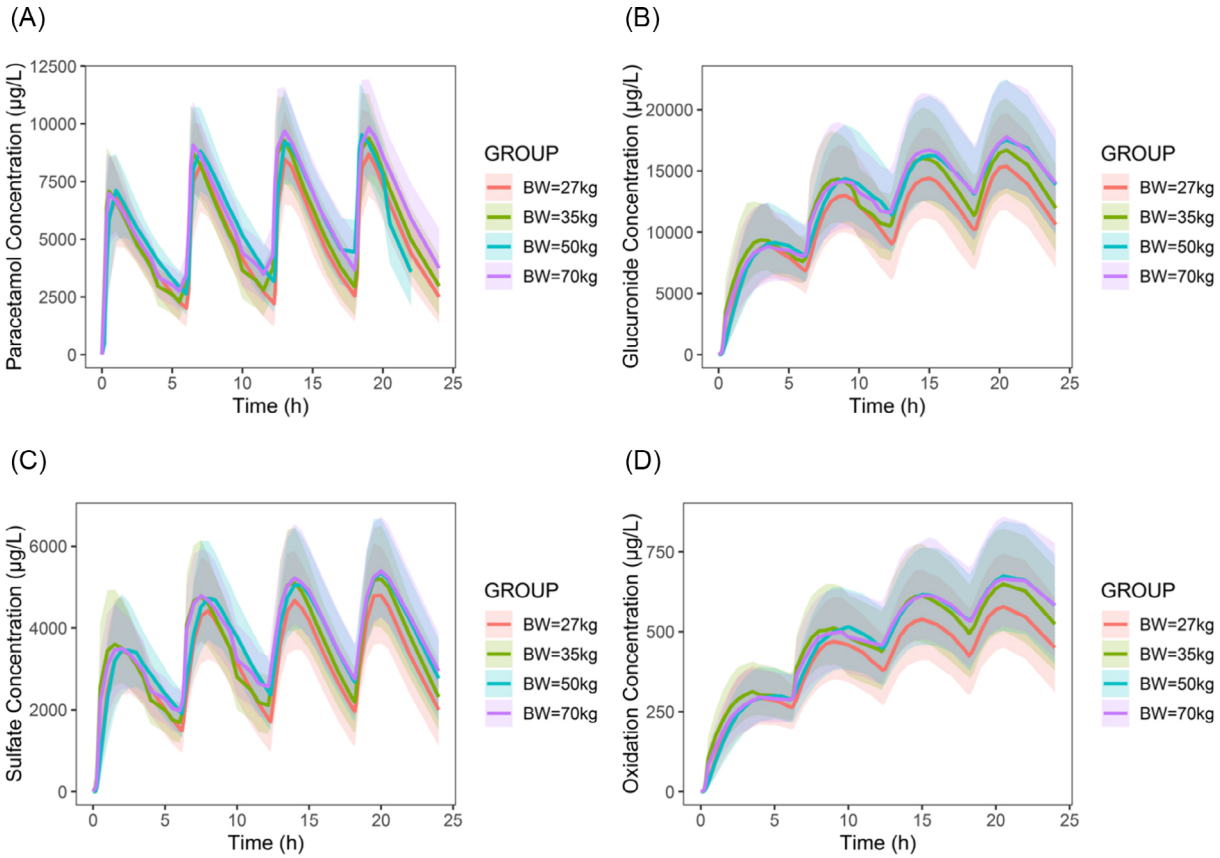


**FIGURE 2** Model-based simulation of the concentrations over time for plasma paracetamol and its metabolites in SMA patients with different body weight in steady state with the dosage of 1000 mg. (A) Paracetamol concentration–time profile; (B) paracetamol-glucuronide concentration–time profile; (C) 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 proteins[27] 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 exogenic 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

