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Cimetidine pharmacokinetics and dosage requirements in children

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Abstract. The pharmacokinetics of cimetidine (10 mg/kg) were investigated in 11 children following an oral dose and in 9 children following an intravenous dose. The children ranged in age from 4–13 years and were undergoing radiology for upper gastrointestinal tract pain. Compared with a group of adults, the children had a higher total body clearance (11.6 ± 3.4 versus 7.0 ± 2.5 ml/min per kg; $P < 0.005$), a larger apparent volume of distribution (1.24 ± 0.40 versus 0.80 ± 0.24 l/kg; $P < 0.005$) and a shorter elimination half-life (83 ± 26 versus 122 ± 16 min; $P < 0.001$) of cimetidine. Renal clearance in children comprised 70% of total body clearance, more than double that of adults (9.0 ± 1.9 versus 4.2 ± 2.1 ml/min per kg; $P < 0.001$). The area under the cimetidine plasma concentration: time curve after the oral dose was on average 42% in children compared with adults. The mechanism for the increased elimination of cimetidine in children is suggested to be an increase in the renal tubular secretory transport of cimetidine in the kidney. A statistically significant negative correlation was observed between age and cimetidine renal clearance. A cimetidine dosage regimen of approximately 30 mg/kg per day in three to four divided doses would be an appropriate dose in children.

Key words: Cimetidine – Children – Pharmacokinetics – Half-life – Clearance

Introduction

Duodenal ulceration and gastric hypersecretion are conditions that afflict not only adults, but also children [1]. It has been suggested that the incidence of duodenal ulceration in children has increased in recent years [8]. The use of cimetidine, an histamine H_2-receptor antagonist, offers a viable form of therapy, alternative to existing surgical methods. Nevertheless, dosage of cimetidine has been somewhat arbitrary, generally in the range 20–30 mg/kg per day [10, 18, 20, 21]. The pharmacokinetics and pharmacodynamics of cimetidine have not been examined in the paediatric population, although Bradbear et al. [4] have reported on cimetidine blood levels in children with cystic fibrosis. This absence of published data, together with the uncertainty of the correct cimetidine dosage in the paediatric population, for whom cimetidine is being prescribed increasingly, prompted the present investigation into the pharmacokinetics of single oral and intravenous doses of cimetidine in children.

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Abbreviations: AUC = area under the cimetidine blood concentration: time curve; V_{ss} = volume of distribution; Cl_T = total systemic clearance; Cl_r = renal clearance; Cl_{nr} = non-renal clearance

Materials and methods

The study population consisted of 18 children, aged between 4 and 13 years (mean 9 years) and weighing between 14 and 41 kg (mean 26 kg). Seven were female and 11 male. They had normal renal, hepatic and cardiovascular functions, but suffered from chronic abdominal pain. They were admitted to hospital for radiology of the upper gastrointestinal tract. In earlier studies it had been demonstrated that pre-medication with cimetidine in children resulted in a marked improvement in the coating properties of a low density barium suspension due to a reduction in gastric juice volume [12].

Single doses of cimetidine, 10 mg/kg, were administered orally in 11 and intravenously in 9 children, with 2 children receiving both formulations at an interval of 14 days. The oral dose was administered after an overnight fast and the intravenous dose was administered over 5 min. Blood was collected for routine laboratory tests and for the determination of cimetidine concentration by a heparin lock catheter placed in a fore-arm vein. Serial blood samples (2 ml) were collected 0, 0.25, 0.5, 1, 2, 3, 4, 5 and 6 h after dosage administration, and in nine of the children all urine was collected over the 6 h sampling period. Blood and urine samples were stored at −20°C prior to analysis. Informed consent was obtained from the parents of the children.

Twelve adult patients, aged 28–64 years and weighing between 54 and 99 kg, served as a control group, details of which have been presented elsewhere [27]. They received a 200 mg IV and oral dose of cimetidine on separate occasions. These patients had no signs of renal, hepatic or cardiovascular dysfunction.

