J. Pharm. Pharmac., 1972, **24**, 615–619 *Received January* 17, 1972

Some factors affecting the absorption of paracetamol

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Blood concentration and urinary excretion data demonstrated that subjects who had ingested 1 g of paracetamol after fasting overnight absorbed the drug up to 5 times more rapidly but to the same extent as when they ingested the drug after a substantial high carbohydrate breakfast. Subjects who had ingested 1 g of paracetamol immediately before sleep at night excreted up to 36% less than when they took the drug at 8.30 a.m.

Drug absorption generally—but not always—proceeds more rapidly if the stomach and upper gastrointestinal tract are free of food. In the non-fasting condition, reduced rate of absorption may be due to any of a number of factors including poor gastrointestinal mixing and complex formation; increased rate of absorption is sometimes found for those substances e.g. riboflavin (Levy & Jusko, 1966) which are absorbed high in the gastrointestinal tract by a specialized mechanism.

Diurnal variation in drug effectiveness is not well documented. Variations in sensitivity to drugs in a circadian pattern have been reported (Halberg, 1959; Marte & Halberg, 1961). Dettli (1967) and Dettli, Spring & Raeber (1967) have postulated a diurnal cycle in the elimination rate constant of sulphonamides, owing to changes in urine pH; no effect on drug absorption was postulated.

We report the effects of food and sleep on the absorption and excretion of *N*-acetyl-*p*-aminophenol (paracetamol) as part of a major study on the bio-availabilities of commercial dosage forms of paracetamol (McGilveray, Mattok & others, 1971).

METHODS

Food study. Four adult male volunteers (150–200 lb) were given 1 g doses of paracetamol, in a commercial tablet formulation, each week for two weeks. The drug was administered with water (200 ml) and additional water (200 ml) was taken hourly for the next 5 h. A 2-way cross-over design was used. The drug was administered alternately after fasting overnight and immediately after a substantial breakfast of orange juice (200 ml), cornflakes (30 g) with milk and "Pop Tarts". Blood samples were taken 20 and 40 min, 1, 1·5, 2, 4 and 6 h, and urine was collected at 1, 1·5, 2, 2·5, 3, 4, 5, 8, 11, 14 and 24 h after ingestion. The complete protocol with fluid intake has been described (Mattok, McGilveray & Cook, 1971).

Sleep study. A second group of 4 male volunteers (150–190 lb) was used in a cross-over study where the dosage form was the same as that used in the "food" study. On one occasion the drug (lg) was administered at 8.30 a.m. before normal daytime activities and on the other, one week later, at 11 p.m. immediately before a period of sleep (8 h). In each case a light meal (orange juice (100 ml), cornflakes (30 g) with milk (100 ml) and one slice of buttered toast) was eaten 1½ h before drug ingestion. Urine collections were usually made at 4, 8, 11, 14, and 24 h after ingestion.

Unchanged paracetamol in blood and urine was determined by the methods of

Table 1. *Blood concentrations of unchanged paracetamol (μg/ml) in 4 subjects when drug (1 g) was ingested after overnight fasting (fast) substantial breakfast (food).*

	Concentration of drug in subject									
	I		II		III		IV		Mean	
Time (min)	Fast	Food	Fast	Food	Fast	Food	Fast	Food	Fast	Food
20	20·6	7·6	19·5	8·6	24·0	1·8	28·1	5·1	23·1	5·8
40	16·5	9·0	16·5	19·0	21·8	8·5	24·0	11·0	19·1	11·9
60	13·0	10·4	13·0	13·5	20·4	14·0	21·2	18·9	16·9	14·2
90	12·0	11·8	12·2	11·5	18·2	18·1	19·1	20·1	15·4	15·3
120	9·0	10·5	11·6	9·3	16·5	18·8	16·8	21·5	13·5	15·0
240	7·2	6·5	4·6	4·8	10·5	12·6	11·0	14·5	8·3	9·6
360	3·0	3·0	2·5	2·8	5·5	7·0	8·1	9·0	4·8	5·5
AUC* ..	52·3	45·2	49·7	44·1	74·9	73·9	86·9	88·0	66·0	62·8
Time to 10 μg/ml†	10	55	10	24	8	45	7	38	8	40

*AUC = Area under the blood level curve (0 to 6 h) μg-h/ml.

†Estimated value.

Brodie & Axelrod (1948) and total paracetamol excreted in urine according to Welch & Conney (1965).

Statistical comparisons were made using the paired *t*-test.

RESULTS AND DISCUSSION

Concomitant administration of food produced little effect on the extent of absorption of paracetamol (Table 1). Measurement of the area under the blood concentration curve to 6 h (AUC) using the trapezoidal rule did not differ significantly in the four fasting subjects and the non-fasting subjects ($P = 0{\cdot}05$) although the mean value was 5% higher in the fasting subjects. The same situation prevailed with the "total" i.e. drug plus metabolites excreted in the urine (Table 2).

