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Pharmacokinetics of Paracetamol (Acetaminophen) after Intravenous and Oral Administration

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Summary. Plasma paracetamol concentrations were measured in 6 volunteers after single intravenous (1000 mg) and oral (500 mg, 1000 mg and 2000 mg) doses of the drug. Paracetamol levels declined multiphasically with a mean clearance after intravenous administration of 352 ± 40 ml/min. A two-compartment open model appeared to describe the decline adequately. Comparison of the areas under the plasma concentration-time curves (AUC) indicated that oral bioavailability increased from 0.63 ± 0.02 after 500 mg, to 0.89 ± 0.04 and 0.87 ± 0.08 after 1000 mg and 2000 mg, respectively. As a consequence of the incomplete bioavailability of paracetamol, as well as its multicompartmental distribution, accurate estimates of its distribution volume and clearance cannot be obtained if the drug is given orally. However, an estimate of its total plasma clearance may be derived from the AUC after a 500 mg oral dose.

Key words: Paracetamol, Acetaminophen, pharmacokinetics, first-pass elimination, intravenous administration

Paracetamol (N-acetyl-paraminophenol; acetaminophen) is a widely used non-narcotic analgesic. It is eliminated in the urine predominantly as sulphate and glucuronide conjugates (Cummings et al., 1967), and has therefore been used as a "model" substrate for examining conjugation mechanisms in man (Triggs et al., 1975; Shively & Vesell, 1975). However, although its absorption characteristics have been studied extensively in man (Heading et al., 1973), its distribution and elimination kinetics have been inadequately investigated. We have therefore examined and compared these aspects of paracetamol kinetics following both intravenous and oral administration to healthy volunteers.

Methods and Materials

Six healthy male subjects consented to participate in the study which had received prior approval from the local ethical committee. All the subjects denied having consumed any drug in the four weeks before the start of the project. On separate occasions (at least one week apart) each volunteer received 1000 mg paracetamol intravenously (as a 20 mg/ml solution over 5 minutes), and 500 mg, 1000 mg, and 2000 mg orally as tablets (Panadol®). Venous blood was withdrawn from an indwelling cannula at 0, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes after the intravenous injection (timed from the mid-point of the 5-minute infusion) and at 0, 30, 60, 90, 120, 180, 240, 300 and 360 minutes after oral dosing. Heparinised plasma was stored at −20° C before analysis in duplicate by gas chromatography (Prescott, 1971).

The decline in plasma paracetamol concentration (C_t) after intravenous administration appeared to be bi-exponential: −

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

and the data was interpreted in the form of a two-compartment open model (Riggs, 1963). The volumes V_1 (central, sampling compartment) and V_2 (peripheral compartment), the intercompartmental rate constants k_{12} and k_{21}, and the true elimination rate constant k_{13} were derived from the hybrid terms A, B, α and β of equation 1 (Riggs, 1963). These hybrid terms were calculated by least-squares regression analysis and the method of residuals. The area under the plasma concentration time curve (AUC) was determined by the trapezoidal rule, and extrapolated to infinity: the latter never exceeded 15% of the total AUC. The terminal (3−6 h) mono-exponential decline in plasma paracetamol concentration after oral dosing was used to calculate the oral half-life of the drug ($T^1/_2$). Bioavailability (F) was determined: −

$$F = \frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{Dose i.v.}}{\text{Dose oral}} \quad (2)$$

and plasma clearance ($\dot{V}p$) as (Riggs, 1963): –

$$\dot{V}p = \frac{\text{Dose i.v.}}{\text{AUC i.v.}} \quad (3)$$

Results

Intravenous Administration

The decline of plasma paracetamol concentrations in our subjects is shown in Figure 1. An initial rapid fall over the first 1.5 h was followed by a mono-exponential decline over the remaining 4.5 h of observation and could be described by the equation (see Table 1): –

$$C_t = 13.8 \cdot e^{-2.55t} + 13.0 \cdot e^{-0.28t} \quad (4)$$

The half-life ($T^1/_{2\alpha}$) of the first exponential ranged from 0.15 to 0.53 hrs (mean = 0.32 h) and that of the second exponential $T^1/_{2\beta}$) ranged from 2.24 to 3.30 h (mean = 2.50 h).

The compartmental volumes and intercompartmental rate constants are shown in Table 1. There was little interindividual variability in apparent distribution volume and, as expected from the multiphasic decline in concentration, β was observed to be a poor estimate of k_{13}. Plasma clearance (equation 3) ranged from 264 to 505 ml/min (352 ± 40 ml/min, mean ± S.E.).