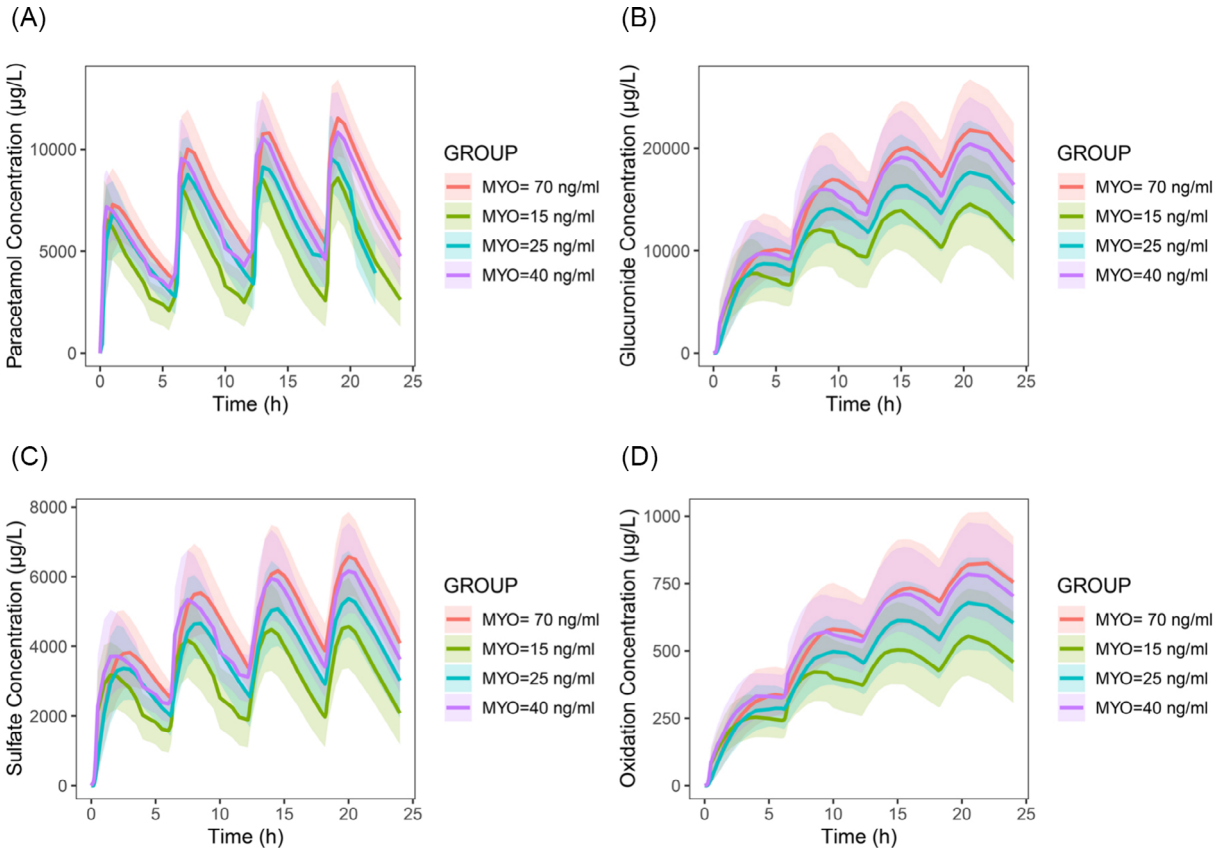


**FIGURE 3** Model-based simulation of plasma paracetamol and its metabolites in 70 kg SMA patients with different myoglobin in steady state with the dosage of 1000 mg. (A) Paracetamol concentration–time profile; (B) paracetamol-glucuronide concentration–time profile; (C) paracetamol-sulfate concentration–time 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 lifelong 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

