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ORIGINAL ARTICLE

Pharmacokinetics of Single Dose Intravenous Paracetamol in Children

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A new intravenous formulation containing paracetamol is now available and widely used in children, but with limited paediatric pharmacokinetic data. This study was aimed at determining the effects of age on the pharmacokinetics (PK) of this formulation of paracetamol in children. Blood samples were obtained from 24 children at 0, 15, 30 minutes, then 1, 2, 4, 6 and 8 hours after the administration of 15 mg kg^{-1} of IV paracetamol. Paracetamol was quantified using an HPLC-UV method, with lower limit quantification of 2200 pg and an intra-assay coefficient of variation of 3%. In the paediatric age groups 2-5 years, 6 -10 years and 11-14 years, total clearance (CL_t) in kg l^{-1}h^{-1}, was 0.41(0.20–0.57), 0.31(0.14–1.10) and 0.37(0.09–0.55) respectively; volume of distribution (V_d) in litres was 0.90(0.7-1.1), 0.95(0.7-1.6) and 0.90(0.4 -1.3) respectively; and elimination half-lives ($t_{1/2}$) in hours was 1.7(1.1-2.6), 2.2(0.6-3.5) and 1.6(1.1-4.7), respectively. The PK parameters (CL_t, V_d and $t_{1/2}$) obtained did not differ significantly among the paediatric age groups (the p- value in all cases was greater than 0.05). In children 2-14 years, there were no significant relationships between the PK parameters and age, weight, height, body weight or body surface area.
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INTRODUCTION

Intravenous paracetamol is commonly used in children for the management of post-operative pain. Until recently, intravenous administration of paracetamol has been achieved through the use of the prodrug propacetamol, which requires *in-vivo* hydrolysis by plasma esterases to yield the active form, paracetamol (Allegaert *et al.,* 2007). However, the high levels of pain associated with intravenous propacetamol, the need for dosage calculation and the low level of plasma esterase activity in children below one year of age pose significant challenges to the optimization and effectiveness of pain control with propacetamol (Morselli *et al.,* 1980; Flouvat *et al.,* 2004; Murat *et al.,* 2005).

Improved stabilization techniques have permitted the development and use of an intravenous form of active paracetamol, which no longer requires the hydrolytic step (Allegaert *et al.,* 2007). Although intravenous paracetamol is frequently used for pain control in children there is just one report (Wurthwein *et al.,* 2005) on the pharmacokinetic properties of this form of paracetamol in children of different ages.

The assessment of this new formulation of paracetamol by Wurthwein *et al.,* (2005) has been done in 7 children aged 10.3 -16.6 years; however there is limited data for younger children in whom this formulation is frequently used. The lack of pharmacokinetic information for this formulation of paracetamol has resulted in it being highlighted as a medicine under surveillance by regulatory bodies such as the Medicines and Healthcare-product Regulatory Agency (MHRA-UK) (SPC, 2009). The present study was therefore conducted to describe the effects of age and body size on the pharmacokinetics of a single dose of intravenous paracetamol in children under 14 years of age.

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MATERIALS AND METHODS

Patients

Following approval by the North of Scotland Research Ethics Committees and authorization by the MHRA-UK, 23 children aged 0 days to 14 years undergoing elective Ear Nose and Throat (ENT) surgery were recruited into the study. Recruitment of parents and children into the study was done when there was anticipation for the need of intravenous paracetamol for post-operative pain relief. Written informed consent was obtained from the parents and for children above 7 years of age, additional written assent was sought. Eligibility and willingness of a child to take part in the study was determined through a brief interview with parent, guardian or the child where appropriate. Children with liver dysfunction, renal impairment and hypersensitivity to paracetamol were excluded following routine pre-operative history and examination.

