Covariates of intravenous paracetamol pharmacokinetics in adults

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Abstract

Background: Pharmacokinetic estimates for intravenous paracetamol in individual adult cohorts are different to a certain extent, and understanding the covariates of these differences may guide dose individualization. In order to assess covariate effects of intravenous paracetamol disposition in adults, pharmacokinetic data on discrete studies were pooled.

Methods: This pooled analysis was based on 7 studies, resulting in 2755 time-concentration observations in 189 adults (mean age 46 SD 23 years; weight 73 SD 13 kg) given intravenous paracetamol. The effects of size, age, pregnancy and other clinical settings (intensive care, high dependency, orthopaedic or abdominal surgery) on clearance and volume of distribution were explored using non-linear mixed effects models.

Results: Paracetamol disposition was best described using normal fat mass (NFM) with allometric scaling as a size descriptor. A three-compartment linear disposition model revealed that the population parameter estimates (between subject variability,%) were central volume (V1) 24.6 (55.5%) L/70 kg with peripheral volumes of distribution V2 23.1 (49.6%) L/70 kg and V3 30.6 (78.9%) L/70 kg. Clearance (CL) was 16.7 (24.6%) L/h/70 kg and inter-compartment clearances were Q2 67.3 (25.7%) L/h/70 kg and Q3 2.04 (71.3%) L/h/70 kg. Clearance and V2 decreased only slightly with age. Sex differences in clearance were minor and of no significance. Clearance, relative to median values, was increased during pregnancy (Fpreg = 1.14) and decreased during abdominal surgery (Fabdcl = 0.715). Patients undergoing orthopaedic surgery had a reduced V2 (Fortcho = 0.649), while those in intensive care had increased V2 (Ficv = 1.51).

Conclusions: Size and age are important covariates for paracetamol pharmacokinetics explaining approximately 40% of clearance and V2 variability. Dose individualization in adult subpopulations would achieve little benefit in the scenarios explored.

Background

Paracetamol (acetaminophen) is the most commonly used drug to treat fever or pain, both as an over the counter drug as well as in the hospital setting [1]. Paracetamol can be administered either in monotherapy or as part of a multimodal approach, resulting in more effective temperature control when combined with non-steroidal anti-inflammatory drugs (NSAIDS) or equivalent analgesia with lower opioid exposure [2-4]. In healthy adults and using on label doses, paracetamol is almost exclusively eliminated by conjugation into either paracetamol glucuronide (47 - 62%) or paracetamol sulphate (25 - 36%), while limited amounts (1 - 4%) are excreted in the urine as unchanged paracetamol or undergo (<10%) oxidation to result in toxic metabolites (N-acetyl-p-benzoquinone, NAPQI) [5,6]. At higher doses, or in specific settings like alcohol abuse or malnutrition, the oxidative pathway may be more active and may result in hepatic necrosis [7]. When used in therapeutic dosages, paracetamol is generally regarded as safe and well tolerated in a variety of patients.

While oral and rectal formulations have been popular for the past century, an intravenous formulation has recently been introduced into clinical care. Such an intravenous
formation can be considered in the immediate postoperative period if the oral route cannot yet be used, while avoiding the unpredictability of absorption and bioavailability following rectal administration. The development of intravenous formulations has allowed time-concentration profile observations unencumbered by absorption variability. In addition to observations in healthy volunteers [8,9], the pharmacokinetics in special populations have been re-evaluated, including geriatric patients, abdominal surgery cases, intensive care patients and women at delivery or in postpartum [10–13].

Pooling of such datasets has the potential to further explore covariates, including weight, gender or disease characteristics [14–16]. Such an effort is of relevance. This is because a unique and single dosing regimen in any adult (i.e. 1 g intravenous paracetamol, q6h for maximal 48 hours) irrespective of other covariates may be an over-simplification, omitting clinical settings with either higher (insufficient effect) or lower clearance (raised risk for toxicity). Information on covariates of intravenous paracetamol disposition may be extrapolated to other routes of administration, or even to other compounds that undergo similar routes of elimination [5,17–19]. The current pooled intravenous paracetamol PK study explores the impact of covariates (e.g. age, weight, pregnancy, intensive care, type of surgery) on paracetamol disposition when compared to similar observations in healthy adult volunteers.

