

PAEDIATRICS

Population pharmacokinetics of single-dose intravenous paracetamol in children

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Editor's key points

- This study aimed at describing the effects of age and body size on the pharmacokinetics (PK) of a single dose of i.v. paracetamol in children under 16 yr of age.
- The two-compartment model with first-order elimination best fitted the data.
- Body weight was expressed allometrically and incorporated into population PK analysis as the only significant covariate.

Background. To determine the pharmacokinetics (PK) of a new i.v. formulation of paracetamol (Perfalgan) in children ≤ 15 yr of age.

Methods. After obtaining written informed consent, children under 16 yr of age were recruited to this study. Blood samples were obtained at 0, 15, 30 min, 1, 2, 4, 6, and 8 h after administration of a weight-dependent dose of i.v. paracetamol. Paracetamol concentration was measured using a validated high-performance liquid chromatographic assay with ultraviolet detection method, with a lower limit of quantification (LLOQ) of 900 pg on column and an intra-day coefficient of variation of 14.3% at the LLOQ. Population PK analysis was performed by non-linear mixed-effect modelling using NONMEM.

Results. One hundred and fifty-nine blood samples from 33 children aged 1.8–15 yr, weight 13.7–56 kg, were analysed. Data were best described by a two-compartment model. Only body weight as a covariate significantly improved the goodness of fit of the model. The final population models for paracetamol clearance (CL), V_1 (central volume of distribution), Q (inter-compartmental clearance), and V_2 (peripheral volume of distribution) were: $16.51 \times (\text{WT}/70)^{0.75}$, $28.4 \times (\text{WT}/70)$, $11.32 \times (\text{WT}/70)^{0.75}$, and $13.26 \times (\text{WT}/70)$, respectively (CL, Q in litres per hour, WT in kilograms, and V_1 and V_2 in litres).

Conclusions. In children aged 1.8–15 yr, the PK parameters for i.v. paracetamol were not influenced directly by age but were by total body weight and, using allometric size scaling, significantly affected the clearances (CL, Q) and volumes of distribution (V_1 , V_2).

Keywords: children; intravenous; paracetamol; pharmacokinetics

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I.V. paracetamol is commonly used in children for the management of postoperative pain. Until recently, i.v. administration of paracetamol has been achieved through the use of the pro-drug propacetamol, which requires *in vivo* hydrolysis by plasma esterases to yield the active form, paracetamol.¹ However, the risks of hypersensitivity and administration site reactions associated with propacetamol pose significant challenges to the optimization of dosage and pain control.^{2–4}

Improved stabilization techniques have permitted the development and use of an i.v. form of paracetamol (Perfalgan), which no longer requires the hydrolysis step for activation.¹ Although i.v. paracetamol is frequently used for pain control in children, there is little pharmacokinetic (PK) data in children of different ages. The PK of this new formulation of paracetamol has been assessed in seven children aged 10.3–16.6 yr;⁵

however, the small number of children and the narrow age range leave the younger age groups in whom this formulation is frequently used, with insufficient PK data. This lack of PK information is one of the reasons that led the Medicines and Healthcare-product Regulatory Agency in the UK (MHRA-UK) to highlight it as a medicine under surveillance.⁶ The aims of the present study were therefore to describe the effects of age and body size on the PK of a single dose of i.v. paracetamol in children under 16 yr of age.

Methods

Patients and drug administration

After approval by the North of Scotland Research Ethics Committees and authorization by the MHRA-UK, the parents of

children admitted for elective surgery were approached for recruitment to the study when there was an anticipated need for i.v. paracetamol for postoperative pain relief. Written informed consent was obtained from the parents, and for children above 7 yr old, additional written assent was sought. Eligibility and willingness of a child to take part in the study was determined through a brief interview with the parent, guardian, and/or where appropriate the child. Children with liver dysfunction, renal impairment, and hypersensitivity to paracetamol were excluded after routine preoperative history and examination.

General anaesthesia was induced either i.v. with propofol 3.5 mg kg⁻¹ or by a facemask with sevoflurane and maintained with isoflurane. After induction of anaesthesia, where medically indicated, each patient was administered paracetamol i.v. over a 15 min period by the study anaesthetist. The following doses were administered: adolescents over 50 kg body weight—1 g; children, 10–50 kg—15 mg kg⁻¹ body weight; children <1 yr—7.5 mg kg⁻¹ body weight.

