Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children

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Aims Paracetamol has a central action for both antipyresis and analgesia. Maximum temperature decrease and peak analgesia are reported at 1–2 h after peak plasma paracetamol concentration. We wished to determine the relationship between plasma and cerebrospinal fluid (CSF) pharmacokinetics in children.

Methods Concentration–time profiles in plasma and CSF after nasogastric paracetamol 40 mg kg^{−1} were measured in nine children who had indwelling ventricular drains. Estimation of population pharmacokinetic parameters was made using both a standard two-stage population approach (MKMODEL) and a nonlinear mixed effect model (NONMEM). Results were standardized to a 70 kg person using an allometric power model.

Results Both approaches gave similar estimates. NONMEM parameter estimates were clearance 10.2 l h^{−1} (CV 47%), volume of distribution 67.1 l (CV 58%) and absorption rate constant 0.77 h^{−1} (CV 49%). Cerebrospinal fluid concentrations lagged behind those of plasma. The equilibration half time was 0.72 h (CV 117%). The CSF/plasma partition coefficient was 1.18 (CV 8%).

Conclusions Higher concentrations in the CSF probably reflect the lower free water volume of plasma. The CSF equilibration half time suggests that CSF kinetics approximate more closely to the effect compartment than plasma, but further time is required for paracetamol to exert its effects. Effect site concentrations equilibrate slowly with plasma. Paracetamol should be given 1–2 h before anticipated pain or fever in children.

Keywords: acetaminophen: pharmacokinetics, CSF, effect compartment; paracetamol, pharmacodynamics

Introduction

Paracetamol is a drug commonly used in children and adults for its antipyretic and analgesic effects. Equilibration half-times for paracetamol analgesia and antipyretic effects are not known. Kelley *et al.* [1] and Granry *et al.* [2] describe the maximum temperature decrease occurring 2 h after peak plasma paracetamol concentrations in children. Nielsen *et al.* [3] and Arendt-Nielsen *et al.* [4], using brief cutaneous application of argon laser pulses as a nociceptive stimulus noted a delay of 1 h between maximum plasma paracetamol concentrations and peak analgesia in adult volunteers.

Paracetamol has a central action for antipyresis in the hypothalamus [5, 6] and is believed to exert its analgesic effect by acting on receptors involving *N*-methyl-D-aspartate (NMDA) and substance P in the spinal cord [7, 8]. Attempts to study the kinetics of paracetamol in the CSF have been limited by the ability to take only single samples from patients and then use pooled data to estimate parameters [9]. We present our results of population based approaches to describe the kinetics of paracetamol in the CSF.

Methods

The study protocol was approved by the Regional Health Authority Ethics Committee. It was explained to families of children studied that we were collecting pharmacokinetic data and that children would receive no treatment benefit from the study. Written informed consent was obtained from all parents.

The children were ventilator dependent and required external ventricular drains for the management of raised intracranial pressure. Children with red blood cells (RBC) in the CSF in excess of $4 \times 10^{10} \text{ l}^{-1}$ (a hundred fold dilution of the normal RBC count) were excluded. Once patients were stable, paracetamol elixir 250 mg 5 ml^{−1} (Wellcome, NZ) was instilled down a nasogastric feeding tube and both arterial blood and CSF sampled at hourly intervals for the first 4 h and then 2 hourly for the subsequent 6 h.

Six of the nine children studied had suffered trauma. Patient 1 was studied on two separate occasions separated by 5 days.

Paracetamol assay

Samples from each patient were collected into tubes with no additive (Becton–Dickinson, USA) and plasma was separated by centrifugation. Samples were either assayed

within 1 day or stored frozen at -20°C and assayed within 72 h. Each set of patient samples was analysed within the same batch by high performance liquid chromatography. The analysis of plasma paracetamol was based on that reported by Starkey *et al.* [10] except that *N*-propionyl-4-aminophenol was selected as an internal standard.