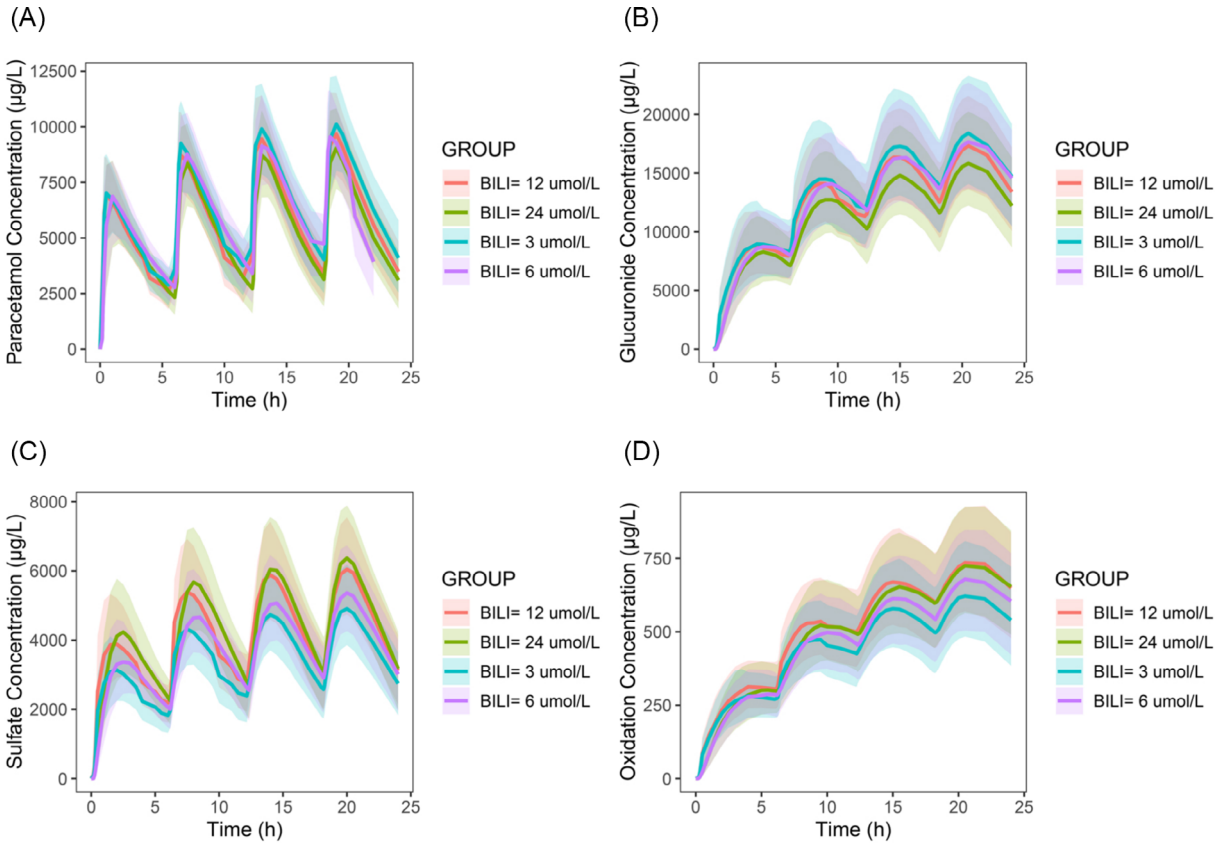


**FIGURE 4** Model-based simulation of plasma paracetamol and its metabolites in 70 kg SMA patients with different bilirubin in steady state with the dosage of 1000 mg. (A) Paracetamol concentration–time profile; (B) paracetamol-glucuronide concentration–time profile; (C) paracetamol-sulfate concentration–time 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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## REFERENCES


1. Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol Clin*. 2015;33:831-846. doi:10.1016/j.ncl.2015.07.004
2. Mercuri E, Sumner CJ, Muntoni F, Darras BT, Finkel RS. Spinal muscular atrophy. *Nat Rev Dis Primers*. 2022;8:52. doi:10.1038/s41572-022-00380-8
3. Nicolau S, Waldrop MA, Connolly AM, Mendell JR. Spinal muscular atrophy. *Semin Pediatr Neurol*. 2021;37:100878. doi:10.1016/j.spen.2021.100878
4. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. *Orphanet J Rare Dis*. 2011;6:71. doi:10.1186/1750-1172-6-71
5. Allegaert K, Peeters MY, Beleyn B, et al. Paracetamol pharmacokinetics and metabolism in young women. *BMC Anesthesiol*. 2015;15:163. doi:10.1186/s12871-015-0144-3
6. Cook SF, Roberts JK, Samiee-Zafarghandy S, et al. Population pharmacokinetics of intravenous paracetamol (acetaminophen) in preterm and term neonates: model development and external evaluation. *Clin Pharmacokinet*. 2016;55:107-119. doi:10.1007/s40262-015-0301-3
7. Owens KH, Murphy PG, Medlicott NJ, et al. Population pharmacokinetics of intravenous acetaminophen and its metabolites in major surgical patients. *J Pharmacokinet Pharmacodyn*. 2014;41:211-221. doi:10.1007/s10928-014-9358-0
8. Kulo A, Peeters MY, Allegaert K, et al. Pharmacokinetics of paracetamol and its metabolites in women at delivery and post-partum. *Br J Clin Pharmacol*. 2013;75:850-860. doi:10.1111/j.1365–2125.2012.04402.x
9. Brehm TT, Wehmeyer MH, Fuhrmann V, Schäfer H, Kluwe J. Severe acute liver injury following therapeutic doses of acetaminophen in a patient with spinal muscular atrophy. *Am J Ther*. 2019;26:e528-e529. doi:10.1097/MJT.0000000000000829
10. Ceelie I, James LP, Gijsen V, et al. Acute liver failure after recommended doses of acetaminophen in patients with myopathies. *Crit Care Med*. 2011;39:678-682. doi:10.5694/j.1326–5377.1999.tb123758.x
11. Hynson JL, South M. Childhood hepatotoxicity with paracetamol doses less than 150 mg/kg per day. *Med J Aust*. 1999;171:497. doi:10.5694/j.1326–5377.1999.tb123758.x
12. Naume MM, Zhao Q, Haslund-Krog SS, et al. Acetaminophen treatment in children and adults with spinal muscular atrophy: a lower tolerance and higher risk of hepatotoxicity. *Neuromuscul Disord*. 2024;34:9-18. doi:10.1016/j.nmd.2023.11.005
13. Zillen D, Movig KLL, Kant G, Masselink JB, Mian P. Impact of malnourishment on the pharmacokinetics of acetaminophen and susceptibility to acetaminophen hepatotoxicity. *Clin Case Rep*. 2021;9(11):e04611. doi:10.1002/ccr3.4611
14. Anderson BJ, Holford NH, Woollard GA, Chan PL. Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. *Br J Clin Pharmacol*. 1998;46:237-243. doi:10.1046/j.1365–2125.1998.00780.x
15. Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. *Br J Clin Pharmacol*. 2000;50:125-134. doi:10.1046/j.1365–2125.2000.00231.x
16. Mian P, van Esdonk MJ, Olkkola KT, et al. Population pharmacokinetic modelling of intravenous paracetamol in fit older people displays extensive unexplained variability. *Br J Clin Pharmacol*. 2019;85:126-135. doi:10.1111/bcp.13770
17. Morse JD, Stanescu I, Atkinson HC, Anderson BJ. Population pharmacokinetic modelling of acetaminophen and ibuprofen: the influence of body composition, formulation and feeding in healthy adult volunteers. *Eur J Drug Metab Pharmacokinet*. 2022;47(4):497-507. doi:10.1007/s13318-022-00766-9
18. Allegaert K, Olkkola KT, Owens KH, et al. Covariates of intravenous paracetamol pharmacokinetics in adults. *BMC Anesthesiol*. 2014;14:77. doi:10.1186/1471-2253-14-77
19. Allegaert K, Palmer GM, Anderson BJ. The pharmacokinetics of intravenous paracetamol in neonates: size matters most. *Arch Dis Child*. 2011;96(6):575-580. doi:10.1136/adc.2010.204552
20. Palmer GM, Atkins M, Anderson BJ, et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth*. 2008;101(4):523-530. doi:10.1093/bja/aen208
21. Lowenthal DT, Oie S, Van Stone JC, Briggs WA, Levy G. Pharmacokinetics of acetaminophen elimination by anephric patients. *J Pharmacol Exp Ther*. 1976;196(3):570-578. doi:10.1016/S0022-3565(25)30450-7
22. Ette EI. Stability and performance of a population pharmacokinetic model. *J Clin Pharmacol*. 1997;37:486-495. doi:10.1002/j.1552–4604.1997.tb04326.x
23. Baranello G, De Amicis R, Arnoldi MT, et al. Evaluation of body composition as a potential biomarker in spinal muscular atrophy. *Muscle Nerve*. 2020;61:530-534. doi:10.1002/mus.26823
24. Leroy-Willig A, Willig TN, Henry-Feugeas MC, et al. Body composition determined with MR in patients with Duchenne muscular dystrophy, spinal muscular atrophy, and normal subjects. *Magn Reson Imaging*. 1997;15:37-44. doi:10.1016/S0730-725X(97)00046–5
25. Wang W, Feng Y, Long Q, et al. A comparative analysis of body composition assessment by BIA and DXA in children with type II and III spinal muscular atrophy. *Front Neurol*. 2022;13:1034894. doi:10.3389/fneur.2022.1034894
26. Watson KS, Boukhloufi I, Bowerman M, Parson SH. The relationship between body composition, fatty acid metabolism and diet in spinal muscular atrophy. *Brain Sci*. 2021;11(2):131. doi:10.3390/brainsci11020131
27. Bartolone JB, Beierschmitt WP, Birge RB, et al. Selective acetaminophen metabolite binding to hepatic and extrahepatic proteins: an in vivo and in vitro analysis. *Toxicol Appl Pharmacol*. 1989;99:240-249. doi:10.1016/0041-008X(89)90006–9
28. Gombash SE, Cowley CJ, Fitzgerald JA, et al. SMN deficiency disrupts gastrointestinal and enteric nervous system function in mice. *Hum Mol Genet*. 2015;24:3847-3860. doi:10.1093/hmg/ddv292
29. Ii T, Oi N, Shioya K, Kawano T, Nakahara S, Matsukura S. A case of progressive spinal muscular atrophy with disorder of intestinal motility improved by administration of erythromycin. *Nippon Naika Gakkai Zasshi*. 1992;81(8):1261-1262.
30. Dahlgren D, Lennernäs H. Intestinal permeability and drug absorption: predictive experimental, computational and in vivo approaches. *Pharmaceutics*. 2019;11(8):411. doi:10.3390/pharmaceutics11080411
31. Spires J, Lai N, Zhou H, Saidel GM. Hemoglobin and myoglobin contributions to skeletal muscle oxygenation in response to exercise. *Adv Exp Med Biol*. 2011;701:347-352. doi:10.1007/978-1-4419-7756-4_47
32. Sen CK. Glutathione: A key role in skeletal muscle metabolism. In: Reznick AZ, Packer L, Sen CK, Holloszy JO, Jackson MJ, eds. *Oxidative stress in skeletal muscle*. Birkhäuser; 1998:127-139. doi:10.1007/978-3-0348-8958-2_8
33. Castillo-Castañeda SM, Cordova-Gallardo J, Rivera-Espinosa L, Chavez-Pacheco JL, Ramírez-Mejía MM, Méndez-Sánchez N. Bilirubin molecular species play an important role in the pathophysiology of acute-on-chronic liver failure. *Int J Mol Sci*. 2024;25(15):8181. doi:10.3390/ijms25158181
34. Zhou J, Tracy TS, Remmel RP. Bilirubin glucuronidation revisited: proper assay conditions to estimate enzyme kinetics with recombinant UGT1A1. *Drug Metab Dispos*. 2010;38(11):1907-1911. doi:10.1124/dmd.110.033829
35. Błauciak M, Ubysz J, Pokryszko-Dragan A, Koszewicz M. The impact of comorbidities and motor impairment on the quality of life of patients with spinal muscular atrophy: a case-control study. *J Clin Med*. 2024;13(14):4184. doi:10.3390/jcm13144184