Methods
Clinical observations
Observations of intravenous paracetamol disposition in different cohorts of adults published in the literature were pooled to explore covariate influences (e.g., gender, age, size, disease characteristics, surgical procedure). Cohorts were retrieved using a PubMed search that included the ‘snowball method’, followed by an invitation to the corresponding authors to provide the raw data (time concentration profiles, clinical characteristics) within a setting of academic collaboration [20]. Patient demographics and age distribution are presented in Table 1 and Figure 1 respectively.

Healthy volunteer studies
Twelve healthy male volunteers (21–25 year, 63–83 kg) were given a single dose of intravenous (IV) propacetamol (1 g, equal to 0.5 g of paracetamol, Pro-Dalfagan, Bristol-Myers Squibb Pharmaceuticals, Braine l’Alleud, Belgium) and 13 blood samples for assay were subsequently collected for up to 24 h afterwards [8]. Paracetamol concentrations were quantified in plasma by reverse High Pressure Liquid Chromatography (HPLC) with UV detection. The lower limit of quantification was 0.1 μg/ml. Intra-assay coefficients of variation (CV) at 0.04, 1.25 and 5 μg/ml were 6.4, 1.9 and 2% respectively, inter-assay CV at 0.5 and 10 μg/ml were 3.3 and 2.2% respectively.

Healthy male (n = 12) and female (n = 14) volunteers (19–34 year, 49–94 kg) were given IV paracetamol (2 g loading dose, followed 1 g intravenous paracetamol 6 hourly, Perfalgan, Bristol Myers Squibb, Paris, France) [9]. Plasma samples (n = 32) were collected for up to 48 h after the loading dose were collected, with specific emphasis after the first and after the final 5th paracetamol dose (at 24 h). All female volunteers were on contraceptives during the study, 13/14 based on oral contraceptives. Paracetamol concentrations were quantified in plasma by reverse HPLC with UV detection. The lower limit of quantification was 0.02 μg/ml. Imprecision and inaccuracy were lower than 3% and within 1% respectively.

Eight healthy female volunteers (27–37 year, 54–74 kg) were studied following a single loading dose (2 g IV paracetamol, Perfalgan, Bristol Myers Squibb, Braine l’Alleud, Belgium or intravenous Paracetamol, Fresenius Kabi, Schelle, Belgium) (1,2,4,6 h) as part of a research project concerning intravenous paracetamol disposition in pregnancy and postpartum [11]. None of these volunteers were on oral contraceptives. Paracetamol concentrations were quantified in plasma by reverse HPLC with UV detection. The lower limit of quantification was 0.08 μg/ml. Coefficients of variation for intra- and inter-day precision and accuracy were all below 15%.

Clinical cohorts
Single dose IV paracetamol (1 g, Perfalgan 10 mg/L solution, Bristol-Myers Squibb, Agen, France) pharmacokinetics have been documented in 40 patients following orthopaedic surgery, with a study design to explore the age related impact (20–88 year, 58–107 kg, male/female = 19/21) [10]. Plasma samples (n = 20) were collected in each patient for up to 24 h. Paracetamol plasma concentrations were quantified in plasma by HPLC. The lower limit of quantification was 0.25 μg/ml. The interday CV for paracetamol was 12.8, 12.5 and 5.1% at 0.398, 2.01 and 10.1 μg/ml respectively.