Two controls (Baxter Diagnostics, Deerfield, IL 60015, USA) were analysed with each batch. The values assigned to these controls were 0.22 mmol l^{-1} (level 1) and 0.40 mmol l^{-1} (level 2). The intrabatch ($n=20$) and inter-batch ($n=22$) precision (%CV) of the control assays were 1.52 and 4.13 for level 1, and 1.28 and 3.65 for level 2. The assay had a sensitivity of 0.002 mmol l^{-1} .

Pharmacokinetic modelling

(A) A first order input, first order elimination, one compartment effect model (see Figure 1) was used to describe the time course of plasma and CSF drug concentrations. The model is shown schematically in Figure 1. The relevant differential equations were:

$$\begin{aligned} d\text{Agut}/dt &= -ka \times \text{Agut}, \quad dC/dt = (\text{Agut} \times ka - C \times CL)/V, \\ d\text{CCSF}/dt &= \ln(2)/teq \times (C \times PC - \text{CCSF}) \end{aligned} \quad (1)$$

Agut is the amount of drug in the gut at any one time. This amount is assumed equal to the dose at time zero. ka is the absorption rate constant (h^{-1}); V is the central compartment volume (l); C is the plasma concentration (mmol l^{-1}); CL is the clearance from the central compartment (l h^{-1}); CCSF is the cerebrospinal fluid concentration (mmol l^{-1}); PC is the CSF/plasma partition coefficient; teq is the equilibration half time (h) between plasma and CSF.

Paracetamol was administered orally and both clearance and distribution volume are confounded by bioavailability. We have used the symbols CL and V to imply CL/Foral and V/Foral after oral administration.

The residual error was described using a power variance model:

$$\text{var}_j = \text{SF}^2 \times (C_j^{\text{PWR}} + V) \quad (2)$$

Figure 1 Diagram of pharmacokinetic model. ka , absorption rate constant (h^{-1}); V , central compartment volume (l); C , plasma concentration (mmol l^{-1}); CL clearance from central compartment (l h^{-1}); CCSF , cerebrospinal fluid concentration (mmol l^{-1}); PC , CSF/plasma partition coefficient; keq , equilibration rate constant (h^{-1}). The keq can be expressed as $\ln(2)/teq$ where teq is the equilibration half-time (h). Agut is the amount of drug in the gut at any one time.

where var_j is the predicted variance of the j th observation, SF is a scale factor indicative of the confidence of the overall structural parameter estimates, C_j is the predicted concentration, PWR (exponent of C_j) and V (baseline measurement noise) are error model parameters. The same PWR and V parameters were applied to both CSF and plasma models for each individual.

The parameter population estimates were standardized for a body weight of 70 kg using an allometric model [11].

$$P_i = P_{\text{std}} \times (W_i/W_{\text{std}})^b$$

where P_i is the parameter in the i th individual, W_i is the weight in the i th individual and P_{std} is the parameter in an individual with a weight W_{std} . The allometric exponential (b) was assumed to be 0.75 for clearance, 1 for volume of distribution and 0.25 for equilibration half-time (teq) [12, 13].

Population parameter estimations

Population parameter estimates were made using two different regression techniques:

(a) standard two stage population method. Individual patient parameter estimates were made using non linear regression with the MK MODEL [14] software package.

(b) nonlinear mixed effect model. This model accounts for both unexplainable inter and intrasubject effects (random effects) as well as measured concomitant effects (fixed effects). The interindividual variability in model parameters was modelled by an exponential variance model. A parameter covariance matrix was incorporated into the structural model. An additive term characterized the residual error. The population mean parameters, interindividual variance and residual variance were estimated using the first order conditional estimate method using subroutine ADVAN 6 of NONMEM [15].

(B) Pooled data from the study by Bannwarth *et al.* [9] were modelled with the MKMODEL [14] program using the same equations as above in order to compare these adult estimates (determined using pooled data) with paediatric estimates. Patients in this study were adults with rheumatic and nerve root compression pain. They were given an intravenous prodrug of paracetamol (propacetamol) and a single CSF paracetamol concentration was measured. A first order input model was used as propacetamol is rapidly metabolised to paracetamol.