Oral Administration

The mean plasma concentrations of paracetamol after 500 mg, 1000 mg and 2000 mg doses are shown in Figure 2. Plasma concentrations reached a maximum at 0.5 to 1.0 hrs after dosing with 500 mg and 1000 mg, but continued to rise for 2 h after 2000 mg. The decline in plasma concentration appeared to be biphasic with a terminal mono-exponential decay after 3 hours. The $T^1/_2$ oral was therefore calculated from the concentrations observed at 3, 4, 5, and 6 hours after dosing (see Table 2). No difference in $T^1/_2$ oral was observed between doses, and no difference was found between $T^1/_{2\beta}$ after intravenous and oral dosing.

Oral bioavailability (equation 2) was incomplete at all dose levels (see Table 2) and was significantly ($P < 0.05$) less after 500 mg than after 1000 mg or 2000 mg.

Discussion

Our study indicates that paracetamol kinetics are more complicated than previously supposed. The decline in plasma concentration after intravenous injection is multiphasic and incompatible with a one-compartment open model. Although we have interpreted our data according to a two-compartment open model this cannot be regarded as a unique solution: not only might more frequent early sampling have revealed a third exponential component to the decline in drug concentration, but "central" compartment sampling is also limited in its ability to recognise small "deep" compartments (Rawlins et al., 1976). The multiphasic decline of plasma paracetamol levels was also observed after oral dosing with 500 mg and 1000 mg, but not after 2000 mg – presumably because of the slower absorption rate at this dose level (see Figure 2).

The slope of the terminal (β) exponential decline in concentration ($0.28 \pm 0.02\ h^{-1}$) was observed to be a gross underestimate of the elimination rate (k_{13}) constant ($0.51 \pm 0.06\ \text{hours}^{-1}$). There was no significant correlation between $\dot{V}p$ and either β or k_{13} ($r = 0.803$, $0.1 > P > 0.05$; $r = 0.153$, $P < 0.1$, respectively). Estimates of the rate of paracetamol elimination can only therefore be obtained by measurement of $\dot{V}p$. Incomplete bioavailability was observed at all dose levels (see Table 2). Since the absorption of paracetamol from the gastrointestinal tract is virtually complete, "first-pass" elimination by the liver or gut wall is likely to account for this. Such an explanation would be compatible with the observation that bioavailiability was significantly less after 500 mg, than after 1000 mg or 2000 mg orally. The absence of significant differences in $T^1/_{2\beta}$ between the three oral doses would not support a hypothesis of dose-dependent elimination.

These observations have important implications for the use of paracetamol as a "model" substrate. First, $T^1/_{2\beta}$ (oral or intravenous) is a poor estimate of the elimination rate of the drug in man. Second, dose-dependent "first-pass" elimination of paracetamol means that estimates of distribution volume and clearance after oral dosing are unacceptable. However, a significant correlation was found between the AUC after an oral dose of 500 mg, and $\dot{V}p$ calculated from the intravenous studies ($r = -0.876$; $P < 0.05$): –

$$\dot{V}p = 728 - 23\ (\text{AUC}) \quad (5)$$

No significant ($P > 0.05$) correlation was observed between $\dot{V}p$, and the AUC after oral dosing with 1000 mg ($r = -0.527$) and 2000 mg ($r = -0.734$) – probably because of the greater variance in bioavailability at these doses (see Table 2). If paracetamol elimination is therefore to be studied quantitatively,

