BIOAVAILABILITY OF DIFFERENT PREPARATIONS OF PARACETAMOL

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- 1 Plasma drug concentrations in eight volunteer subjects following oral administration of six preparations of paracetamol have been studied.
- 2 Significant interindividual differences in plasma paracetamol concentration were found within 1 h but there were no consistent differences between the different drug preparations. The results indicate that all the preparations have equivalent bioavailability.
- 3 In four subjects, tested with the same preparation on two occasions, the findings suggest that drug absorption may differ from one occasion to another.

Introduction

Differences in bioavailability between branded formulations are now known to affect many drugs. In clinical practice those affecting digoxin (Lindenbaum, Mellow, Blackstone & Butler, 1971), chloramphenicol (Glazko, Kinkel, Alegnani & Holmes, 1968), phenytoin (Tyrer, Eadie, Sutherland & Hooper, 1970), tolbutamide (Varley, 1968) and chlorpropamide (Monro & Welling, 1974) are of particular importance because of the close dosage control required with such agents.

Persistent complaints of poor analgesic response following ingestion of certain brands of paracetamol by patients attending a local General Practice Unit prompted us to investigate absorption of this drug from several preparations available. An earlier study (Gwilt, Robertson, Goldman & Blanchard, 1963) suggested that only slight differences were to be expected but that absorption would be optimal from preparations containing sorbitol, possibly because of faster tablet dissolution (Walters, 1968). One such preparation was included in this study.

Methods

Subjects

Eight volunteer subjects (four male and four female), aged 21-44 years, took part in the study. All were healthy and gave negative histories for drug consumption before and during the study.

Procedure

Each subject was tested on six occasions at least

one week apart. Following an overnight fast, paracetamol (2 g) as powder or as four 0.5 g tablets was administered with water (200 ml). The different drug preparations were given in randomised order to avoid possible sequence effects. One cup of coffee was allowed at 1 h, one Bath bun and butter at 2 h and lunch at 4 h on each occasion. Venous heparinized blood samples were taken before and at 0.5, 1, 1.5, 2, 3, 4 and 6 h following drug administration. On a subsequent occasion repeat tests were done on four subjects to estimate repeatability of the procedure. Plasma samples were stored at 4°C for up to one week and their unconjugated paracetamol concentrations estimated in duplicate by the method of Dordoni, Wilson, Thompson & Williams (1973). Repeatability of the estimates was of a high order. Fisher's intraclass correlation $r_I = 0.99$ ($n = 60$, $P < 0.001$). Plasma elimination constants were estimated from the plasma drug concentrations at 1.5 to 6 h by the method of least squares and areas under the curves by the trapezoid rule.

Drug preparations

The six preparations tested were:

- A Paracetamol powder (Martindale Samoore)
- B Paracetamol tablets B.P. (W.B. Pharmaceuticals 4227 B3)
- C Paracetamol tablets B.P. (Boots 94V)
- D Paracetamol tablets B.P. (Unichem D331438)
- E Panadol (Winthrop 2KH184)
- F Panasorb (Winthrop 1KC299)

Fig. 1 Mean plasma concentrations of paracetamol in eight subjects following oral administration of paracetamol (2 g) as six different preparations. The six sets of data are offset by 1 h each for convenience.

Results

Mean plasma concentrations of paracetamol in the eight subjects following administration of the six drug preparations are shown in Figure 1. The six profiles were similar but differed slightly at the early sampling times. Individual values of drug concentration at 0.5 h varied over a wide range (17.8–57.7 µg/ml) and a within-subject comparison of the preparations which yielded the highest

(Preparation C: 39.2 µg/ml) and the lowest (Preparation D: 30.1 µg/ml) mean concentrations indicated a significant difference (paired t -test = 3.045, $P < 0.02$). Analysis of variance of this concentration and of the area under the concentration/time curve for all the data revealed significant differences between individuals but not between preparations (Table 1). The mean distri-

Table 1 Analysis of variance of plasma paracetamol concentration in eight subjects following administration of six different preparations

Source of variance	Sum of squares	Degrees of freedom	Mean square	F	P
(a) Plasma concentration at 0.5 h					
Between individuals	1919	7	274	4.48	< 0.01
Between preparations	453	5	90	1.48	NS
Residual	2144	35	61		
Total	4516	47			
(b) Area under concentration/time curve					
Between individuals	37370	7	5339	28.68	< 0.01
Between preparations	404	5	81	0.44	NS
Residual	6516	35	186		
Total	44290	47			
(c) Ratio a : b					
Between individuals	0.0574	7	0.0082	1.78	NS
Between preparations	0.0328	5	0.0066	1.43	NS
Residual	0.1614	35	0.0046		
Total	0.2516	47			

Table 2 Plasma paracetamol concentrations ($\mu\text{g/ml}$) of four subjects following administration of the same preparation on two occasions

Subject	Preparation	Plasma paracetamol concentrations at time (h)							Area under curve ($\mu\text{g. h ml}^{-1}$)
		0.5	1	1.5	2	3	4	6	
1	B	27.7	38.0	29.8	22.9	16.0	12.5	8.2	130
		42.0	37.0	31.4	25.3	17.6	12.8	7.4	140
2	B	23.9	36.7	27.1	22.3	14.1	9.3	3.5	100
		35.1	30.9	25.0	21.3	14.6	10.4	5.6	113
3	C	32.2	25.8	21.3	17.0	12.0	7.4	4.8	92
		22.3	22.6	19.9	17.0	10.4	8.5	4.0	84
4	C	22.1	30.9	25.8	19.4	11.4	6.9	2.4	83
		38.6	31.9	23.9	20.5	12.2	6.9	2.9	94

bution volume (V_d) = 0.78 (range 0.61-0.97) l/kg and the mean plasma elimination constant (K_{el}) = 0.33 (range 0.27-0.39). Neither differed significantly between preparations.

Results of the repeated tests performed on four subjects are shown in Table 2. There were substantial differences in the plasma paracetamol concentrations only at the 0.5 h sampling time. Repeatability was assessed as follows:

0.5 h values included: $r_I = 0.88$

0.5 h values excluded: $r_I = 0.98$

Discussion

The experiments described here have shown that following administration of different paracetamol preparations plasma drug concentrations varied widely. The range of concentrations present at the early sampling times is probably sufficient to cause wide variation in analgesic response to drug administration under fasting conditions. Occasional failure of response, as indicated by the complaint which prompted the present work, is therefore to be expected. It is apparent, however, that such variability cannot be ascribed to consistent differences between the various drug

preparations and there is therefore no evidence of differences in bioavailability between them. The slight difference revealed between the preparations yielding the highest and the lowest mean plasma concentrations is unlikely to be of much biological, as opposed to statistical, significance.

A significant proportion of the variability in plasma drug concentration can be ascribed, as expected, to differences between individuals. Such differences cannot be identified for certain from this study but they probably include differences in gastric emptying on which paracetamol absorption is strongly dependent (Heading, Nimmo, Prescott & Tothill, 1973; Nimmo, Heading, Tothill & Prescott, 1973), as well as in drug distribution volume and elimination found here. Much of the variability in this study however, is unexplained. The repeated experiments done on four individuals showed that the repeatability was very poor at an early sampling time (0.5 h), suggesting that absorption, and by implication gastric emptying, may differ from one occasion to another even in the fasting state. Whether such differences are of clinical importance remains to be seen.

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