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PARACETAMOL DISPOSITION IN NORMAL SUBJECTS AND IN PATIENTS TREATED WITH ANTIEPILEPTIC DRUGS

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1 The serum concentration profile of paracetamol has been determined after administration of single 1000 mg intravenous and oral doses in six normal subjects and six epileptic patients on chronic antiepileptic drug therapy. The urinary excretion of free and conjugated paracetamol has also been determined.

2 Following intravenous administration, serum paracetamol concentration declined with first-order kinetics. Both elimination rate and total body clearance were higher in the epileptic patients, although in neither case was the difference statistically significant.

3 The oral bioavailability (mean ± s.e. mean) was significantly lower in the epileptic patients than in the normal subjects (0.77 ± 0.03 and 0.89 ± 0.02 respectively, $P < 0.01$), whereas the urinary excretion total (free + conjugated) paracetamol was almost identical in the two groups.

4 It is suggested that the lower bioavailability of paracetamol in the epileptic patients results from enhancement of first-pass metabolism, secondary to enzyme induction.

Introduction

Chronic administration of therapeutic agents such as barbiturates and phenytoin, or exposure to environmental contaminants such as DDT, lindane, certain food additives, may induce the activity of drug metabolizing enzymes in hepatic microsomes (Conney, 1967; Kuntzman, 1969; Parke, 1975). A large number of clinically important drug interactions have been attributed to this mechanism (Breckenridge, 1975; Hunter & Chasseaud, 1976). In most cases, the interactions described involve drugs with low hepatic extraction ratios at physiological rates of liver blood flow. For this group of drugs (e.g. antipyrine, phenylbutazone, coumarin anticoagulants) an increase in the rate of hepatic metabolism results in a shortening of the serum half-life and a reduction in steady state serum concentration (Wilkinson & Shand, 1975).

The situation is quite different for drugs which have a high hepatic extraction ratio. Whereas enzyme induction has a negligible effect on the serum half-life of these compounds, it markedly reduces their systemic availability after oral administration (Gibaldi, Boyes & Feldman, 1971; Rowland, 1972; Perrier & Gibaldi, 1974; Wilkinson & Shand, 1975). Although the theoretical aspects of this phenomenon have been carefully analysed, very little experimental evidence is available in man (Meikle, Jubiz, Matsukura, West & Tyler, 1969; Alván, Piafsky, Lind & von Bahr, 1977).

In this study the effects of enzyme induction on the disposition of a drug subject to a relatively high hepatic blood clearance have been investigated. The kinetics of paracetamol after oral and intravenous dosing have been compared in healthy subjects and epileptic patients treated with known enzyme-inducing agents. Paracetamol has been selected as a model drug because it is almost completely eliminated by biotransformation, mainly in the liver (Mrochek, Katz, Christie & Dinsmore, 1974; Koch-Weser, 1976), and has a moderately high extraction ratio as indicated by a blood clearance of approximately 350 ml/min and evidence of first-pass effect at therapeutic dosages (Rawlins, Henderson & Hijab, 1977). Furthermore, paracetamol has been previously used as a model drug in pharmacokinetic studies designed to assess changes in the rate of drug metabolism

(Shively & Vesell, 1975; Triggs, Nation, Long & Ashley, 1975).

Methods

Subjects

Six healthy volunteers and six epileptic patients, whose ages ranged from 19 to 42 years, consented to take part in the study. The two groups were closely matched for age, sex and body weight. The healthy subjects had not been been receiving drug therapy regularly for at least 6 months preceding the study. The epileptic patients were residents at the Chalfont Centre for Epilepsy, and were receiving chronic treatment with a combination of at least two antiepileptic drugs known to produce enzyme induction (phenobarbitone, primidone, phenytoin and carbamazepine). The only exception was a 42-year-old epileptic patient who was receiving phenytoin alone (400 mg daily).

Each subject received the following two treatments in random order separated by a 1-week interval: a single oral dose (1000 mg) of paracetamol, and a similar dose injected intravenously over 5 min. The oral preparation was in the form of effervescent paracetamol (Panadol effervescent, Winthrop) dissolved in 75 ml water. For intravenous use paracetamol (50 mg/ml) was dissolved in a sterile vehicle of 40% v/v propylene glycol and 10% v/v ethyl alcohol in water. In order to avoid the effects of circadian variations in the disposition of paracetamol (Shively & Vesell, 1975), the time of administration was kept constant at 08.00 h after an overnight fast. Blood samples (10 ml) were taken at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after administration. A urine sample was collected over the period of blood sampling. Apart from slight irritation at the injection site during intravenous injection, no adverse effects were observed.