(C) There are no data describing equilibration half-times for either analgesia or antipyresis in humans. Kelley *et al.* [1] have reported the time course of the plasma paracetamol concentration-temperature response seen after administration of 11.6 mg kg^{-1} paracetamol given orally to children aged 11 months – 11.5 years (mean 5.9, s.d. 3.1 years). We modelled their data using a first order absorption, first order elimination pharmacokinetic model with delayed effects accounted for by an effect compartment model [16] using MKMODEL. An additive term characterized the residual error. Patient weights were not reported in the paper by Kelley *et al.* [1]. We assumed a mean weight of 20 kg for a 6 year old child [17] in order to apply an allometric size model to pharmacokinetic parameter estimates.

A sigmoid Emax pharmacodynamic model was used for

Figure 2 Time-concentration profiles (s.e. mean) for plasma and CSF after nasogastric paracetamol 40 mg kg⁻¹ (patient 1b). Profiles fitted using nonlinear regression with MKMODEL. Plasma is represented as +; CSF as x.

temperature reduction:

$$E = E_0 + (E_{\max} \times C_e^N) / (EC_{50}^N + C_e^N) \quad (3)$$

where E_0 is the baseline response (fixed at 0), $E_{\max}$ is the max temperature reduction (°F), C_e (mmol l⁻¹) is the concentration in the effect compartment, EC_{50} (mmol l⁻¹) is the concentration producing 50% $E_{\max}$, and N is the Hill coefficient.

The data points for the mean plasma paracetamol concentration and mean temperature difference were read from Figures 2 and 6 of Kelley *et al.*'s [1] paper.

Results

Patient demographic data are shown in Table 1. A typical time-concentration profile for plasma and CSF is shown in Figure 2. The time-concentration profiles for subject 9 are shown in Figure 3. This subject had the highest equilibration half-time of those studied.

Pharmacokinetic parameter estimates for plasma and CSF paracetamol derived using the MKMODEL and NONMEM programs are shown in Tables 2 and 3. Geometric mean population estimates and their coefficients of variation are included in each table.

Pharmacokinetic parameter estimates based on naïve pooled data from Bannwarth *et al.* [9] were k_a 33.6 h⁻¹, CL 24.4 l.h⁻¹, V 76.9 l, t_{eq} 2.1 h, PC 1.1, SF C 0.0034 mmol l⁻¹, SF $CCSF$ 0.0029 mmol l⁻¹.

Pharmacokinetic and pharmacodynamic parameter estimates (%CV) based on naïve pooled data from Kelley *et al.*

Figure 3 Time-concentration profiles (S.E. mean) for plasma and CSF after nasogastric paracetamol 40 mg kg⁻¹ (patient 2). The fits for NONMEM and MKMODEL are demonstrated. ▲ plasma observations, ■ CSF observations, -- MKMODEL plasma, --- MK model CSF, — NONMEM plasma, ---- NONMEM CSF.

[1] were k_a 9.76 (29) h⁻¹, CL 9.85 (4.4) l.h⁻¹, V 57.8 (2.4) l, t_{eq} 0.99 (0) h, $E_{\max}$ 5.37 (129), EC_{50} 0.064 (94) mmol l⁻¹, N 2.41 (44), SF C 2.18×10^{-3} mmol l⁻¹, SF effect 0.144 mmol l⁻¹. The correlation matrix for these estimates is shown in Table 4. The effect compartment-response curve for these data is shown in Figure 4.

Discussion

Paracetamol exhibits negligible protein binding [18] and has a high lipid solubility. A linear process for its transport into the brain based on passive diffusion is postulated [18, 19]. We report a CSF to plasma partition coefficient (PC) of 1.18 (CV 8%). Modelling of Bannwarth *et al.*'s pooled data [9] gave a similar estimate. The partition coefficient estimate is similar to the alcohol partition coefficient between CSF and serum measured in rats [20] and would be predicted for drugs that distribute in plasma water but which do not bind to plasma proteins [21] because plasma water occupies 90% of plasma by volume.

The increase in the CSF red cell counts in patients 4 and 5 were due to intraventricular bleeding at the time of injury. Bleeding was not continuous and there was subsequent clearing of red blood cells from the CSF. The estimated equilibrium half times for these two patients were similar to those of the other subjects with minimal CSF RBC counts.