As part of a study on IV paracetamol tolerance during repeated administration in adults admitted in medium (high dependency) and intensive care, paracetamol concentrations were quantified in 38 medium and intensive care patients (34–82 year, 53–120 kg, male/female = 27/11) after the first administration (1 g, Perfalgan, Bristol-Myers Squibb BV, Woerden, The Netherlands) [12]. Blood samples were collected up to 6 h after initiation of intravenous administration with a ‘trough’ concentration recorded before the second administration. Paracetamol serum concentrations were quantified with fluorescent polarization immunoassay (Cobas Integra 400, Roche Diagnostics, West Sussex, UK). Lower limit of detection of the analysis was 0.2 μg/ml. Within-run variation and total variation for low as well as high
| Reference | ref 8 | ref 9 | ref 11 | ref 10 | ref 12 | ref 13 | ref 11 | ref 11 | Ref 11 |
|-----------|-------|-------|--------|--------|--------|--------|--------|--------|--------|
| Characteristics | 12 healthy males | 12 healthy males | 8 healthy females | Orthopaedic surgery | High dependency and IC, 38 cases | Abdominal surgery | Caesarean delivery | Postpartum early | Postpartum late, |
| | | | 14 healthy females | | 40 cases | | 20 cases | | 41 cases |
| | | | | | | | | | 8 cases (15 weeks) |
| | | | | | | | | | 7 cases (1 year) |
| Study design | Single iv bolus, 0.5 g | Single iv bolus, 2 g | Single iv bolus, 1 g | Single iv bolus, 1 g | Single iv bolus, 1 g | Single iv bolus, 1 g | | |
| | | | | Maintenance 1 g q6h | Maintenance 1 g q6h | Maintenance 1 g q6h | | |
| Weight | 63-83 kg | 49-94 kg | 54-74 kg | 58-107 kg | 53-120 kg | 57-101 kg | 57-110 kg | 52-88 kg | 50-87 kg |
| Age | 21-25 years | 19-34 years | 27-37 years | 20-88 years | 34-82 years | 44-85 years | 31, SD 5.8 years | 31, SD 5.8 years | 50-87 kg |
| Sampling strategy | 13 samples/case up to 24 h | 32 samples/case up to 48 h | 4 samples/case up to 24 h | 8 samples/case up to 6 h | 2x9 samples/case up to 72 h | 4 samples after loading dose + up to 24 h | 4 samples/case, up to 48 h | 4 samples/case, up to 48 h | 4 samples/case, up to 6 h |
| Analytical technique | HPLC-uv | HPLC-uv | HPLC-uv | HPLC | HPLC | HPLC | HPLC-uv | HPLC-uv | HPLC-uv |
| LLOQ | < 0.1 μg/ml | < 0.02 μg/ml | < 0.08 μg/ml | < 0.25 μg/ml | < 0.2 μg/ml | n.a. | < 0.08 μg/ml | < 0.08 μg/ml | < 0.08 μg/ml |
| CV% | <6.4% | < 3% | < 15% | < 12.8% | < 7.5% | n.a. | < 15% | < 15% | < 15% |

[IC = intensive care; iv = intravenous; SD = standard deviation, HPLC = High Pressure Liquid Chromatography; LLQ = lower limit of quantification; CV = coefficients of variation].
concentrations (9.9, 32.9 and 97.4 \(\mu g/ml\)) were within a range of 0.7-5.8% and 4.4-7.5% respectively.

Twenty patients received IV paracetamol (1 g, 6 hourly, up to 48–72 h, Perugal Bristol-Myers Squibb Ltd, Auckland, New Zealand) after major abdominal surgery (44–85 year, 57–101 kg, male/female = 8/12) [13]. Plasma samples were collected over 2 intervals (day of surgery and 2–3 days afterwards). Paracetamol concentrations were quantified by HPLC.

Repeated dose IV paracetamol pharmacokinetics (loading dose 2 g, followed by 1 g 6 hourly for 24 h) were collected in a cohort of 41 women undergoing caesarean delivery [11]. A subgroup of 8/41 women initially included at delivery were recruited for a second single loading dose (2 g paracetamol) PK study 10–15 weeks after delivery and 7/8 women were re-evaluated a third time (single loading dose, 2 g) about one year after delivery [11]. Blood samples were collected after the loading dose (1, 2, 4 h) with subsequent collection at trough (6, 12, 18 and 24 h). More recently, 8 additional observations in women undergoing caesarean delivery were collected, resulting in 49 observations at delivery. Paracetamol plasma concentrations were determined by HPLC. The lower limit of quantification was 0.08 \(\mu g/ml\). Coefficients of variation for intra- and inter-day precision and accuracy were all below 15%.

**Pharmacokinetic analysis**

Population parameter estimates were obtained using non-linear mixed effects modeling (NONMEM 7.3, Globomax LLC, Hanover, MD, USA). This software accounts for population parameter variability (between subjects) and residual variability (random effects) as well as parameter differences predicted by covariates (fixed effects). The population parameter variability (or between subject variability, BSV) for structural model parameters were assumed to be log-normally distributed across the population.

\[
Ci = F \ e^{CVCP + SDCP}
\]

\[
C_i = TVC_i e^{\eta_{CLbsv} + \eta_{CLbov}}
\]

\[
V_i = TVV e^{\eta_{Vbsv} + \eta_{Vboc}}
\]

\(\eta_{CLbsv}\) is the difference between individual (\(CL_i\)) and population mean (\(TVCL\)), \(\eta_{CLbov}\) is the difference in \(CL\) between occasions. \(\eta_{Vbsv}\) is the difference between individual (\(Vi\)) and population mean (\(TVV\)), and \(\eta_{Vboc}\) is the difference in \(V\) between occasions.