36. Abresch RT, Carter GT, Jensen MP, Kilmer DD. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. *Am J Hosp Palliat Care*. 2002;19(1):39-48. doi:10.1177/104990910201900109
37. Lager C, Kroksmark AK. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. *Eur J Paediatr Neurol*. 2015;19(5):537-546. doi:10.1016/j.ejpn.2015.04.005
38. Ørngreen MC, Andersen AG, Eisum AS, et al. Prolonged fasting-induced hyperketosis, hypoglycaemia and impaired fat oxidation in child and adult patients with spinal muscular atrophy type II. *Acta Paediatr*. 2021;110(12):3367-3375. doi:10.1111/apa.16074
39. Kozer E, Greenberg R, Zimmerman DR, Berkovitch M. Repeated supratherapeutic doses of paracetamol in children—a literature review and suggested clinical approach. *Acta Paediatr*. 2006;95(10):1165-1171. doi:10.1080/08035250600580503
40. Siegers CP, Loeser W, Gieselmann J, Oltmanns D. Biliary and renal excretion of paracetamol in man. *Pharmacology*. 1984;29:301-303. doi:10.1159/000138026
41. Schuitmaker M, Anderson BJ, Holford NH, Woollard GA. Pharmacokinetics of paracetamol in adults after cardiac surgery. *Anaesth Intensive Care*. 1999;27:615-622. doi:10.1177/0310057X990270061
42. van der Heijden LT, Mian P, Hias J, et al. Highly variable paracetamol pharmacokinetics after multiple oral dosing in frail older people: a population pharmacokinetic analysis. *Drugs Aging*. 2022;39:83-95. doi:10.1007/s40266-021-00912-z

## SUPPORTING INFORMATION

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

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