Influence of food on the absorption of the *p*-chlorophenolic ester of chlorophenoxyisobutyric acid in man

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1 A study was designed to investigate the effect of a fatty meal on the absorption of chlorophenoxyisobutyric acid (CPIB) in six healthy adult volunteers after oral administration of the *p*-chlorophenolic (PCP) ester of CPIB.

2 Plasma concentrations of CPIB when administered with food were higher than those observed in the fasting state. The $C_{\max}$ in the former case was $24.0 \pm 4.6 \text{ mg l}^{-1}$ as against a value of $15.2 \pm 6.9 \text{ mg l}^{-1}$ in the latter ($P < 0.01$).

3 The pharmacokinetic parameters measured were found to be linear with the dose administered. This could be due to low plasma concentrations of CPIB unable to cause a saturation of the plasma protein binding of this drug.

4 It is concluded that a fatty meal enhances the absorption of this hypolipidaemic drug.

Keywords absorption chlorophenoxyisobutyric acid food

Introduction

The influence of food on the rate and the amount of drug absorbed after oral administration is now well documented (Mellander, 1978). However, this effect remains largely unpredictable. Most commonly, for a large number of drugs food has been shown to reduce the systemic availability. For some others food has no influence on their absorption. On the other hand, for certain lipophilic drugs like griseofulvin, nitrofurantoin and α -propoxyphene, food is reported to enhance both the rate and the amount of drug absorbed (Welling, 1977).

The *p*-chlorophenolic ester (PCP) of chlorophenoxyisobutyric acid (CPIB) (Laboratoires Sarget, Bordeaux, France) is a hypolipidaemic drug shown to be effective in both hypercholesterolaemic and hypertriglyceridaemic states. Preliminary studies (Houin, 1981, unpublished results) have shown that plasma concentrations of CPIB in fasting volunteers were lower as compared to those in patients undergoing treatment with this drug and thus taking both the drug and food. In view of this observation and also because of the high lipophilic

nature of the drug, we planned a study to investigate the effect of food on the gastro-intestinal absorption of CPIB.

Methods

Six healthy volunteers participated in the study. Written consents were obtained from all of them after the aim and design of the experiment were clearly explained to them. None of them had a history suggestive of kidney, renal, cardiac, pulmonary or allergic disease and the results of their routine laboratory tests for serum proteins, potassium, calcium, phosphorus, $p\text{CO}_2$, blood urea nitrogen, cholesterol, glucose, uric acid, bilirubin, transaminases, electrophoresis and bromosulphophthalein excretion test were all normal. The subjects were instructed not to take any drug during 1 week before the start of the study. Care was taken to see that they had not received any drugs known to be inducers of microsomal enzymes for at least 1 month before

the study since it has been shown that the metabolism of CPIB is very sensitive to such drugs (Houin & Tillement, 1978).

Each subject received two capsules (275 mg CPIB and 125 mg PCP) on each of two occasions separated by an interval of 2 weeks, once in a fasting state and once with a standard breakfast in a randomised cross over fashion. The breakfast consisted of butter 0.5 g/kg body weight, two slices of bread and 250 ml milk and coffee. On both the occasions, the subjects refrained from lunch for up to 4 h after drug ingestion.

Blood samples

Blood samples were obtained from the subjects before drug administration and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4.5, 6, 8, 10, 12, 24, 36 and 48 h following drug administration. Blood was collected from the antecubital veins in heparin and after centrifugation plasma was separated immediately and stored at -20°C until analysis.

Urine collections

Prior to drug administration 24 h urinary collections of all the subjects were made. Following drug administration hourly urinary collections were made for the first 6 h, two hourly collections for the next 6 h and finally 24 hourly collections were made for the next 5 days after drug administration.

The volume and pH of the urine samples were measured soon after the collections were complete and then stored at -20°C in order to prevent hydrolysis of CPIB glucuronide conjugate (Faed & McQueen, 1979).

Drug assays

Unchanged plasma and urinary CPIB and PCP concentrations were measured using a gas liquid chromatographic method previously described (Houin *et al.*, 1975). Conjugates of both these compounds were estimated after hydrolysis

using 6N HCl at 100°C for 30 min. The sensitivity of this method was 0.1 mg/l and the coefficient of variation varied from 5–7% in the range of the concentrations measured for both the compounds.