Residual unexplained variability (RUV) was modelled using additive and proportional terms. The variance of the RUV (\(\eta_{RUV,i}\)) was also estimated.

\[
Ci = F \ e^{CVCP + SDCP}
\]

\(Ci\) is to concentration in the individual, \(F\) is the model predicted concentration, \(CVCP\) is the coefficient of variation for the proportional error, and \(SDCP\) is the standard deviation of the additive error. Data from each assay laboratory was assigned individual.

The first order conditional interaction estimate method using ADVAN3 TRAN4 was used to estimate population mean parameters, between subject variance and residual variance. Convergence criterion was 3 significant digits. Initial analyses suggested a three-compartment disposition model for paracetamol and the model was parameterized in terms of clearance (CL), inter-compartment clearances (\(Q2, Q3\)), central volume (\(V1\)) and peripheral volumes (\(V2, V3\)). The population parameter variability was modelled in terms of random effect (\(\eta\)) variables. Each of these variables was assumed to have mean 0 and a variance denoted by \(\omega^2\), which was estimated. The covariance between two elements of \(\eta\) (e.g. CL and V) is a...
measure of statistical association between these two variables. Their covariance is related to their correlation \( R \) i.e.

\[
R = \frac{\text{covariance}}{\sqrt{w_{CL}^2 \times w_{V}^2}}
\]

The covariance of parameter variability was incorporated into the model.

**Covariate analyses**

a) **Size**

We investigated three measures of body size

- **Total body weight (TBW) (kg)**
- **Fat Free Mass (FFM)**

Fat free mass (FFM) can be predicted from TBW and height (H, m) [21].

\[
FFM = WHS_{\text{max}} \cdot H^2 \cdot \left( \frac{TBW}{WHS_{50} \cdot H^2 + TBW} \right)
\]

where WHS\(_{\text{max}}\) is the maximum FFM for any given height (H, m) and WHS\(_{50}\) is the TBW value when FFM is half of WHS\(_{\text{max}}\). For men, WHS\(_{\text{max}}\) is 42.92 kg/m\(^2\) and WHS\(_{50}\) is 30.93 kg/m\(^2\) and for women WHS\(_{\text{max}}\) is 37.99 kg/m\(^2\) and WHS\(_{50}\) is 35.98 kg/m\(^2\).

- **Normal fat mass (NFM)**

Normal fat mass (NFM) is an extension of the concept of predicted normal weight [22] with a parameter (\( F_{\text{fat}} \)) which accounts for different contributions of fat mass (i.e. TBW minus FFM)

\[
NFM = FFM + F_{\text{fat}} \cdot (TBW - FFM)
\]

Instead of assuming a fixed value of \( F_{\text{fat}} \) in all cases the idea of NFM is to estimate the value of \( F_{\text{fat}} \) that is most appropriate for the parameter being predicted. If \( F_{\text{fat}} \) is estimated to be zero then FFM alone is required to predict size while if \( F_{\text{fat}} \) is 1 then size is predicted by TBW. Other estimates of \( F_{\text{fat}} \) reflect different weighting of body composition components.

The parameter values were standardised for a body size using an allometric model [23,24].

\[
Pi = P_{\text{std}} \times \left( \frac{X_i}{W_{\text{std}}} \right)^{PWR}
\]

where \( P_i \) is the parameter in the \( i \)-th individual, \( X_i \) is a measure of body size (TBW, FFM or NFM) in the \( i \)-th individual and \( P_{\text{std}} \) is the parameter in an individual with a standard size \( W_{\text{std}} \). The PWR exponent is 0.75 for clearance and 1 for distribution volumes [25-27]. Thus total drug clearance may be expected to scale with a power of \( \alpha \) with the allometric model:

\[
CL_i = CL_{\text{std}} \times \left( \frac{X_i}{70} \right)^{3/4}
\]

where CL\(_{\text{std}}\) is the population estimates for CL.

b) **Age**

The effect of age (years) on clearance or distribution volumes was investigated using a scaling factor (\( F_{\text{AGECL}}, F_{\text{AGEV}} \)). The majority of patients were either younger than 40 years or older than 60 years (Figure 1). The formula for FFM was based on adults aged up to 60 years. Consequently if patients were aged above 60 years, then a scaling factor (\( F_{\text{AGE}} \)) was applied to CL or V population estimates.