Analytical procedure

Cimetidine was measured in blood and urine by a modification [28] of the HPLC method of Randolph et al. [22]. Both inter-day and intra-day assay coefficients of variation were less than 5%.

Pharmacokinetic analysis

The area under the cimetidine blood concentration : time curve to 6 h was determined by the linear trapezoidal method, with extrapolation to infinity (AUC) by the addition of C^6/β, where C^6 is the blood concentration at 6 h and β the terminal slope, which was determined by linear regression analysis of the terminal data points. The half-life was calculated as $0.693/\beta$. The volume of distribution (V_{ss}) was calculated from intravenous data by the method of Benet and Galeazzi [2] using moment analysis. Total systemic clearance (Cl_T), renal clearance (Cl_r) and non-renal clearance (Cl_{nr}) were calculated as:

Cl_T = Dose/AUC
Cl_r = Amount in urine/AUC (zero to 6 h)
$Cl_{nr} = Cl_T - Cl_r$

Statistical analysis

Comparison of pharmacokinetic data between the two groups was conducted by the non-parametric Mann-Whitney *U*-test. Correlations between variables were calculated by the Spearman rank correlation coefficient [9] with $P < 0.05$ considered statistically significant. All data are tabulated as mean ± SD.

Results

The absorption and disposition data for cimetidine are summarised in Table 1, and Fig. 1 shows a representative plot following intravenous and oral cimetidine administration in two separate children. Following oral intake of cimetidine, the peak blood concentration of 2.4 ± 1.1 (range 0.8–4.6) mg/l was reached after 1.9 ± 0.9 (range 0.5–3.0) h. Statistically significant changes in the pharmacokinetic parameters were observed between children and adults. In children, the AUC after oral dosage was reduced by an average of 58% ($P < 0.001$), the volume of distribution was increased by 55% ($P < 0.005$), and the half-life of cimetidine in children of 83 ± 26 min was considerably shorter ($P < 0.001$) than in adults (122 ± 16 min). The cimetidine total body clearance in children was 66% higher than in adults (11.6 ± 3.4 versus 7.0 ± 2.5 ml/min per kg; $P < 0.005$), being almost solely due to an enhanced renal clearance (9.0 ± 1.9 versus 4.2 ± 2.1 ml/min per kg; $P < 0.001$), which comprised 70% of total body clearance. Although only determined in three children, the non-renal clearance appeared to be higher in children by about 40% (Table 1). In the two children who received both the intraven-

Table 1. Comparison of pharmacokinetic data on cimetidine between children and adults

Parameter	Children	Adults	Significance (*P*)
(a) Intravenous			
Volume of distribution (V_{ss}: l/kg)	1.24 ± 0.4 (11)[a]	0.8 ± 0.24	0.005
Total systemic clearance (Cl_T: ml/min per kg)	11.6 ± 3.4 (11)	6.9 ± 2.5	0.005
Renal clearance (Cl_r: ml/min per kg)	9.3 ± 1.5 (3)	4.2 ± 2.1	—[b]
Non-renal clearance (Cl_{nr}: ml/min per kg)	3.9 ± 0.5 (3)	2.7 ± 0.8	0.025
Percent excreted unchanged in urine	70.3 ± 2.4 (3)	57.2 ± 11.9	NS[c]
Half-life (min)	86.9 ± 28.5 (9)	121.6 ± 16.0	—[b]
(b) Oral			
Half-life (min)	86.6 ± 32.3 (11)	121.6 ± 16.0	—[b]
Renal clearance (ml/min per kg)	8.9 ± 2.3 (6)	4.2 ± 2.1	—[b]
AUC (mg/l × min/mg per kg)	43.4 ± 14.4 (11)	102.7 ± 40.4	0.001
Percent excreted unchanged in urine	35.1 ± 13.8 (6)	41.4 ± 14.0	NS[c]
(c) Combined data			
Half-life (min)	83.5 ± 26.4 (18)	121.6 ± 16.0	0.001
Renal clearance (Cl_r: ml/min per kg)	9.0 ± 1.9 (9)	4.2 ± 2.1	0.001