Blood sampling

Blood was sampled from a peripheral line inserted for routine clinical use. Before the paracetamol administration, 30 µl of blood was spotted on to a Guthrie card, ensuring that the blood soaked through to the other side of the card. This sampling procedure was repeated in triplicate at 15, 30, 60 min, 2, 4, 6, and 8 h from the end of the infusion. Blood spotted on to the Guthrie cards was allowed to dry at room temperature overnight, in darkness, and stored in sealed airtight plastic bags at 4°C in a secured fridge until chromatographic analysis.

Analysis of paracetamol

Paracetamol extraction

Paracetamol was extracted as described previously.⁷ In brief, a 6 mm disc was punched out from the centre of one of the blood spots on the Guthrie card and placed in an Eppendorf micro test tube. To this was added 200 µl of ammonium formate buffer (20 mM, pH 3.5) and 200 ng of 2-acetamidophenol (internal standard) and vortex mixed (Stuart Auto Vortex Mixer SA2, Rhys International Ltd, Greater Manchester, UK) for 2 min. Protein was then precipitated by the addition of 24.6 µl of 30% perchloric acid followed by centrifugation at 13 000g for 5 min. The supernatant was then stored for later use.

Chromatographic analysis

All reagents were purchased from Fisher Scientific, UK. Paracetamol whole-blood concentration was quantified using a high-performance liquid chromatographic assay, with ultraviolet detection based on the method described by Oliveira and colleagues,⁷ and validated according to the International Conference on Harmonisation's guidelines for validating analytical methods.⁸ In brief, after paracetamol extraction, 20 µl of the supernatant prepared above was introduced onto a Hichrom 3.5 µ C18 (100×4.6 mm) column (Hichrom Ltd, Reading, UK) maintained at 25°C using a Gilson 231 sample injector

(Anachem Ltd, Luton, UK). An isocratic mobile phase [methanol/0.1% triethylamine buffer (pH 3.5)—20/80] was used at a flow rate of 0.8 ml min⁻¹ (Gilson pumps, Anachem Ltd). The wavelength of detection was fixed at 244 nm on a Waters 486 Absorbance Detector (Waters Ltd, Elstree, UK) to quantify the analytes. The lower limit of quantification (LLOQ) for the method was 900 pg on column, equivalent to 1 mg litre⁻¹ of whole blood. The intra- and inter-day coefficient of variation (CV%) at the LLOQ (1 mg litre⁻¹) ranged from 14.3% to 20%. The validation range for the assay was 1–100 mg litre⁻¹. The mean relative error (RE%) was always <15% at 3 and 30 mg litre⁻¹ (11% and 7%, respectively). The likelihood-based method (M3) for handling data below the quantification limit (BQL) was utilized in the present study.⁹ This approach maximized the likelihood for the data above the limit of quantification while treating BQL data as censored.

Population PK modelling of paracetamol

From the 33 children, a total of 159 blood paracetamol concentrations were collected and subjected to PK analysis using non-linear mixed-effects modelling using the software package, NONMEM (version VII, ICON Development Solutions, Ellicott City, MD, USA). PK parameter modelling was performed using the first-order conditional estimation with interaction. Potential models considered were the classical linear one- and two-compartment models, and inter-individual variability (IIV) in clearance and volume of distribution were estimated using an exponential scale. The covariance of clearance and volume of distribution IIV was also incorporated into the model. Residual variability was estimated only by the proportional component since the additive component was close to 0 and hence ignored. The equation for the residual variability was as follows:

$$C_{ij} = C_{pred,ij} \times (1 + \varepsilon_{p,ij})$$

To enable comparison of the paediatric PK parameter estimates with adult values, the parameters obtained were standardized to adult weight using allometric-size scaling. Clearance (CL, in litres per hour), inter-compartmental clearance (Q, in the case of a two-compartment model), and apparent volumes of distribution (V₁ and V₂, in litres) were scaled to a weight of 70 kg as follows:

$$CL_i = \theta_{CL} \times \left(\frac{WT_i}{70}\right)^{0.75}$$

$$V_{1i} = \theta_{V_1} \times \left(\frac{WT_i}{70}\right)$$

$$Q_i = \theta_Q \times \left(\frac{WT_i}{70}\right)^{0.75}$$

$$V_{2i} = \theta_{V_2} \times \left(\frac{WT_i}{70}\right),$$

where WT_i is the weight of the i th child and θ the population parameter estimate of an adult with weight 70 kg.