c) **Sex**

The male was taken as the standard and a scaling factor (\( F_{\text{SEXCL}} \)) estimated if the patient was female:

\[
CL = F_{\text{AGECL}} \times F_{\text{SIZECL}} \times F_{\text{SEXCL}} \times CL_{\text{std}}
\]

d) **Other covariates**

A similar approach, using a scaling factor was taken with other covariates [pregnancy (\( F_{\text{PREG}} \)), postpartum (\( F_{\text{PP}} \)), intensive care (\( F_{IC} \)), high dependency care (\( F_{HD} \)); abdominal surgery (\( F_{\text{ABD}} \)) and orthopaedic surgery (\( F_{\text{ORTHO}} \)] and their impact on clearance or volume respectively, e.g.

\[
CL = F_{\text{AGECL}} \times F_{\text{SIZECL}} \times F_{\text{SEXCL}} \times F_{\text{PREG}} \times F_{\text{ICCL}} \times F_{\text{HDCL}} \times F_{\text{ABDCL}} \times CL_{\text{std}}
\]

\[
V^2 = F_{\text{SIZEV2}} \times F_{\text{AGEV2}} \times F_{\text{ORTHOV2}} \times F_{\text{ICV2}} \times V_{\text{std}}
\]

**Quality of fit**

The quality of fit of the pharmacokinetic model to the data was sought by NONMEM’s objective function and by visual examination of plots of observed versus predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at \( \alpha = 0.05 \). An objective function change of 6.635 (\( p < 0.01 \)) was used to determine covariate inclusion. Bootstrap methods provided a means to evaluate parameter uncertainty [28]. A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check (VPC) [29], a modeling tool that estimates
the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations. Simulation was performed using 1000 subjects with characteristics taken from the pooled population. For data such as these where covariates such as dose, size, sex, age, or pathology are different for each patient, we used a prediction corrected VPC (PC-VPC) [30].

Simulation
A simulation study was performed to investigate both concentration variability in a 25 year old 70 kg healthy adult volunteer given a standard dose of intravenous paracetamol 1 g 6 hourly for 36 h, and typical time-concentration profiles in a 68 year old 70 kg male in intensive care, a 25 year 70 kg pregnant woman in her third trimester, the same woman 2 months postpartum weighing 60 kg, and a 68 year old 70 kg male undergoing abdominal surgery. The drug was infused over 15 minutes. Pharmacokinetic parameter estimates and their variability from this current pooled study were used to predict individual time-concentration profiles.

Results
The pooled analysis included 2755 paracetamol observations in 189 individuals. The clinical characteristics and medical conditions of the individual studies were already mentioned in the methods section, but the pooled dataset of adults had a mean weight of 73 kg (range 49.2–120 kg) and age 46 years (range 19–88.5 year). The distribution of ages was shown in Figure 1. All data were above the lower limit of quantification reported from each of the individual studies.

The model building process is shown in Table 2. A three compartment disposition model was better than a one or two-compartment model. Size scaling using NFM and allometry reduced the objective function more than either TBW or NFM. The estimate for $\text{FFatCL} \approx 1$ ($\text{FFatCL} = 0.989$) and when this estimate was fixed at 1, the objective function change was small. Fixing $\text{FFatCL} = 0$ increased the objective function ($\Delta \text{OBJ} = 19.238$). We had concerns that pregnant women may require a further “correction factor” but this turned out to be unnecessary since there was no improvement in the objective function when applied to either clearance or volume of distribution. Both clearance and the peripheral volume of distribution $V_2$ were reduced in the elderly, but when elderly

Table 2 Key model building steps and associated objective function changes

| Basic model                                                                 | OBJ  |
|----------------------------------------------------------------------------|------|
| 1-compartment - no size scaling                                            | 8350.263 |
| 2-compartment - no size scaling                                            | 5804.790 |
| 3-compartment – no size scaling                                            | 5762.275 |
| 3-compartment – no size scaling + individual study centre RUV              | 5210.072 |
| +BOV                                                                       | 5024.826 |
| +BOV + allometric scaling FFM                                              | 4956.866 |
| +BOV + allometric scaling TBW                                              | 4942.960 |
| +BOV + allometric scaling NFM                                               | 4927.983 |
| +BOV + allometric scaling NFM FfatCL = 1                                   | 4924.844 |
| +BOV + allometric scaling NFM FfatCL = 0                                    | 4946.221 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV                          | 4908.588 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL                 | 4900.989 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL         | 4900.663 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4893.125 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4888.551 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4876.427 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4875.077 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4839.712 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4827.174 |
| +BOV + allometric scaling NFM FfatCL = 1 + FAGEV + FAGECL + FSEXCL - FSEXCL | 4827.284 |

An OBJ decrease of 6.635 ($p < 0.01$) for these nested models was deemed significant for covariate inclusion.