Measurement of paracetamol concentration in serum and urine

The concentration of free (unconjugated) paracetamol was determined in serum (2 ml) and urine (1 ml) samples by gas-liquid chromatography according to the method of Prescott (1971a). For the determination of total (free and conjugated) paracetamol, diluted urine samples (1 ml) were incubated with β-glucuronidase containing sulphatase activity (extracted from *Helix pomatia*, Sigma) at 37°C and at pH 5.2 for 20 h. These conditions were found in preliminary experiments to be optimal for hydrolysis. At the completion of the incubation period the samples were added to 2 ml 0.2M glycine buffer (pH 9.0) and then extracted according to the method of Prescott (1971b). The gas-chromatograph (Perkin Elmer F33) was equipped with dual flame ionization detectors and fitted with a glass column 1.7 m long, 3 mm i.d., filled with 2.5% OV 17 on Gas Chrom Q 100–120 mesh. Temperatures were 235°C for the column and 275°C for injection port and detector. Carrier gas (N_2) flow was adjusted to an inlet pressure of 175 kN/m^2.

Pharmacokinetic analysis

Although a bicompartmental model has previously been used to describe paracetamol kinetics (Rawlins *et al.*, 1977), the short distributive phase could not be characterized accurately in the present study due to the limited number of early samples. A kinetic analysis could, however, be satisfactorily performed according to a one-compartment open model. The elimination rate constant (K_{el}) was calculated by linear regression from the terminal part of the curve. The area under the curve (AUC) was determined by the trapezoidal rule and extrapolated to infinity. The total serum clearance, Cl, was calculated as Dose/$AUC^{iv}_{0-\infty}$ (Wilkinson & Shand, 1975). The volumes of distribution, $V_{dextrap}$ and V_{darea} were calculated respectively as Dose/C_0 (where C_0 is the concentration at zero time) and as Cl/K_{el} (Odar-Cederlöf and Borga, 1974).

The oral bioavailability (F) was calculated as $AUC_{0-\infty}/AUC^{iv}{}_{0-\infty}$. By assuming complete absorption, F was also predicted for each individual from intravenous data according to the formula (Rowland, 1972):

$$F = 1 - \frac{fm\,(Dose)}{LBF \,.\, \lambda \,.\, AUC^{iv}_{0-\infty}}$$

where fm is the fraction metabolized by the liver, λ the ratio of the concentration of paracetamol in whole blood to the concentration of the drug in the serum and LBF the liver blood flow, which was assumed to be 1.55 l/min (Levine, 1973). λ was determined at various concentrations of paracetamol in three epileptic patients and in two normal subjects and was found to average 1.18 ± 0.02 (s.e. mean) ($n = 10$). fm was substituted for 1 — fe (where fe is the fraction excreted unchanged in the urine) on the assumption that all metabolism was hepatic.

Results

After approximately 1–1.5 h following intravenous administration, serum paracetamol levels declined monoexponentially in both healthy volunteers and epileptic patients (Figure 1). Following oral administration in the healthy volunteers, serum levels rose rapidly within 0.5 h to values similar to those found at corresponding times after intravenous administration, declining with a similar pattern

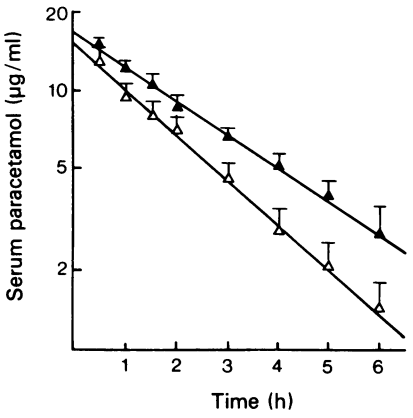

Figure 1 Serum paracetamol concentration (mean ± s.e. mean) after a single 1000 mg i.v. dose in six normal subjects (▲) and six epileptic patients (△)

thereafter. Therefore the time concentration curves following both routes of administration were very similar, although levels were generally slightly lower after the oral dosing (Figure 2). A different pattern was observed after oral administration in the epileptic patients. Serum levels rose rapidly within 0.5 h to relatively low peak values and remained at all sampling times clearly lower than those observed after intravenous administration (Figure 2). Kinetic parameters calculated according to a one compartment open model are illustrated in Tables 1 and 2. Values for $V_d$extrap were similar to those for $V_d$area. Serum half-lives were shorter and total serum clearances were higher in the patients than in the normal subjects, but due to the relatively large inter-individual variability, in neither case was the difference statistically significant ($0.05 < P < 0.10$).