Although there was little or no difference in the amount of drug absorbed (and excreted) when the subjects did or did not have food, there were marked differences in the rate of absorption with each subject. This is demonstrated (Fig. 1) in the rising portion of the blood level curve and in the urinary excretion rate curves (cf. Fig. 2). Blood concentrations of the drug at 20 and 40 min and urinary excretion rates at 1, 1·5 and 2 h were significantly greater ($P = 0{\cdot}05$) in the fasting subjects.

Relative absorption rates were estimated from the blood concentration data by applying the equation of Wagner & Nelson (1964) for a one compartment model. Levy & Yamada (1971) have suggested that paracetamol elimination may be better described as a biexponential process and Shibasaki, Konishi & others (1971) have

Table 2. *Cumulative urinary excretion (mg) of "total" paracetamol when the drug (1 g) was ingested after fasting overnight and after food i.e. breakfast.*

	Subject							
	I		II		III		IV	
Time (h)	Fast	Food	Fast	Food	Fast	Food	Fast	Food
1	29	20	48	31	63	13	56	18
1·5	82	50	118	91	111	50	112	63
2	129	90	173	170	179	70	186	110
24	688	643	706	659	670	600	800	718
Kel (h^{-1})	0·21	0·21	0·25	0·25	0·23	0·23	0·24	0·24
$t\frac{1}{2}$ (h)	3·1	3·1	2·8	2·8	2·7	2·7	2·9	2·9

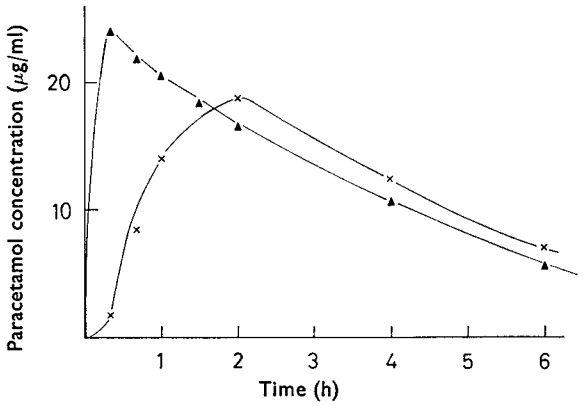

FIG. 1. Blood concentration of paracetamol in one subject (III) when the drug (1 g) was ingested after fasting overnight (▲) and after breakfast (x).

supported this with data from experiments with rabbits. However, we found no strong indication of an initial distributive phase and the Wagner-Nelson equation appeared appropriate. The other assumptions made were that the volume of distribution of paracetamol remains the same in the fasting and non-fasting conditions, that all the rates of distribution, metabolism and elimination remain the same and only the absorption rate is changed. Since the blood concentration peak in all subjects in the fasting state appeared to be passed (Table 1) before the first blood sample (20 min), interpolated points were used to derive the rate constants and half lives of absorption (Table 3). It is evident, from these parameters (Table 3) that the absorption of paracetamol was more rapid in the fasting condition; this is also reflected in the urine data (Table 2). Total amounts excreted in the first 2 h after ingestion are consistently higher for the fasting subjects. Elimination rate constants (Table 3) calculated from the semi-log blood concentration profiles for each person were similar in the fasting and non-fasting subjects. Thus any differences in profiles for the fasting and non-fasting subjects do not appear to be attributable to elimination processes i.e. metabolism and excretion. There was also good agreement between

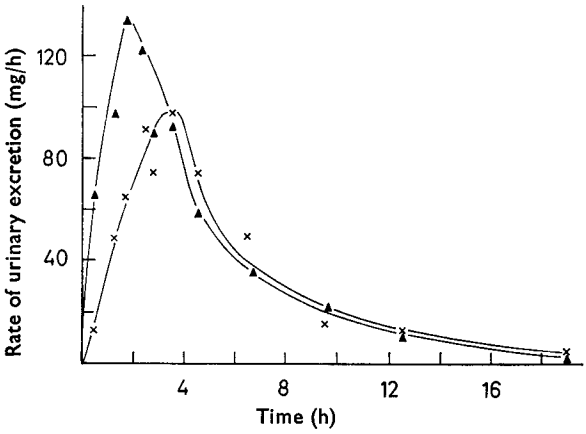

FIG. 2. Urinary excretion of "total" paracetamol by one subject (III) when the drug was ingested after fasting overnight (▲) and after breakfast (x).

rates calculated from urine data when the drug was ingested with or without food (Table 2).