[BOV = between occasion variability; RUV = residual unexplained variability; FFM = fat free mass; TBW = total body weight; NFM = normal fat mass; CL = clearance; Abd = abdominal surgery; preg = pregnant; IC = intensive care; HD = high dependency care; ortho = orthopaedic surgery].
patients undergoing abdominal surgery were accounted for; this reduction was no longer apparent. Sex differences in clearance were minor and of no significance. Clearance, relative to the population median, was increased during pregnancy (FPREG = 1.14), and decreased during abdominal surgery (FABD = 0.715). Clearance was not different in postpartum women. Patients undergoing orthopaedic surgery had a smaller V2 (FORTHO = 0.649) while those in intensive care had an increased V2 (FICV = 1.51). Once these covariate effects were established we were unable to determine any further effect attributable to sex. The final covariates of value to describe clearance were allometry using TBW, pregnancy and abdominal surgery.

\[
CL = F_{SIZECL} \times F_{PREGCL} \times F_{ABDCL} \times CLstd
\]

The final covariates of value to describe V2 were allometry using NFM, age, orthopaedic surgery and intensive care.

\[
V2 = F_{SIZEV2} \times F_{AGEV2} \times F_{ORTHOV2} \times F_{ICV2} \times V2std
\]

Table 3 Standardised intravenous paracetamol population pharmacokinetic parameter estimates

| Parameter  | Estimate | BSV   | BOV   | 95% CI  |
|------------|----------|-------|-------|---------|
| CLstd (L·h⁻¹·70 kg⁻¹) | 16.7     | 0.246 | 0.231 | 15.2, 17.8 |
| FPREGCL    | 1.14     | -     | -     | 1.02, 1.27 |
| FABDCL     | 0.715    | -     | -     | 0.548, 0.832 |
| V1std (L·70 kg⁻¹) | 24.6     | 0.555 | -     | 21.7, 27.1 |
| Q2std (L·70 kg⁻¹) | 67.3     | 0.257 | -     | 56.1, 79.7 |
| V2std (L·70 kg⁻¹) | 23.1     | 0.496 | 0.051 | 20.2, 26.1 |
| FICV       | 0.778    | -     | -     | 0.503, 0.933 |
| FORTHOV2   | 0.649    | -     | -     | 0.485, 0.876 |
| FICV       | 1.51     | -     | -     | 1.07, 2.90 |
| FAGEV2     | 0.838    | -     | -     | 0.702, 0.968 |
| Q3         | 2.04     | 0.713 | -     | 1.69, 2.81 |
| V3         | 30.6     | 0.789 | -     | 20.4, 64.3 |

(BSV is the between subject variability, CLstd = standardized clearance; preg = pregnancy; IC = intensive care; abd = abdominal surgery; ortho = orthopaedic surgery; BOV = between occasion variability; CI = confidence interval).

The paracetamol pharmacokinetic parameter estimates were the same as those predicted from paediatric data scaled using allometry with TBW [14]. Mature clearance, achieved within the first few years of life was 16.2 L/h/70 kg (BSV 0.45, BOV 23.5) and Vss was 63.2 L/70 kg. However, the best descriptor of size may not necessarily provide new information about size scaling approaches. After allometric scaling and size standardization, pregnancy, and abdominal surgery, but not gender were significant covariates of clearance, explaining 40% of clearance variability. Age, intensive care and orthopaedic surgery in part (38%) explained the variability in distribution.

Table 4 The correlation of parameter between-subject variability

|        | CL   | V2   | V1   | Q2   | Q3   | V3   |
|--------|------|------|------|------|------|------|
| CL     | 1    | -    | -    | -    | -    | -    |
| V2     | 0.060| 1    | -    | -    | -    | -    |
| V1     | 0.265| 0.734| 1    | -    | -    | -    |
| Q2     | 0.254| 0.793| -0.170| 1   | -    | -    |
| Q3     | 0.956| 0.134| 0.432| 0.136| 1    | -    |
| V3     | 0.379| -0.818| 0.530| -0.750| 0.544| 1    |

(CL = clearance; V = distribution volume; Q = intercompartmental clearance).
be total body weight, but rather may differ with each
drug. Lean body mass (LBM) is appropriate for remifen-
tanil, while propofol clearance in obese adults and non-
obese adults and children is best predicted using TBW
as the size descriptor with theory based allometry
[31-34]. Paracetamol appears best described using nor-
mal fat mass (NFM) with allometric scaling as a size de-
scriptor. This approach is versatile [34] because in
addition to FFM (FFM is similar to LBW but excludes
lipids in cell membranes and for all practical purposes
these two descriptors are indistinguishable) there is an
additional parameter, Fat that characterizes the con-
tribution of fat mass (TBW-FFM) to the apparent allomet-
ric size of the body. This parameter is drug specific (it
depends on the physico-chemical characteristics of the
compound) and also specific to the PK parameter such
as clearance or volume of distribution [35].