[a] Number of observations
[b] See combined data
[c] Not significant ($P > 0.05$)

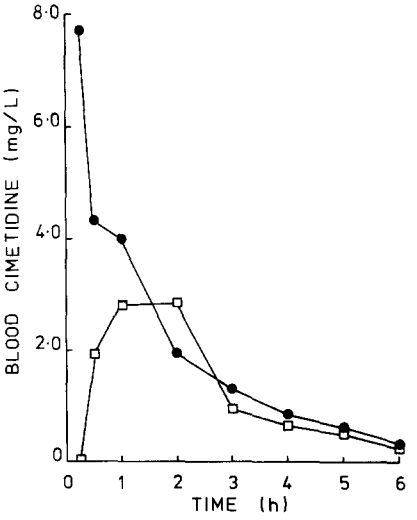

Fig. 1. Blood cimetidine concentration-time profile following a 10 mg/kg intravenous (●) and oral (□) dose in two separate children aged 12 and 9 years respectively

Table 2. Summary of statistical correlations between subject physical characteristics and cimetidine pharmacokinetic variables

Parameter	Number of observations	r_s[a]	Significance (*P*)
Age vs body weight	18	0.05	NS[b]
vs half-life	18	0.54	0.025
vs AUC (oral)	11	0.28	NS
vs Cl_T (ml/min)	9	−0.37	NS
vs Cl_T (ml/min per kg)	9	−0.43	NS
vs Cl_r (ml/min)	9	−0.11	NS
vs Cl_r (ml/min per kg)	9	−0.60	0.05
vs V_{ss} (l)	9	−0.28	NS
vs V_{ss} (l/kg)	9	0.38	NS
Body weight vs half-life	18	0.41	0.05
vs V_{ss} (l)	9	0.67	0.05
vs Cl_T (ml/min)	9	0.50	0.05
vs Cl_r (ml/min)	9	0.67	0.05

[a] Spearman rank correlation coefficient
[b] Not significant ($P > 0.05$)