Height (metres) was measured using the length measuring board for children less than 2 years old, whilst the height measuring board was used for older children. Weight (kg) was measured with a baby scale for children under 2 years old, and the stand-on scale was used for children older than 2 years. The body mass index (BMI) and body surface area (BSA) were calculated using the following formulae:

$$BMI = \frac{Body\ weight\ (kg)}{Height(m)^2}$$

$$BSA = Body\ weight(kg)^{0.425}\ x\ Height(cm)^{0.725} x\ 0.007184$$

(DuBois and DuBois, 1916)

Drug administration

General anaesthesia was induced either intravenously with propofol 3.5 mg kg^{-1} or by facemask with sevoflurane and maintained with isoflurane. After induction of anaesthesia, where medically indicated, each patient was administered paracetamol intravenously over a 15 minute period by the study anaesthetist. The following doses were administered: 1 gram for adolescents with over 50 kg body weight; 15 mg kg^{-1} body weight for children of 10-50 kg and 7.5 mg kg^{-1} body weight for children less than 1 year.

Blood sampling

Blood was sampled with a syringe from a peripheral line inserted for routine clinical use, and this line was different from the site of infusion of the paracetamol. Before the administration of the paracetamol, 30 µl of blood was spotted on Guthrie cards, ensuring an effective soaking of blood through to the other side of the card. This sampling procedure was repeated at 15 min, 30 min, 60 min, 2 hrs, 4 hrs, 6 hrs and 8 hrs after the infusion. All the cards were allowed to dry overnight at room temperature in the dark, stored in plastic bags at 4°C in a secured fridge until chromatographic analysis was done.

Biochemical analysis of Paracetamol

Paracetamol Extraction

Paracetamol was extracted as previously described (Oliveira *et al.,* 2002). 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. A volume of 200 µl of ammonium formate buffer (20 mM, pH 3.5) and 200 ng of 2-acetamidophenol (internal standard) were added to the contents of the Eppendorf micro test tube and vortexed (Stuart Auto Vortex Mixer SA2, Rhys international Ltd, Greater Manchester, UK) for 2 minutes. Protein content of the mixture was precipitated by the addition of 24.6 µl of 30% perchloric acid followed by centrifugation at 13000 g for 5 minutes. The supernatant, which was separated from the proteins, was then stored for later use.

Chromatographic analysis

Paracetamol whole blood concentration was quantified using a high performance liquid chromatographic assay, with ultraviolet detection (HPLC-UV) based on the method described by Oliveira *et al.,* and validated according to the International Conference on Harmonisation's guidelines for validating analytical methods (Oliveira *et al.,* 2002; ICH, 2005). In brief, following paracetamol extraction, 20 µl of the supernatant was introduced onto a Hichrom 3.5 µ C18 (100 x 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/minute (Gilson pumps, Anachem Ltd. Luton, UK). The wavelength of detection was fixed at 244 nm on a Waters 486 Tunable Absorbance Detector (Waters Ltd. Elstree, UK) to quantify the analytes. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for the method were 900 pg and 2200 pg respectively on column; equivalent to 1 μg mL^{-1} and 2.5 μg mL^{-1} of whole blood.

The intra-assay coefficients of variation at the LLOD and LLOQ were 15% and 3% respectively. The validation range for the assay was 0.1 μg mL^{-1}-100 μg mL^{-1}. Accuracy expressed as relative error was always less than 15% at 3 μg mL^{-1} and 30 μg mL^{-1} (11%, 7%). A CV of 10.3% determined at 3μg/ml was taken as the precision.

Pharmacokinetic parameter calculations

The individual PK parameters were calculated based on a linear one compartmental model with instantaneous input and first order output. A semi-logarithmic plot of the function: $LogC = LogC_o - kt/2.3$ was obtained from at least five blood samples. The concentration at t = 0 (C_0) was used to calculate the volume of distribution [$Vd = Dose/C_o$]. The slope of the line [$Slope = (LogC_2 - LogC_1)/(t_2 - t_1)$] was used to calculate the elimination rate constant k_e [$k_e = Slope \times 2.303$], elimination half-life ($t_{1/2}$) [$t_{1/2} = 0.693/k_e$] and total clearance (CL) [$CL = k_e \times V_d$]. Additionally, CL_t and V_d were normalized to 1 kg body weight of child.