Table 1 Demographic data.

Patient	Age	Weight (kg)	Gender	Diagnoses	CSF drainage (ml h ⁻¹)	RBC/WBC (10 ⁶ l ⁻¹)
1	5 years	16	female	Brainstem encephalitis	9	410/3
2	7 months	8	male	Dandy Walker cyst	9	220/12
3	12 years	50	male	Closed head injury	6	775/2
4	11 years	30	male	Closed head injury	3	29855/52
5	5 months	8	male	Subdural haematoma	10	10275/44
6	12 years	40	female	Compressed skull fracture	5	34/1
7	8 years	45	male	Acute extradural haematoma	4	244/1
8	2 years	14	female	Post fossa tumour	4	1300/1
9	5 years	20	male	Closed head injury	5	2440/1

ID Number	k_a (h^{-1})	CL ($l\ h^{-1}$)	V (l)	t_{eq} (h)	PC	SF C ($mmol\ l^{-1}$)	SF CCSF ($mmol\ l^{-1}$)
1a	0.96	10.4	48.6	1.11	1.56	0.26	0.83
1b	2.75	30.0	80.6	1.19	1.43	0.14	0.62
2	0.54	12.4	52.4	5.03	0.95	1.19	1.20
3	0.95	8.6	86.1	0.23	1.08	0.72	0.56
4	1.18	6.3	49.5	0.50	1.05	3.79	1.81
5	2.09	4.5	49.4	0.60	1.11	2.40	2.30
6	0.19	14.8	54.4	0.17	1.13	1.05	0.63
7	0.20	14.5	53.0	0.37	1.19	0.52	0.68
8	0.39	9.7	37.2	4.20	1.48	5.10	2.93
9	0.07	10.0	13.3	0.71	1.26	1.17	0.54
Geometric mean	0.56	10.6	47.8	0.78	1.21	0.99	0.99
%CV	115	51	51	112	16	112	63

Table 2 Parameter estimates obtained using MKMODEL.

ID Number	k_a (h^{-1})	CL ($l\ h^{-1}$)	V (l)	t_{eq} (h)	PC
1a	1.05	32.6	47.2	0.89	1.17
1b	0.41	25.2	21.1	0.89	1.29
2	0.69	11.5	53.1	8.88	1.34
3	0.87	8.8	84.4	0.22	1.10
4	1.27	6.8	51.3	0.57	1.11
5	2.00	4.4	48.7	0.59	1.09
6	0.50	13.5	126.4	0.29	1.15
7	0.49	12.7	111.7	0.42	1.18
8	0.85	9.6	52.8	3.41	1.28
9	0.46	14.4	131.6	0.41	1.18
Geometric mean	0.77	10.2	67.1	0.72	1.18
%CV	49	47	58	117	8
SF	C 2.9 $mmol\ l^{-1}$		CCSF	2.1 $mmol\ l^{-1}$	

Table 3 Parameter estimates obtained using NONMEM.**Table 4** Correlation matrix for PK-PD estimates for Kelly *et al.*'s [1] data.

	V	CL	k_a	E_{max}	EC_{50}	N	t_{eq}
V	1						
CL	-0.42	1					
k_a	0.51	-0.45	1				
E_{max}	-0.01	0.008	-0.03	1			
EC_{50}	-0.028	0.009	-0.03	0.99	1		
N	0.009	-0.11	0.11	-0.96	-0.97	1	
t_{eq}	2.7×10^{-13}	-4.5×10^{-13}	-1.4×10^{-13}	-4.2×10^{-14}	-9.1×10^{-16}	-7.5×10^{-15}	1

CSF RBC counts do not seem to indicate any marked alteration in paracetamol equilibration. The CSF loss from the external ventricular drains, required to maintain an intracranial pressure below 20 mmHg, did not exceed $10\ ml\ h^{-1}$ in any child. Paracetamol clearance by this route is minor when compared with clearance from the plasma of $10\ l\ h^{-1}$.