The oral bioavailability was incomplete in both groups and was significantly lower in the patients than in the normal volunteers ($P < 0.01$). There was a relatively good agreement between the predicted and the observed bioavailability, although in both groups predicted values were slightly lower than those observed (Table 2). There was a particularly good agreement between the predicted and observed decrease in oral availability in the patients (12% and 13% respectively).

The recovery of total and free paracetamol in urine is illustrated in Table 3. About 60–70% of the dose could be recovered over 6 h following administration of the drug. There was no significant difference between recoveries following oral and intravenous administration. The recovery was almost identical on both occasions in the patients, while a marginally lower value was observed in the normal subjects after oral dosing. The latter discrepancy was entirely due to very low recovery in a single subject in whom a urine void was lost during the collection period.

Only a very small fraction of the dose was excreted as free paracetamol. The ratio of free to total drug in the urine was lower in the patients but the difference did not reach statistical significance.

Discussion

The distribution and elimination kinetics of paracetamol after oral and intravenous administration in normal subjects has been recently investigated in

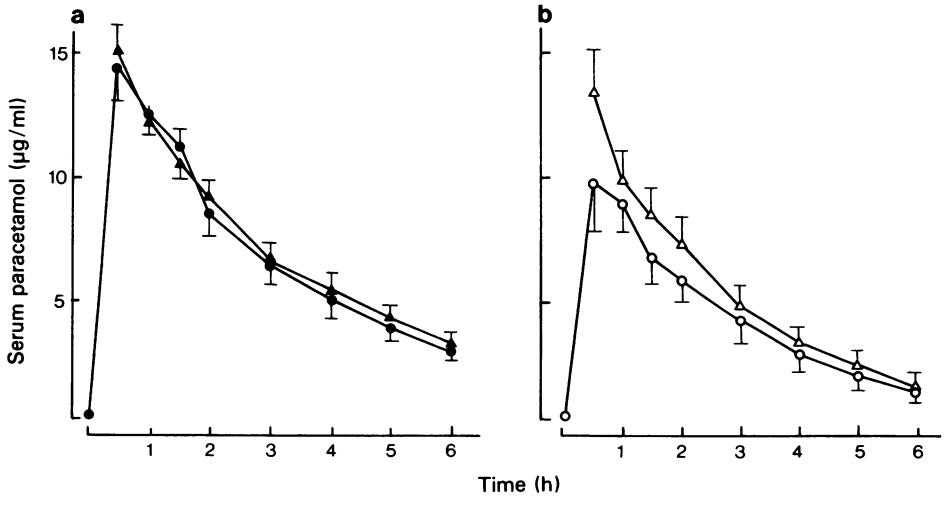

Figure 2 Serum paracetamol concentration (mean ± s.e. mean) following a single 1000 mg oral (●, ○) or intravenous (▲, △) dose in a) six normal subjects and b) six epileptic patients.

Table 1 Kinetic parameters (mean ± s.e. mean) calculated after intravenous administration of paracetamol (1000 mg).

	Healthy subjects	*Epileptic patients*
C_0 (μg/ml)	16.0 ± 1.4	14.9 ± 2.1
V_d extrap (l/kg)	0.94 ± 0.08	1.05 ± 0.11
V_d area (l/kg)	0.96 ± 0.11	1.11 ± 0.14
K_{el} (h^{-1})	0.292 ± 0.036	0.381 ± 0.028*
$T_{\frac{1}{2}}$ (h)	2.52 ± 0.25	1.88 ± 0.17*
$AUC^{iv}_{0-\infty}$ ($mg\ l^{-1}\ h^{-1}$)	55.3 ± 1.9	38.3 ± 6.4**
Cl ($l\ h^{-1}$)	19.3 ± 2.5	29.4 ± 4.4 *

*$P < 0.10$, ** $P < 0.05$ (Student's t-test)

Table 2 Kinetic parameters (mean ± s.e. mean) calculated after oral administration of paracetamol (1000 mg).

	Healthy subjects	*Epileptic patients*
$AUC^{oral}_{0-\infty}$ ($mg\ l^{-1}\ h^{-1}$)	49.4 ± 1.8	29.3 ± 5.1**
F (observed)	0.89 ± 0.02	0.77 ± 0.03*
F (predicted from i.v. data)	0.83 ± 0.02	0.73 ± 0.04*

* $P < 0.01$, ** $P < 0.05$ (Student's t-test)