Significant covariates were identified throughout the process of model building and evaluation, by both visual examination of the scatter plots of conditional IIV obtained for each PK parameter vs each covariate and the improvement in the goodness of fit of the model. Forward inclusion of a covariate into the model required a reduction in the objective function value (OFV) of at least 3.84 (which corresponds to $P < 0.05$, d.f. = 1).

The model was evaluated using graphs of residuals and weighted residuals vs predicted paracetamol concentrations. Additionally, measured paracetamol concentrations were plotted separately against the predicted concentrations to visually assess the deviations of the model predicted from observed concentrations. A visual predictive check (VPC) was also generated for the final model and principal component analysis (PCA) performed to investigate any possible

subgroups within the patient population which were not identified during the model development.

Results

Thirty-three children aged 1.8–15 yr of age were recruited to this study (Table 1). All the children had a BMI within the range 14.1–25.4 kg m⁻².¹⁰

A two-compartment model best described the data, with a marked reduction in the OFV (60.7 units, $P = 7 \times 10^{-15}$) when compared with a one-compartment model. The inclusion of weight as an *a priori* covariate resulted in significant improvement in the goodness of fit and a 41.5 unit decrease in the OFV ($P = 1 \times 10^{-10}$). In addition, the IIV (CV%) in CL and V_1 were significantly reduced from 34.9% and 72.1% to 26.6% and 63.0%, respectively, by the inclusion of WT as an *a priori* covariate on clearance and volume parameters in the two-compartment model. The population parameter

Table 1 Characteristic data for patients from whom blood samples were obtained

Subject	Gender	Age (yr)	Weight (kg)	Height (cm)	Dose (mg)	Samples
1	F	7.5	30.3	125	450	3
2	F	5.8	25.1	119	375	6
3	F	7.0	19.7	118	300	8
4	M	12.0	45.6	148	675	3
5	M	4.6	18.5	112	280	7
6	F	10.3	32.9	139	490	7
7	F	11.1	34.9	138	525	7
8	F	11.9	39.2	146	600	6
9	F	4.5	16.7	103	255	4
10	M	4.2	17.6	108	255	5
11	M	4.1	16.8	103	255	4
12	F	7.0	36.3	131	540	4
13	F	15.0	51.0	156	750	7
14	M	4.1	19.6	107	300	3
15	F	4.5	18.6	107	280	6
16	F	13.0	56.0	149	840	5
17	M	3.0	14.6	095	220	5
18	F	3.1	16.0	098	240	5
19	F	6.4	20.9	114	315	4
20	F	7.8	28.7	131	435	7
21	M	4.8	26.0	121	390	3
22	M	4.8	19.7	110	300	6
23	M	11.0	36.0	138	540	6
24	M	1.8	13.7	090	210	4
25	F	9.9	26.7	131	400	6
26	F	7.4	24.7	123	370	5
27	F	9.1	36.2	133	540	7
28	M	4.7	22.9	107	340	7
29	F	12.5	53.7	155	1000	7
30	F	3.9	19.9	102	300	7
31	F	12.9	55.2	162	1000	6
32	M	13.1	43.4	144	650	7
33	M	6.8	30.9	127	460	6

Table 2 Part of the model-building process to reach the final PK model of paracetamol showing the effect on the variance of PK parameters in the model. Final model: $CL \text{ (litre h}^{-1}\text{)} = \theta_{CL} \times (WT/70)^{0.75}$; $Q \text{ (litre h}^{-1}\text{)} = \theta_Q \times (WT/70)^{0.75}$; $V_1 \text{ (litre)} = \theta_{V_1} \times (WT/70)$; $V_2 \text{ (litre)} = \theta_{V_2} \times (WT/70)$. WT, weight (kg); ω_{CL} , inter-individual variability in CL; ω_{V_1} , inter-individual variability in central volume; ω_Q , inter-individual variability in inter-compartmental CL; ω_{V_2} , inter-individual variability in peripheral volume; $Corr_{CL,V_1}$, correlation between CL and V_1 ; σ , residual variability; CV%, percentage coefficient of variation; OFV, objective function value of the model; ΔOFV indicates a change in OFV relative to the previous model; a ΔOFV of -3.84 is significant at $P < 0.05$ (1 d.f.) and a ΔOFV of -10.83 is significant at $P < 0.001$ (1 d.f.)