Plasma paracetamol concentrations between 0.06 and $0.13\ mmol\ l^{-1}$ have been associated with an antipyretic effect [22]. These concentrations were reported without consideration of delayed effects and our predicted effect compartment concentrations suggest lower steady state concentrations would be effective. A pharmacodynamic model for fever reduction by paracetamol has not been reported. E_{max} and EC_{50} are estimated from the observed concentration and temperature change data. Imprecision in

EC_{50} and E_{max} parameter estimates is expected because an effect intensity greater than 50% of predicted E_{max} was not observed [1, 23]. The parameter correlation is almost 1 between E_{max} , EC_{50} and Hill coefficient.

Despite this limitation, the sigmoid E_{max} model describes the data and is superior to other models because the observed data profile is concave upwards. A linear model describes a straight line. A log-linear model describes a curve which is concave-downwards and is incapable of predicting the baseline temperature when no drug is present [16]. A quadratic model describes a similar shape and fits the data as well as the sigmoid E_{max} model, but is incapable of predicting a maximum effect which we would expect for a biological system.

Although the estimate of the maximum temperature reduction has a high CV, an E_{max} of $5.4^\circ\ F$ ($3^\circ\ C$) would

Figure 4 Effect compartment concentration-temperature reduction curve for paracetamol antipyresis. Data from Kelley *et al.* [1] modelled using a first order absorption, first order elimination pharmacokinetic model with delayed effects accounted for by an effect compartment model. The hysteresis loop described by Kelley *et al.* [1] has been 'collapsed'.

be clinically reasonable. Several studies have shown fever reductions of up to 3° F after either paracetamol (10–12.5 mg kg⁻¹) or ibuprofen (5–10 mg.kg⁻¹) [24–26]. Temperature reduction associated with doses above 12.5 mg kg⁻¹ paracetamol has not been investigated. We would not expect a reduction in temperature to below the normal 98.6° F (37° C) when paracetamol is used to reduce a fever of 104° F (40° C). Because Emax may reflect the difference between fever temperature and normal temperature, it may be conditional upon degree of fever. Furthermore, higher fever temperatures may not be able to be reduced completely to normal.

The model functions well for the estimation of the equilibration half-time (*teq*) from Kelly *et al.*'s [1] data, but not for estimating EC₅₀ and Emax. The correlation between *teq* and other estimated parameters was low. We assumed that temperature would be constant over the period of 6–8 h if no antipyretic agent was given and Kelly *et al.* [1] report a return to baseline temperature at the end of 8 h. The use of an effect compartment model to explain this temperature response is empirical. The pharmacological and physiological mechanisms by which paracetamol causes a reduction of fever are complex. It is possible, however, that distribution to the effect compartment is the rate limiting step.

The absorption rate constant reported in other series [24, 27] ranges from 1 to 10 h⁻¹. Our estimate of 0.78 h⁻¹ is low because gastric emptying and intestinal motility may have been delayed due to the cerebral insult [28, 29] or morphine analgesia [30].

The population distribution volume of 67.1 l (NONMEM) is similar to that reported in other series (56–70 l) [31]. The lower MKMODEL estimate reflects the methods by which population parameters are estimated. The outcome of standard two stage method is skewed by outlying values more than NONMEM [32]. Distribution volumes estimated using pooled data from both Bannwarth [9] (76.9 l) and from Kelley [1] (57.8 l) were similar to those reported previously [31]. These estimates are lower than those derived in a study of the kinetics of paracetamol after rectal administration following major surgery [33]. In this previous study we estimated a distribution volume (*V/F*) of 133 l (CV 56%). The relative bioavailability (*F*) of

paracetamol from this rectal formulation has not been determined. Seideman *et al.* report [34] a relative bioavailability of paracetamol from suppositories of 80% that from oral formulations. In addition, rectal absorption is erratic and variability in bioavailability can range from 24 to 98% (mean 52%) of oral tablets [35].