Statistical analysis

Data is presented as mean values with SD, or medians with ranges, as appropriate. The Kruskal Wallis test was used to compare the calculated PK parameters among the age groups, 2-5 years, 6-10 years and 11-14 years. A difference was considered significant at $P < 0.05$. The relationship between the PK parameters and age, body weight, height, body mass index (BMI) and total body surface area (BSA) were analysed using Pearson's Correlation test. A Pearson's Correlation coefficient (r) with $P < 0.05$ was considered significant.

RESULTS

A total of twenty three (23) children were recruited into the study. Adopting the ICH age classification (ICH, 2000), the children were categorised into three age groups: 2-5 years (8 children), 6-10 years (7 children) and 11-14 years (8 children). A representative plasma paracetamol concentration versus time curve is as shown in Figure 1. The curve depicts a typical exponential decay of paracetamol plasma concentration over time, from which the non-compartment model was built and used to estimate the PK parameters.

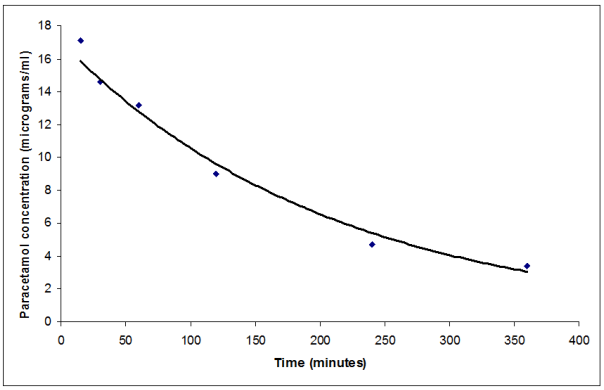

Figure 1: Representative of a blood concentration versus time plot for a child of 13 years of age

The Kruskal Wallis analysis of the pharmacokinetic parameters for the paediatric age groups are presented in Table 1. Median (min - max) CL, Vd and $t_{1/2}$ are provided for paediatric age groups; 2-5 years, 6-10 years and 11-14 years. There were no significant differences in the median CL_t, V_d and $t_{1/2}$ with age. Median CL_t normalized to 70 kg body weight for the three groups were 28.7, 21.7 and 25.9 lh^{-1}, respectively.

A summary of the body size indicators and the Pearson's correlation coefficients, together with their significance values are presented in Table 2. The estimated BMIs were from 14.1-25.4 kg m^{-2}, which was lower than the cut-off of 30 kg m^{-2} (Cole *et al.,* 2000), showing that none of the children was

Table 1: Pharmacokinetic parameters of paracetamol in children administered 15 mg kg^{-1} of i.v paracetamol. Data are given as median (range).

Age	CL(range)	V_d(range)	$t_{1/2}$(range)
2-5	0.4(0.2-0.6)	0.9(0.7-1.1)	1.7(1.1-2.6)
6–10	0.3(0.1-1.1)	0.9(0.7-1.6)	2.2(0.6-3.5)
11–14	0.4(0.1-0.6)	0.9(0.4-1.3)	1.6(1.1-4.7)
P-value	0.79	0.83	0.81

obese. Although there was a weak negative correlation for Vd and CL, and a weak positive correlation for $t_{1/2}$, with age, weight, height, BMI and BSA, these correlations were not significant.

Table 2: Relationship between body size indicators and PK parameters of patients recruited (n = 23)

Variables	Vd	CL	$t_{1/2}$
	r(p value)	*r(p value)*	*r(p value)*
Age (years)	-0.1(0.69)	-0.3(0.17)	0.4(0.11)
Weight (kg)	-0.2(0.48)	-0.3(0.14)	0.3(0.23)
Height (m)	-0.1(0.56)	-0.3(0.13)	0.3(0.14)
BMI (kg m^{-2})	-0.1(0.76)	-0.3(0.19)	0.2(0.47)
BSA (m^2)	-0.2(0.50)	-0.4(0.09)	0.3(0.14)

The relationships were assessed by the Pearson's correlation test; r is the Pearson's correlation coefficient, p is the level of significance in brackets