Model	One-compartment (no covariates)	Two-compartment (no covariates)	Two-compartment (allometric WT)
OFV	583.804	523.133	481.603
ΔOFV	—	-60.67	-41.53
P-value	—	6.7×10^{-15}	1.2×10^{-10}
PK parameter			
CL (litre h ⁻¹), θ_{CL}	8.202	8.101	16.51
V ₁ (litre), θ_{V_1}	15.84	11.48	28.40
Q (litre h ⁻¹), θ_Q	—	4.88	11.32
V ₂ (litre), θ_{V_2}	—	4.24	13.26
ω_{CL} (CV%)	34.1%	34.9%	26.6%
ω_{V_1} (CV%)	49.6%	72.1%	63.0%
$Corr_{CL,V_1}$	80.5%	75.2%	56.4%
σ (CV%)	26.6%	19.8%	17.7%

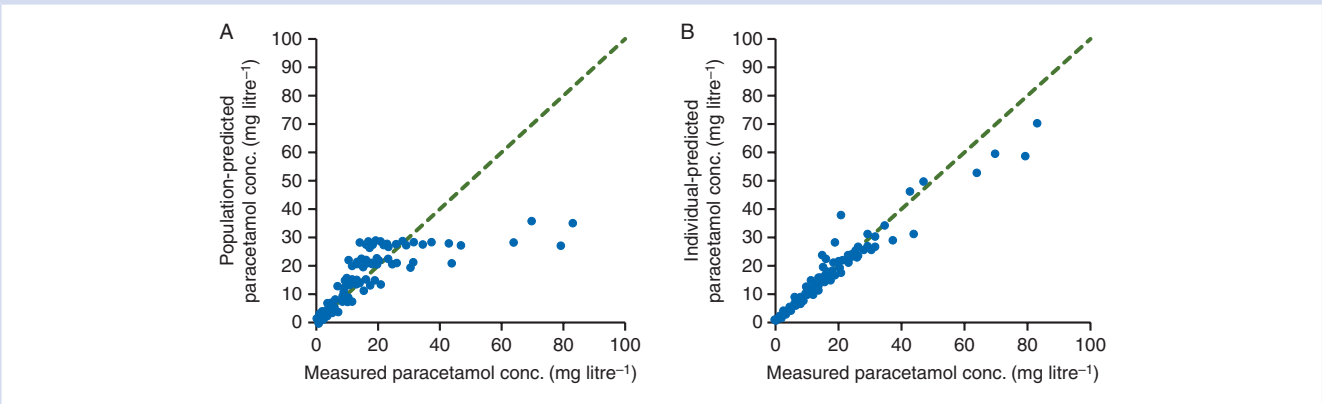


Fig 1 Plots of population-predicted (A) and individual-predicted (B) vs measured paracetamol concentrations. The dashed line indicates the line of perfect agreement.

estimates and their IIV covariance matrix are reported in Table 2. The final model produced an OFV of 481.603.

The other covariates tested [gender, height, age, BMI, and body surface area (BSA)] were not statistically significant and therefore were not included in the final model. The final population models for paracetamol CL, V_1 , Q, and V_2 were: $CL = 16.51 \times (WT/70)^{0.75}$, $V_1 = 28.4 \times (WT/70)$, $Q = 11.32 \times (WT/70)^{0.75}$, and $V_2 = 13.26 \times (WT/70)$, where CL and Q are in litres per hour, WT in kilograms, and V_1 and V_2 in litres.

Because the additive term of the residual error variance approached 0, it was removed resulting in a proportional error model. The residual (unexplained) variability in the final model was reduced to 17.7% (from 26.6% in the base model) corresponding to an SD of 2.51 mg litre⁻¹ at the mean detected paracetamol concentration of 14.7 mg litre⁻¹.