Gwilt, Robertson & others (1963) estimated that the average peak time of paracetamol in blood was 45 min and inferred that concentrations below 10 μg/ml at this time represented low absorption. They found no significant difference between fasting and non-fasting 45 min blood concentrations of the drug. Although the mean estimated value in our fasting subjects (18·6 μg/ml) at 45 min was higher than that of the non-fasting subjects (12·3 μg/ml), one subject, II, had a higher blood concentration when the drug was taken in the non-fasting state. However, measure-

Table 3. *Effect of food on absorption and elimination rate constants for paracetamol*

	Absorption				Elimination			
	K (h^{-1})		$t_{\frac{1}{2}}$ (h)		K (h^{-1})		$t_{\frac{1}{2}}$ (h)	
Subject	Fast	Food	Fast	Food	Fast	Food	Fast	Food
I	7·0	1·4	0·1	0·5	0·26	0·26	2·7	2·7
II	4·6	1·5	0·2	0·5	0·35	0·35	2·0	2·0
III	4·6	1·4	0·2	0·5	0·26	0·26	2·7	2·7
IV	7·0	1·4	0·1	0·5	0·26	0·26	2·7	2·7
Mean	5·6	1·4	0·2	0·5	0·28	0·28	2·5	2·5

ment at 45 min is unsuitable since the peak paracetamol concentration in the fasting subject had passed while in the non-fasting subject it usually had not been reached. Blood concentrations 20 min after ingestion provide a better basis for comparison of absorption rates, since at this time blood concentrations are rising or close to the maximum in both fasting and non-fasting subjects (Table 1). This time shift is also apparent from the times to reach 10 μg/ml (Table 1) which again reflect the significantly ($P < 0·05$) more rapid absorption in the fasting subjects (8 min *vs* 45 min).

Thus the presence of food in the stomach retards absorption of paracetamol but the speed with which it reaches the peak in blood suggests that gastric absorption could be considerable and that food interferes by delaying tablet disintegration and dissolution.

The experiment to assess the effect of sleep was designed so that the day and night ingestions followed similar routines except that the night ingestions were followed by a period of sleep whereas the day ingestions were followed by normal daytime activities. Overnight excretion data were obtained by collecting urine 4 and 8 h after ingestion. Control subjects drank 200 ml of water each hour for 5 h after taking the drug and were therefore able to collect urine samples more frequently. However, since urine flow might have influenced the excretion rate, two of the subjects confirmed the daytime results with no additional fluid after ingestion and 4 urine collections in 24 h. Urinary excretion data for one subject as described in Fig. 3 show that all the points in the terminal phases of the three excretion profiles described fall close to a common line. Thus overall elimination of the drug does not appear to be affected by urine flow or altered during the sleep period. This suggests that the excretion and metabolism processes which determine the elimination rate are also not affected by sleep. The diurnal independence of the rates of metabolism was supported by comparing the ratios of free to "total" paracetamol excreted after day and night ingestion (Table 4). The ratios free to "total" drug excreted in the 8 h period immediately after drug ingestion are, within experimental precision, consistent in each subject. This

Table 4. *Cumulative excretion (mg) of free* (F) *and total* (T) *paracetamol after pre-sleep i.e. night and post-sleep i.e. day ingestion (dose, 1 g).*

	Subject and time of ingestion							
	I		II		V		VI	
Time (h)	Day	Night	Day	Night	Day	Night	Day	Night
4 (T)	318	228	340	140	280	132	285	251
8 (T)	590	353	528	296	470	270	478	423
8 (F)	24	14	14	8	26	12	19	18
8 (F/T), (%) ..	4·0	3·9	2·6	2·7	5·8	5·5	4·0	4·2
11 (T)	651	433	601	350	538	355	559	502
24 (T)	718	509	706	444	644	475	647	586

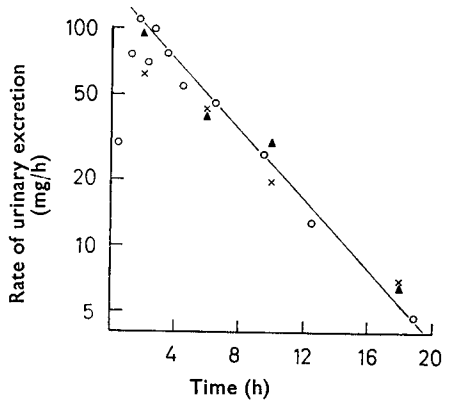

FIG. 3. Urinary excretion of "total" paracetamol by one subject (VI) when the drug (1 g) was ingested (i) immediately before sleep (x) (4 urine samples); (ii) at 8.30 a.m. (▲) (4 urine samples and (iii) at 8.30 a.m. (o) (11 urine samples).

indicates that there was no change in the pattern of metabolism of the absorbed drug during sleep. However, increased residence time of the drug in the gastrointestinal tract could allow increased metabolism to a form which is not absorbed or not detected in the assay.

However, from the cumulative urine excretion data (Table 4) it appears that much less paracetamol is absorbed and therefore eliminated after pre-sleep than post-sleep ingestion. Each of the 4 subjects excreted less paracetamol when the drug was taken before sleep than after morning ingestion. We cannot, at present, be sure of the cause of this reduced absorption.

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