The population clearance estimates of 10.6 l h⁻¹ (MKMODEL) and 10.2 l h⁻¹ (NONMEM) are at the lower range of those reported for adults (12–21 l h⁻¹) [31]. Analysis of Kelley's [1] data gave an estimate of 9.9 l h⁻¹. Autret *et al.* [36], using an intravenous prodrug of paracetamol, report a clearance of 4.5 l h⁻¹ in neonates, rising to 14 l h⁻¹ beyond the neonatal period (if a mean weight of 7 kg is assumed for infants). We have previously reported a clearance (CL/*F*) of 18 l h⁻¹ (CV 42%) [33] after rectal administration in children with a mean age of 8 years. The actual clearance is probably lower as the relative bioavailability is less than 1.

Paracetamol elimination in children is usually expressed in terms of half-life [37–40] and clearance data are few. The manner in which the liver metabolises paracetamol changes with age. There is a reversal of the usual adult ratio of 2:1 with respect to glucuronidation *vs* sulphation of paracetamol in young children. This pattern reverses to adult pattern at the age of 12 years [37]. Analysis of Bannwarth *et al.*'s [9] pooled data gave a clearance of 24 l h⁻¹ after an intravenous preparation which is at the upper range reported for adults [31]. We have analysed our data using size as the first covariate in an attempt to explain differences between individuals. Clearance is a nonlinear function of size [41]. Our lower clearance in children may reflect maturational changes with age or illness severity and the concomitant perfusion limited supply of cofactors such as oxygen or sulphate may have contributed. Alternatively, the higher clearance in adults may be due to enzyme induction from environmental factors, such as exposure to alcohol [42].

There is considerable interindividual variation in paracetamol clearance. A three fold range in the elimination rate constants for the formation of sulphate and glucuronide conjugates has been described in comparisons between normal adult mono- and di-zygotic twins [43]; covariance between clearance and volume of distribution was not addressed. Parameter estimates for clearance and volume of distribution for patient 1 on the two separate occasions are quite different. Environmental factors such as altered temperature homeostasis may have contributed. However, the fit for time-concentration data on the first occasion was not as good as the second. There was a two fold increase in the SF parameter.

The *posthoc* NONMEM pharmacokinetic parameter estimates differ from MKMODEL estimates in patient 9. Both sets of parameters adequately describe time-concentration profiles. However, sampling was truncated at 6 h for this child, soon after the peak concentration. NONMEM predictions have greater merit with respect to such truncated data as predictions are influenced by the population estimates. The MKMODEL estimate is less robust and this is reflected by the parameter correlation between *ka*, *V* and CL which was almost one for this individual.

Subject 2 demonstrated an unusually delayed appearance of paracetamol in the CSF. The *teq* estimate for this child

was substantially higher than any other child. Further, there was a difference between the *teq* estimate from NONMEM (5 min) and from MKMODEL (9 min). Both estimates provide poor descriptions of the observed CSF concentrations (Figure 3) before the peak at 3 h. This child had a cystic posterior fossa tumour which caused noncommunicating hydrocephalus possibly contributing to the delayed transfer of paracetamol to the CSF.

We estimate a plasma to CSF standardized equilibration half-time of 0.72 h (CV 117%) (NONMEM) and 0.78 h (CV 112%) (MKMODEL). This equilibration half-time is less than that estimated for an effect compartment used to explain paracetamol antipyresis (*teq* 0.99 h). The longer equilibration half-times derived from PK-PD modelling suggest that concentrations in the CSF do not directly reflect those at the effect site. Further time is required for paracetamol to act on receptors in both the spinal cord and hypothalamus and exert an effect. This phenomenon has been described with opioid analgesia. When opioids are administered parenterally to rodents, peak analgesia lags behind maximum brain concentrations [44–47].

Analysis of Bannwarth *et al.*'s [9] pooled data estimated a longer *teq* of 2.1 h in adults than the *teq* obtained in this cohort of children. This may reflect the inaccuracies introduced when using the pooled data from Bannwarth *et al.*'s study [9] or may be indicative of some disruption of the blood brain barrier in the children from this current study.

This work was supported in part by grants from Auckland University and SmithKline Beecham Pharmaceuticals.

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(Received 4 November 1997,
accepted 20 April 1998)