Model evaluation

The plots of observed paracetamol concentrations against both population- and individual-predicted paracetamol concentrations in the final model, Figure 1, demonstrated a reasonable agreement around the line of identity, although with a slight under-prediction, particularly at higher paracetamol concentrations. There are two possible reasons for the two-compartmental model under-prediction particularly at higher paracetamol concentrations. The first is inherent errors in the blood sampling technique where, despite flushing, traces of administered paracetamol remaining in the peripheral infusion line led to higher concentrations in the early collected samples. A second plausible explanation is that 10–20% of paracetamol is bound to red blood cells which could affect the partitioning of the drug into plasma

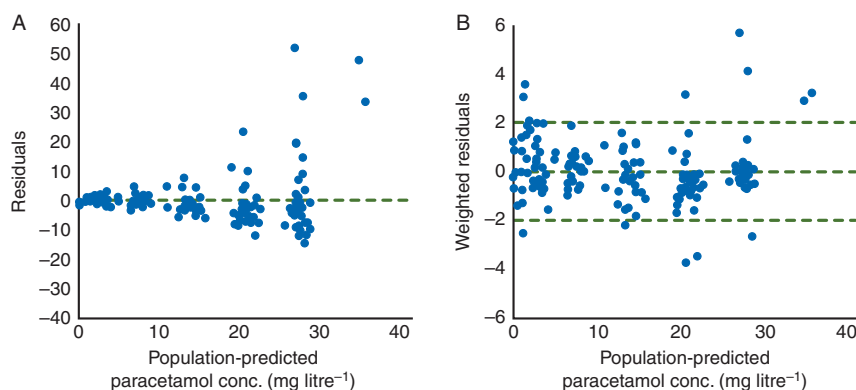


Fig 2 Plots of residuals (A) and weighted residuals (B) vs population-predicted paracetamol concentration from the final model.

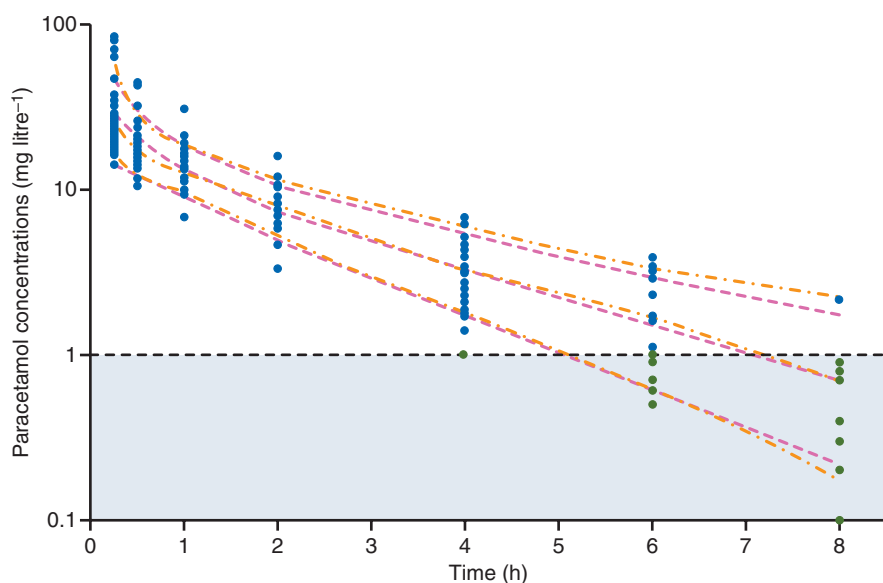


Fig 3 Visual predictive check of the final model fitted to the full data set ($n=159$). A plot of the time course of the observed paracetamol concentrations along with the median and 80% prediction intervals (dashed line) for the simulated values ($n=1000$ per patient time point) and the corresponding median and percentiles (dash-dotted line) for the observed concentrations (blue circle). Shaded area includes concentrations below the assay limit of quantification (green circle).

and hence the blood/plasma ratio of the measured paracetamol concentration particularly at higher concentrations.

The scatter plots of residuals vs model-predicted paracetamol concentrations demonstrated that they were randomly distributed and the weighted residuals lay within ± 2 units of the null ordinate of perfect agreement (Fig. 2). Results for the evaluation of predictive performance of the final model obtained from the full data set, using a VPC, are demonstrated in Figure 3.

In order to test the overall influence of any individual on model parameters, the matrix of the standardized structural parameters and variance components was subjected to PCA and the determinant of this matrix was used to test for

multi-collinearity in the data. A determinant value of 0.05 (considerably greater than the limit of 1×10^{-5}) indicated that multi-collinearity is not a problem for the data, that is, none of the correlation coefficients was particularly large. PCA resulted in extraction of four components that explained over 80% of the variance in parameter estimates of the final model. The results of PCA did not ascertain any underlying trends not identified by earlier analysis, thus giving evidence for validity of the final model.