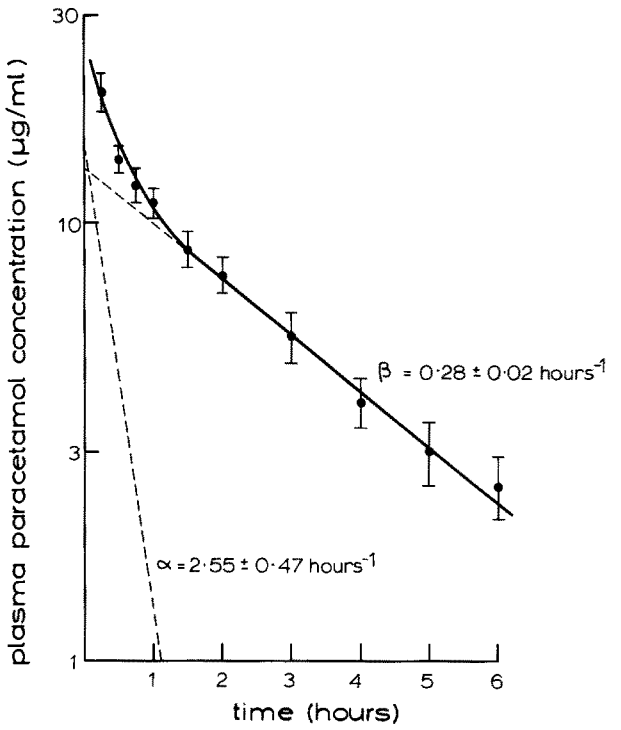

Fig. 1. Plasma concentrations of paracetamol (logarithmic scale) ± S.E.M. after the intravenous administration of 1000 mg to six volunteers. The solid line represents the least-squares regression equation: –
$C_t = 13.8 \cdot e^{-2.55t} + 13.0 \cdot e^{-0.28t}$
The dashed lines represent the fast and slow exponential slopes

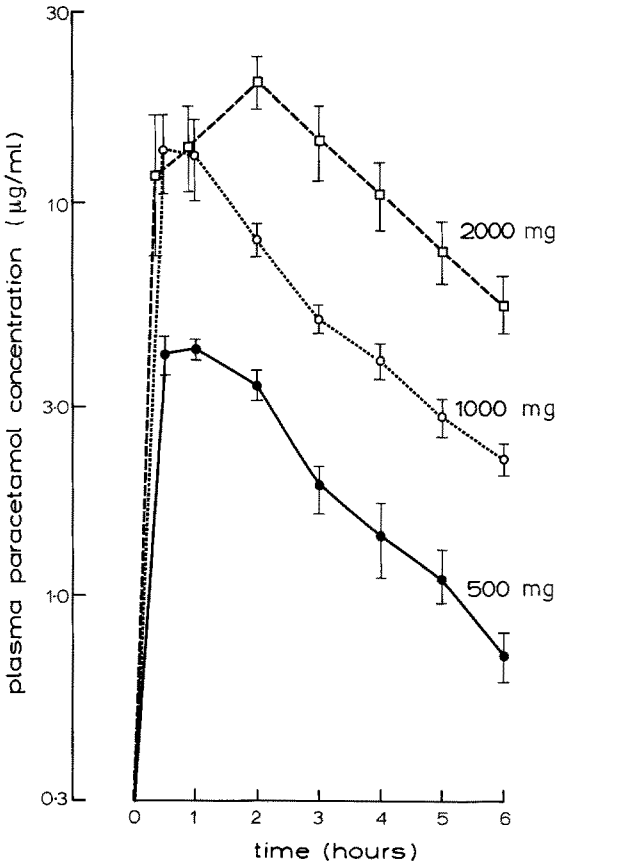

Fig. 2. Plasma concentrations of paracetamol (logarithmic scale) ± S.E.M. after the oral administration of 500 mg, 1000 mg and 2000 mg to six volunteers

Table 1. Pharmacokinetic variables calculated after the intravenous administration of 1000 mg paracetamol (mean ± S.E.M.)

A	= 13.8 ± 2.5 μg/ml
α	= 2.55 ± 0.47 hrs^{-1}
B	= 13.0 ± 1.0 μg/ml
β	= 0.28 ± 0.02 hrs^{-1}
AUC	= 50.5 ± 5.7 μg/ml · h
$\dot{V}p$	= 352 ± 40 ml/min
V_1	= 0.60 ± 0.07 l/kg
V_2	= 0.35 ± 0.02 l/kg
k_{12}	= 0.95 ± 0.27 hrs^{-1}
k_{21}	= 1.41 ± 0.18 hrs^{-1}
k_{13}	= 0.51 ± 0.06 hrs^{-1}

Table 2. Pharmacokinetic constants calculated after oral administration of paracetamol (mean ± S.E.M.)

Dose (mg)	Area under plasma concentration-time curve (μg/ml · hour)	Apparent half-life (hrs)	Bioavailability
500	15.6 ± 3.4	2.79 ± 0.35	0.63 ± 0.02
1000	44.0 ± 3.7	2.68 ± 0.17	0.89 ± 0.04
2000	87.6 ± 12.6	2.31 ± 0.18	0.87 ± 0.08

or to be used as a "model" substrate, clearance should either be measured directly (after intravenous administration) or inferred from an estimate of the AUC after 500 mg orally. In our study doses were not adjusted for body size and the subjects' weights ranged from 65–72 kg. It would therefore be advantageous for studies utilizing equation 5 to administer the drug in a dose of 7 mg/kg body weight.

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