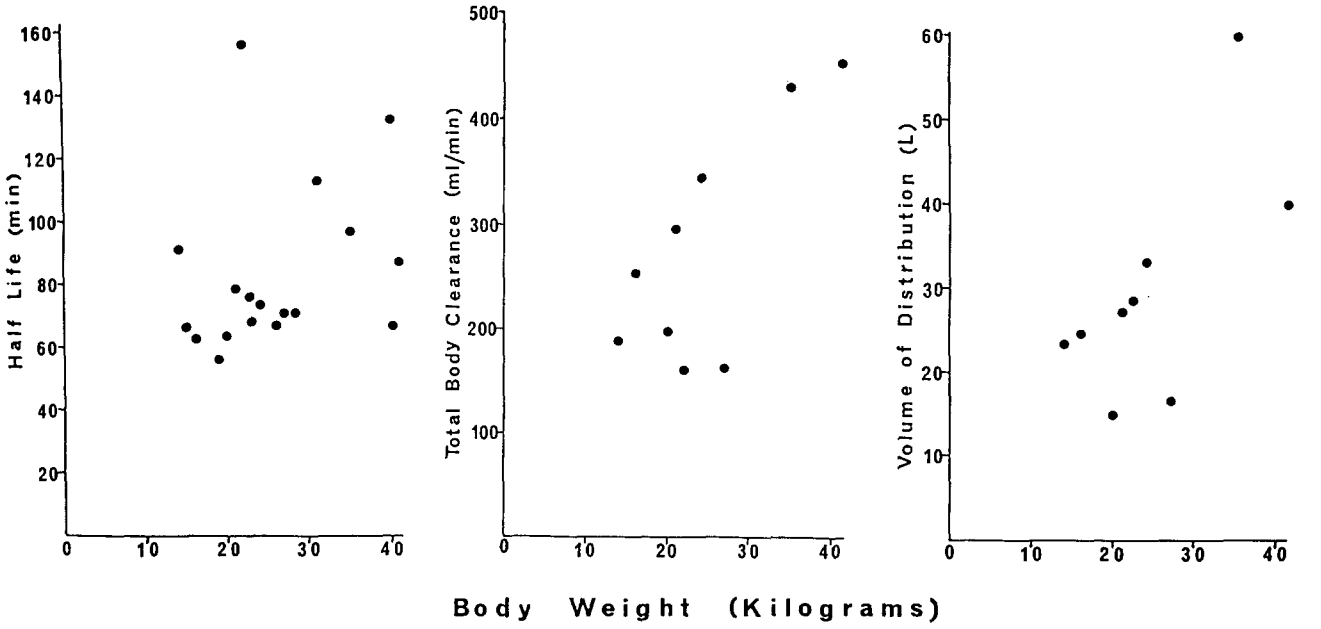

Fig. 2. Correlations between (**a**) half-life and body weight ($r_s = 0.41$) left hand panel, (*b*) total body clearance and body weight ($r_s = 0.50$) middle panel, and (**c**) volume of distribution and body weight ($r_s = 0.67$) right hand panel, of cimetidine in children

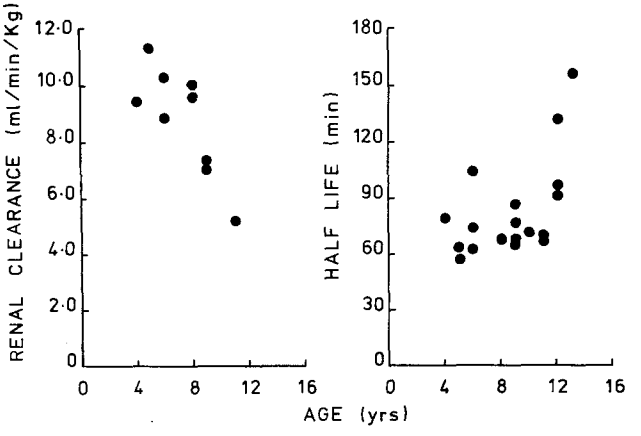

Fig. 3. Correlations between age and (**a**) renal clearance in ml/min per kg ($r_s = 0.60$) left hand panel, and (**b**) half-life ($r_s = 0.54$), right hand panel, of cimetidine in children

ous and oral dosage formulations, their absolute bioavailabilities were calculated to be 51% and 57%.

Table 2 summarises the correlations between patient characteristics and kinetic variables. Half-life, volume and distribution, total body and renal clearances were correlated with statistical significance with body weight (Fig. 2, Table 2); however, only half-life and renal clearance corrected for body weight correlated with statistical significance to age (Fig. 3, Table 2).

No adverse effects were associated with the study.

Discussion

Information on the pharmacokinetics of cimetidine in children is scarce even though its use is increasing in that section of the population [21]. Although Cox et al. [7] and Bradbear et al. [4] reported on blood levels of cimetidine in children with cystic fibrosis, their data were not amenable to pharmacokinetic analysis. However, a recent study in 13 children aged between 1 and 12 years [6], who were admitted to a paediatric intensive care unit and treated with intravenous cimetidine for prophylaxis of stress ulceration, showed a kinetic disparity with adults similar to that in this study. Their reported values of half-life (1.44 ± 0.41 h), total body clearance (14.2 ± 2.8 ml/min per kg) and apparent volume of distribution ($V\beta$: 2.1 ± 0.6 l/kg) are similar to those in this study (1.39 ± 0.44 h, 11.6 ± 3.4 ml/min per kg and 1.4 ± 0.4 l/kg, respectively) even though the two paediatric populations were dissimilar in underlying pathology. They observed statistically significant correlations between age and total body clearance and between age and volume of distribution, but these disappeared when corrected for body weight. No correlation was found between age and half-life. The present study amplifies the data of Chin et al. [6] by investigating, firstly, outpatient children and, secondly, the oral pharmacokinetics of cimetidine. Although only studied in two children, the absolute cimetidine bioavailabilities of 51% and 57% were in the range of those found in adults (30%–100%, mean 60% ± 23% [27]), suggesting a similar extent of cimetidine absorption in children and adults.