A review of paracetamol pharmacokinetics as reported
in literature [17,18,36-44] suggests that clearance de-
creases by 0.4%/year and volume of distribution de-
creases by 0.3%/year (using the young, 25 year old as the
standard). This is equivalent to 20% decrease in CL and
15% decrease in volume of distribution from age 25 to
age 75. The age distribution in this current study did not
facilitate the use of a linear or exponential function to
investigate this change. Although we noted a 12% de-
crease in V2 in the elderly, the contribution that age
made to clearance was overshadowed by the reduced
clearance noted in the elderly cohort who had abdom-
inal surgery. These patients comprised an older cohort
(age 67, range 49–85 years), and the severity of illness or
frailty may have further contributed to reduced clea-
rance. Wynne reports a further large decrease (36%) in
clearance in frail elderly compared to healthy elderly
[44]. A similar explanation may apply to the elderly co-
hort undergoing orthopaedic surgery who had a reduced
volume of distribution. Volume changes probably reflect
increased fat per kilogram body weight in the elderly,
together with incomplete distribution of this non-
lipophilic drug into body fat. Increased paracetamol clear-
ance was observed during late trimester pregnancy, even
after size scaling.

Others have reported an apparent oral clearance 58%
higher in pregnant women compared to non-pregnant
women [45,46]. After allowing for allometry and size
models, we report a smaller increase in clearance than
this estimate. The higher clearance in pregnant women
(F\textsubscript{pregCL} = 1.14) is due to a higher than proportional in-
crease in glucuronidation, a proportional increase in oxi-
dation and a subproportional increase in primary renal
elimination [11]. Potentially hepatotoxic metabolites
were not quantified in the maternal serum [11,46]. This
increased clearance was no longer present 2–3 months
after delivery when clearance was indistinguishable from
the population mean [11].

There are data suggesting that women taking steroid
oral contraceptives have increased glucuronidation of
paracetamol of up to 50% and the impact of both preg-
nancy and oral contraceptives on intravenous paracetamol
disposition [47,48]. Has recently been confirmed and may

| Table 5 Effect of covariate analysis on variance (\(\omega^2\)) of Clearance |
|-----------------------------------------------|
| Sequential nested model | PPVT\(^2\) | BSVR\(^2\) | BOV\(^2\) | PPVP\(^2\) | PPVP\(^2\)/PPVT\(^2\) |
|--------------------------|----------|----------|----------|----------|------------------|
| No covariates            | 0.19     | 0.19     | 0        | 0        | 0                |
| Allometric scaling (TBW) | 0.19*    | 0.0889   | 0.0557   | 0.0487   | 0.256            |
| Allometric scaling (NFM) | 0.19*    | 0.0799   | 0.0557   | 0.0544   | 0.286            |
| \(F_{AGECL}\)            | 0.19*    | 0.0803   | 0.0513   | 0.0584   | 0.3074           |
| \(F_{ICL}\)             | 0.19*    | 0.0605   | 0.0533   | 0.0762   | 0.401            |
| \(F_{ORTHOCL}\)        | 0.19*    | 0.0605   | 0.0533   | 0.0762   | 0.401            |

* = assumed from no covariate model estimate.

| Table 6 Effect of covariate analysis on variance (\(\omega^2\)) of V2 |
|-----------------------------------------------|
| Sequential Nested Model | PPVT\(^2\) | BSVR\(^2\) | BOV\(^2\) | PPVP\(^2\) | PPVP\(^2\)/PPVT\(^2\) |
|--------------------------|----------|----------|----------|----------|------------------|
| No covariates            | 0.437    | 0.437    | 0        | 0        | 0                |
| Allometric scaling (TBW) | 0.437*   | 0.396    | 0.00297  | 0.03803  | 0.087025         |
| Allometric scaling (NFM) | 0.437*   | 0.348    | 0.00325  | 0.08575  | 0.196224         |
| \(F_{AGEV2}\)            | 0.437*   | 0.304    | 0.00272  | 0.13028  | 0.298124         |
| \(F_{ICV2}\)             | 0.437*   | 0.299    | 0.00222  | 0.13578  | 0.310709         |
| \(F_{ORTHOV2}\)         | 0.437*   | 0.246    | 0.00258  | 0.1652   | 0.378032         |

* = assumed from no covariate model estimate.
be driven by oestradiol [49]. In the current pooled analysis, we were unable to show that sex was a covariate.