DISCUSSION

To our knowledge, this is the first report that describes the non-compartmental pharmacokinetics of this new formulation of intravenous paracetamol in children aged 2-14 years. The PK parameters obtained for paracetamol in this study agree closely with those derived from propacetamol studies performed in children and adults (Bannwarth *et al.,* 1992; Autret *et al.,* 1993; Hahn *et al.,* 2003; Flouvat *et al.,* 2004). The PK values, CL_t, V_d and $t_{1/2,}$ obtained were not significantly affected by age, weight, height, BMI or BSA, lending further support to the suggestion that the overall mechanisms involved in paracetamol elimination have reached adult capacity by the age of 2 years (Miller *et al.,* 1976). Although the half-life for paracetamol obtained is similar to that reported by Wurthwein *et al.,* (2005), the median values for the CL_t/70 kg (21.7 - 28.7 lh^{-1}) are far higher compared to the 13.2 lh^{-1} reported by Wurthwein *et al.,*. The reasons for this difference are not clear but could however be attributed to the size of study subjects recruited in the study by Wurthwein *et al.,* which included only 7 subjects.

As 80 to 90% of the parent paracetamol compound is known to be deactivated by hepatic glucuronidation or sulphonation (Prescott, 1980), differences in the plasma clearance, might reflect a difference in the maturation of liver metabolizing enzymes in the patient population. The developmental pathway for glucuronide and sulphate metabolism is reported to be different in children younger than 12 years of age, in whom sulphonation is believed to be the predominant pathway (Alam *et al.,* 1977). Evidence for this is demonstrated by the increasing ratio of glucuronide to sulphate with age: neonates 0.35; children 0.8; and adults 1.8 - 2.3 (Levy *et al.,* 1975; Alam *et al.,* 1977). Uridine glucuronosyl transferases (UGT) activity is also reported to be low at birth and reach adult levels by 3 months (Onishi *et al.,* 1979). This finding is supported by Zaya *et al.* (2006), who reported a positive correlation between UGT levels and postnatal age. Sulfotransferases however have been demonstrated to be mature at birth and compensate for the deficient glucuronidation (Alam *et al.*, 1977). The compensation provided by sulfotransferses activity may explain the lack of an age effect we observed for paracetamol clearance in our study population.

Phase I oxidation by hepatic Cytochrome P450 2EI enzymes has been reported to complement phase II glucoronidation and sulphonation in the clearance of paracetamol especially at higher doses (Manyike *et al.,* 2000), and there have been reports linking the presence of obesity to increased activity of this enzyme (O'Shea *et al.,* 1994; Lucas *et al.,* 1998). Although phase I enzymes are known to reach adult levels by the first year of life (Strolin *et al.,* 2005), the normal BMIs of the children included in the current study reduces the possible contribution from these phase I enzymes.

The V_d was also independent of age and the median value of 66.5 l/70 kg, obtained in this study is within values previously reported (56 - 70 l/70 kg) for children and adults (Prescott, 1996; Hahn *et al.*, 2003). V_d is largely affected by the proportion of water and fat in the body. For instance, the V_ds for hydrophilic drugs in neonates and young infants are reported to be higher than those in adults (Silber *et al.,* 1975), which has been explained by the constitution of extracellular water and total body water of 60 and 75% respectively in neonates, and 20 and 50% respectively in adults (Friis-Hansen, 1998). However the V_d of lipid soluble small molecules, such as paracetamol, is not affected by age, as they distribute in tissues rather than in extracellular body water (Kearns *et al.,* 2003).

The range of median $t_{1/2}$s we obtained (1.6 – 2.2 h) for the paediatric age groups agrees with the range (1.0 – 2.8) previously reported for both children and adults (Bannwarth *et al.,* 1992; Autret *et al.,* 1993; Prescott, 1996; Wurthwein *et al.,* 2005). Being a derived PK parameter, $t_{1/2}$ is related to the two fundamental PK parameters, Cl and V_d, (directly to clearance, and inversely to distribution volume), which explains why it is not also influenced by age in our study.

CONCLUSION

This study has demonstrated that the pharmacokinetics of intravenous paracetamol is not affected by age in children aged 2-14 years. The total clearance, volume of distribution and elimination half-life of intravenously administered paracetamol in children are similar to those obtained in adults.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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