The dose received by the children of 10 mg/kg was much larger than that in adults (2.9 mg/kg), although the absolute amounts remained the same. Therefore, the observed changes may have been a reflection of a larger dose rather than a different population. However, Bodemar et al. [3] have reported linearity of both absorption and clearance for cimetidine between doses of 200 and 800 mg in adult patients; thus it is felt that the differences observed are real and not due to differences in dosage between the two population groups.

Total body water and extracellular water amounts decline from infancy to adulthood with a small increase in plasma volume [13]. In adults, cimetidine is distributed into total body water with a small degree of intracellular or tissue bind-

ing [24]. Therefore, the increase in distribution volume of cimetidine in children is probably due to an increase in tissue binding, rather than to differences in body fluid composition.

Increased hepatic metabolic clearances of drugs in children have been reported, e.g. phenobarbitone [14], theophylline [19], which have been attributed to a higher oxidative enzyme activity per unit liver mass [16]. These observations generally have not been extended to drugs that are cleared by the kidney, although anecdotal case reports showing increased dosage requirements for procainamide [15] and disopyramide [17], two drugs predominantly renally cleared in children, suggest extension of this phenomenon to the kidney. Recent studies demonstrating increased clearances of cephalothin [23] and procainamide [25] in children tend to confirm this general observation. The increased total body clearance of cimetidine was almost entirely due to a substantial increase in its renal clearance in children, as about 70% of the intravenous dose was recovered in urine as unchanged drug. The mechanism for this could be either an increase in the relative kidney blood flow and/or an increase in the renal tubular secretory capacity for cations. Although West et al. [29] showed PAH secretion reached adult values at about the 7th month, similar studies have not been conducted with cationic drugs. Cimetidine renal clearance declines with advancing age, so that between 20–40 and 40–60 years the decline is about 30% [26]; therefore, children renally clear cimetidine at a rate almost double that of young 20 to 40-year-old adults. Hence, this study demonstrates increased renal clearance of a cationic drug in children, indicating that the phenomenon reported for hepatically cleared drugs may also extend to renally cleared drugs. The reduced half-life of cimetidine in children is a hybrid reflection of their increased volume of distribution and total body clearance. These changes in cimetidine intravenous pharmacokinetics resulted in a 60% decrease in the area under the plasma concentration: time curve after oral dosage compared with adults, even though the extent of absorption was the same.

Cimetidine dosage in children has been somewhat empirical, but is usually between 20 and 30 mg/kg per day [10, 18, 20]. This dosage has been based upon an adult dose of 1–1.2 g/day, which in a 70 kg adult is equivalent to between only 14 and 17 mg/kg per day. No reason has been given for the apparently increased dosage. Nowadays, the adult dose is usually 400 mg twice daily (11 mg/kg per day) [11], which produces a steady-state blood concentration of about 0.71 mg/l based on published pharmacokinetic data. To produce the same concentration in children requires a daily dose of 24 mg/kg per day, and 36 mg/kg per day would be required to produce the same blood level (1.1 mg/l) as the original adult dose of 1.2 g. Basal and stimulated gastric acid secretion in children of the age range studied are comparable to secretion in adults when the data are corrected for body weight [1]. McNeish and Ayrton [20] demonstrated an 87.5% healing rate for duodenal ulceration in eight children on a cimetidine dose of between 20 and 30 mg/kg per day. Nevertheless, adverse reactions to cimetidine have been reported in children [18], and the potential also exists for cimetidine to inhibit drug metabolism in children [5]; therefore, careful patient monitoring is required when cimetidine is prescribed for children. Based on these considerations and on pharmacokinetic grounds, an oral dosage regime of 24–36 mg/kg per day in three to four divided doses would appear to be optimal in children with peptic ulcer disease.

In conclusion, in the paediatric population, cimetidine is cleared at a faster rate, with an enlarged distribution volume and shorter half-life, with no overt change in bioavailability. Therefore, a dosage regimen of approximately 30 mg/kg per day in three to four divided doses, with careful monitoring of patient response, would appear to be appropriate for children.

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