Figure 2 demonstrates to what extent these patient-related covariates affect the time-concentration profiles when compared to a reference 25 year old healthy volunteer. Predictions for healthy volunteer are not different from plots of typical individual with pathology. The mean concentration of 11.6 mg/L across all groups is consistent with the assumed target concentration of 10 mg/L associated with pain reduction of 2.6/10 [50]. Little is known about pharmacodynamic covariate effects in adults. Despite identification of pharmacokinetic covariate influences, the unexplained parameter variability still remains high (60% for CL) and dose individualization or subpopulation ‘tailored’ dosing would achieve little benefit in the scenarios observed. Target concentration intervention would be of little value. It is of use if a response, such as blood pressure, is substitute for measuring the clinical disease state that is being treated. When the medicine is working well or it is not working at all the clinical disease state may appear to be the same. It is assumed that trying to reach a typical response that is usually associated with benefit is better than giving everyone the same dose. The second reason for using target concentration intervention is when group based dosing (e.g. using weight) is not enough to reduce the between subject variability so that the medicine can be used safely and effectively. Target concentration intervention can only work however if the within subject variability is small enough so that dose individualization is really predictive for future

Figure 2 Visual predictive check for the paracetamol 2-compartment model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all observed concentrations. Right hand plot shows prediction percentiles (10%, 50%, and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas).

Figure 3 Time-concentration profiles for a 25 year old 70 kg healthy adult volunteer given a standard dose of intravenous paracetamol 1 g 6 hourly and typical time-concentration profiles a 25 year 70 kg pregnant woman in her third trimester and a 68 year old 70 kg male undergoing abdominal surgery.
use of the medicine in the same patient. The clearance co- 
variate analysis on variance (ω²) only accounts for 40% of 
the between subject variability for paracetamol.

Aside from the absence of additional benefit, there may 
also be a higher risk of developing hepatotoxicity when 
dose is increased beyond 4 g per day. At least, there are 
conflicting reports on the association of raised amino-
transferase concentrations (>3 times upper limits of nor-
mal) in healthy adults receiving paracetamol [9,51,52].

Conclusions

Size and age are important covariates for paracetamol 
pharmacokinetics, with additional impact of clinical pa-
tient characteristics like pregnancy, abdominal and ortho-
paedic surgery. However, dose individualization based on 
these covariates would achieve little clinical benefit in the 
scenarios explored. Since changes in overall paracetamol 
clearance do not necessary result in proportional changes 
of the different metabolic elimination routes, further stud-
ies on paracetamol metabolism in these specific popula-
tions are warranted to identify populations at risk.

Abbreviations

BOV: Between occasion variability; BSV: Between subject variability; 
Cl: Confidence interval; CV: Coefficients of variation; FFM: Free 
fat mass; HPLC: High pressure liquid chromatography; IV: Intravenous; 
LBM: Lean body mass; NAPQI: N-acetyl-p-benzoquinoneimine; NFM: Normal 
fat mass; NONMEM: Non-linear mixed effects modeling; NSAIDs: Non-steroidal 
anti-inflammatory drugs; OBI: Objective function change; PC: Prediction 
corrected; PK: Pharmacokinetics; Q2 and Q3: Intercompartment clearances; 
TBW: Total body weight; V1: Central volume of distribution; V2 and 
V3: Peripheral volumes of distribution; PC-PVC: Prediction corrected visual 
predictive check; WHS: Weight Height Scaler.

Competing interests

Besides the funding from agencies mentioned below, the authors declare that 
they have no other competing interests.

Authors’ contributions

KA took the initiative to contact the different groups and pool the available 
data and built the pooled data. Data were verified by the other authors 
(KTO, MDvW, MdM, BJA). BJA performed the population PK analysis. All 
authors participated in the subsequent interpretation of this analysis, and 
were involved in drafting the manuscript or revising it critically for important 
intellectual content. All authors have read and approved the final 
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