Discussion

This report describes the population PK of a new formulation of i.v. paracetamol in children aged 1.8–15 yr. The two-

compartment model with first-order elimination best fitted our data. Earlier PK studies that involved i.v. administered paracetamol in both adults and children have also reported a two-compartment model to be most appropriate.^{5 11}

The PK parameters we obtained for paracetamol in this study agree closely with those derived from propacetamol studies performed in children and adults.^{3 12–15} Patient co-variables such as age, height, BSA, and BMI did not significantly affect any of the PK parameters (CL, V_1 , V_2 , and Q). However, total body weight significantly affected the PK of i.v. paracetamol in the children studied.

An effect of age (especially post-menstrual age) has been demonstrated for paracetamol when infants and neonates were studied.^{16 17} The lack of an age effect on paracetamol plasma clearance and inter-compartmental clearance, in the current study, is most likely due to the older age of our study population when compared with neonates and infants. This supports the suggestion that the overall mechanisms involved in paracetamol elimination reach adult capacity by the age of 2 yr.¹⁸ This is further supported by Anderson and colleagues,¹⁵ who reported that the clearance of paracetamol, after i.v. propacetamol, increased to 84% of the value of older children by the end of the first year of life. The value of CL obtained (16.5 litre h⁻¹) in our study is higher than the 13.2 litre h⁻¹ reported by Wurthwein and colleagues,⁵ but similar to that reported by Anderson and colleagues¹⁵ of 16 litre h⁻¹.

The obtained value of CL in the present study was also close to that previously reported for paracetamol in adults (standardized to a 70 kg weight) after i.v. infusion (an average value of 19.7 litre h⁻¹^{11 19–22} compared with 16.5 litre h⁻¹ in the present study). The slightly reduced estimate of CL in children when compared with adults could be due to environmental factors or hepatic enzyme induction in adults due to alcohol or medication such as the oral contraceptives.¹⁵

Besides the Phase II glucuronidation and sulphonation, Phase I oxidation by hepatic Cytochrome P450 2EI enzymes are also involved in the clearance of paracetamol, especially at higher doses,²³ and there have been reports linking the presence of obesity to increased activity of this enzyme.^{24 25} The normal BMI of our patient population rules out a likely contribution from these Phase I enzymes, which are known to reach adult levels from 1 yr of age onwards.²⁶

The lack of a significant effect of age on the central and peripheral volumes of distribution (V_1 and V_2) is also likely to be due to body composition being quite close to adult values in the children that were studied. Dramatic differences in volumes are only seen in neonates. Extracellular water and total body water constitute 60% and 75%, respectively, in neonates and 20% and 50%, respectively, in adults,²⁷ translating into higher V_d for hydrophilic drugs in neonates and young infants when compared with adults.²⁸

Body size descriptors, such as total body weight, BMI, BSA, and height, have been speculated to play a role in drug disposition, and hence dose determination. However, the particular descriptors that affect the PK of i.v. paracetamol in

children have not been reported. In the current study, when total body weight was expressed allometrically and incorporated into population PK analysis, which is the formal method of assessing body size effects on PK parameters,²⁹ it had a significant effect on the PK of i.v. paracetamol. A recent meta-analysis by Green and Duffull³⁰ has reported that total body weight best describes the volume of distribution and that these variables have a direct proportionality relationship. This finding supports our current analysis, in which total body weight, scaled to the power 1, significantly affected V_1 and V_2 [$V_1=28.4 \times (WT/70)$; $V_2=13.26 \times (WT/70)$].

The effect of weight on drug elimination is justifiably expected, given the increase in physiological function with increasing body mass. However, the best weight descriptor for the clinically important elimination parameter, clearance, is still elusive, as none of the known descriptors adequately accounts for the route of elimination (renal or hepatic).³⁰ In the current study, mass expressed as total body weight, scaled to the allometric power 0.75, significantly affected the CL of i.v. paracetamol. Although our present analysis did not include weight expressed in terms of lean body weight (LBW), which has been reported to be the best weight descriptor for CL,³¹ the normal body weight of our study population gives credence to our findings.

Conclusion

We have demonstrated that the PK of i.v. paracetamol is not affected by age in children aged 2–15 yr. However, body size described by total body weight in allometric terms significantly affected both clearance and volume of distribution of i.v. paracetamol in children. Due to the limitations of the data, it is not possible to comment on the PK of i.v. paracetamol in children younger than 2 yr of age, although for children above this age, the current dose recommendations based on body weight would seem to be appropriate.

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Declaration of interest

None declared.

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