Table 3 Recovery of free and conjugated paracetamol in urine expressed as mean ± s.e. mean

	i.v. administration	*Oral administration*
Healthy subjects		
Total amount recovered (free + conjugated (mg)	657 ± 86	601 ± 72
Fraction free (%)	2.4 ± 0.6	2.0 ± 0.4
Epileptic patients		
Total amount recovered (free + conjugated) (mg)	682 ± 53	677 ± 33
Fraction free (%)	2.0 ± 0.5	1.8 ± 0.3

detail by Rawlins *et al.* (1977). Our data in normal subjects are in very close agreement with theirs. In particular, there is a remarkable similarity of the oral bioavailability determined after a 1000 mg dose (0.89 in both studies) despite the use of different formulations. The incomplete oral bioavailability of paracetamol has been interpreted as evidence of first-pass metabolism on the assumption that gastrointestinal absorption is complete (Rawlins *et al;* 1977). Occurrence of first-pass metabolism is further suggested by our observation that the urinary recovery of free plus conjugated paracetamol after oral administration was similar to that after intravenous administration in both normal subjects and epileptic patients.

Oral bioavailability was significantly lower in our patients than in normal subjects. This observation is in line with our hypothesis that paracetamol metabolism is enhanced by concurrent administration of antiepileptic drugs. In fact, by assuming that elimination is entirely due to hepatic metabolism, it can be calculated (Wilkinson & Shand, 1975) that for a liver blood flow of 1.55 l/min the hepatic extraction ratio averaged 0.17 in the normal subjects and 0.27 in the patients. According to these values, the pharmacokinetic pattern of paracetamol should be intermediate between that of a highly extracted and that of a poorly extracted compound. Therefore, stimulation of its metabolism should result in a moderate decrease of both systemic availability and biological half-life (Wilkinson & Shand, 1975). The hypothesis that first-pass metabolism rather than incomplete absorption is responsible for the lower bioavailability of paracetamol in epileptic patients is supported by the urinary data and by the good agreement between predicted and observed decrease of bioavailability. It is of interest that predicted values were slightly lower than those observed. The discrepancy may be due to the occurrence of saturation kinetics during the absorption process or, alternatively, to part of metabolism taking place outside the liver, in which case the estimates of hepatic extraction ratios given above would err on the high side.

The first hypothesis is supported by the observation that the oral bioavailability of paracetamol is significantly higher after a 1000 mg than after a 500 mg dose (Rawlins *et al.,* 1977). Occurrence of extra-hepatic metabolism cannot be excluded on the basis of our results alone but there is considerable evidence that this is unlikely. Paracetamol is metabolized mainly by conjugation with glucuronic acid and, to a lesser extent, with sulphuric acid (Cummings, King & Martin, 1967). Both of these reactions are known to take place largely in the liver (Koch-Weser, 1976). Moreover, the fact that paracetamol metabolism is not altered in anephric patients compared with normal subjects indicates that the kidney does not play a significant part in the biotransformation of the drug (Lowenthal, Øie, van Stone, Briggs & Levy, 1976). The higher blood clearance of paracetamol in epileptic patients is likely to be a consequence of increased hepatic metabolism (as is also suggested by the slightly lower ratios of free to conjugated drug in the patients' urine), but enzyme induction *per se* is not necessarily the mechanism involved.

Although the enzyme system responsible for glucuronide formation is inducible (Blaschke, Berk, Rodkey, Scharschmidt, Collison & Waggoner, 1974; Lecamwasam, 1975; Parke, 1975), animal studies indicate that the stimulation of hepatic microsomal enzymes by phenobarbitone is associated with changes in several other measures of liver function, each of which could theoretically result in enhancement of metabolic drug clearance. These include increased concentration in the hepatocyte of the Y organic anion-binding protein (Reyes, Levy, Gatmaitan & Arias, 1971), increased bile flow (Redinger & Small, 1973) and increased liver blood flow (Ohnaus, Thorgeirsson, Davies & Breckenridge, 1970; Branch, Shand, Wilkinson & Nies, 1974; Nies, Wilkinson, Rush, Strother & McDevitt, 1977). The latter is unlikely to account for the faster elimination of paracetamol since the metabolic clearance of this drug in man is considerably lower than the average blood flow to the liver (Lowenthal *et al.,* 1976).

Apart from the theoretical interest in terms of a pharmacokinetic model, our results may have important clinical implications. It has been suggested that the hepatoxicity of paracetamol is related to the formation of a toxic highly-reactive metabolite in liver microsomes (Mitchell & Potter, 1975; Davis, Simmons, Harrison & Williams, 1976). Induction of its metabolism by other drugs may theoretically increase the susceptibility to the development of acute necrosis of the liver. Indeed, this has been shown to be the case in laboratory animals (McLean & Day, 1975) and the observation that patients receiving enzyme-inducing agents fare particularly badly after a paracetamol overdose suggests that a similar effect takes place in man (Wright & Prescott, 1973).

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