Calculations

Individual plasma and urinary concentrations of the drugs were concomitantly interpreted according to a model with two compartments, a peripheral from which absorption occurs and the other, a central. The fitting of the curves was performed using an Tektronix 4052 microcomputer by an iterative non linear regression Gauss-Newton algorithm (D'Athis *et al.*, 1978). Comparisons were made using the Student's *t*-test adapted for paired values.

Results

The physical characteristics of the subjects studied are presented in Table 1. There was one female among the six subjects who participated in the investigations. All the subjects were young adults.

In plasma, PCP was present only in trace amounts and its metabolite was undetectable. In urine, on the other hand, both the parent drug and metabolites of CPIB and PCP were present. A semilogarithmic plot of mean plasma concentrations of CPIB vs time after each administration is shown in Figure 1. The differences between unchanged and total CPIB at each point of time in plasma ranged from 2–4 mg/l.

It is seen (Figure 1) that plasma concentrations of CPIB were higher at all points of time measured when the drug was taken with breakfast as compared to those when CPIB was ingested in the fasting state. The $C_{\max}$ in the former case was significantly higher ($P < 0.01$). Logarithmic differences between the means of the infinite and the actual urine excretion of total and unchanged CPIB vs time are depicted in Figure 2.

The principal pharmacokinetic parameters of

Table 1 Characteristics of the subjects investigated

	Subjects					
	1	2	3	4	5	6
Weight (kg)	50	59	70	78	60	49
Age (years)	24	28	21	27	27	25
Height (m)	1.65	1.72	1.80	1.85	1.75	1.72
Sex	M	M	M	M	M	F

Figure 1 Semilogarithmic plot of the plasma concentrations (means $\pm$ s.d.) vs time of CPIB administered with food (●) or in fasting state (○).

CPIB are indicated in Table 2. Unchanged plasma $C_{\max}$ of CPIB taken with food was 23.97 ± 4.83 mg/l as against 15.23 ± 5.58 mg/l when ingested without food. The corresponding values for total CPIB were 26.4 ± 4.83 mg/l and 19.02 ± 4.67 mg/l ($P < 0.01$).

Unchanged CPIB excretion in urine was slightly higher when it was administered with breakfast. The excretion of total CPIB (conjugated + unconjugated) was about 24% higher when ingested with food as compared to that administered in the fasting state. However, no statistically significant differences were seen between the two conditions of drug administration. The increase in the excretion of unchanged CPIB after food was of the order of 15%.

The areas under the plasma concentrations vs time curves were similar for CPIB whether administered without or with food. Total plasma clearance calculated assuming total systemic availability was also similar under the two conditions.

Figure 2 Semilogarithmic plots of the residual amounts of total and unchanged CPIB vs time. The values represent means $\pm$ s.d. (■ total CPIB, fed state, □ total CPIB, fasting state, ● unchanged CPIB, fed state, ○ unchanged CPIB, fasting state).

Table 2 Means $\pm$ s.d. of the pharmacokinetic parameters of unchanged and total CPIB in the subjects investigated

Conditions		$C_{\max}$ (mg l ⁻¹)	$t_{\max}$ (h)	U_x (% administered dose)	CLT/F (ml min ⁻¹)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V/F (l)	AUC (mg l ⁻¹ h)
Unchanged CPIB		15.2	5.6	8.0	7.2	1.6	17.7	10.2	722.5
		$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	A	6.9	2.9	5.1	2.1	0.3	3.4	2.0	242.9
	B	23.0**	4.8	9.2	6.5	1.0	38.8	20.7	733.3
		$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
Total CPIB		4.6	0.7	6.8	1.5	0.6	23.4	10.6	134.0
		19.0	4.7	46.1	6.9	0.9	29.3	17.0	794.5
		$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
	A	8.5	1.2	9.3	3.2	0.6	10.2	8.7	381.7
	B	26.4	4.8	57.3	5.6	1.4	22.6	9.8	973.8
		$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
		6.8	1.6	27.5	2.7	0.5	6.4	2.6	390.4

A: Fasting state

B: Fed state

**: $P < 0.01$

Discussion

The pharmacokinetic parameters of CPIB obtained in the study reported here are in agreement with those previously reported after clofibrate administration, the ethyl ester of clofibric acid (Gugler & Hartlapp, 1978; Gugler *et al.*, 1979; Faed & McQueen, 1979). It is reported that about 5–20% of the dose administered is excreted in urine as the unchanged compound and the glucuronide accounts for 80–85% of the dose ingested (Houin, 1975; Gugler, 1978). In the present study, we observed that the total excretion in the urine was only 46–57% of the dose administered. It is not clear why this is so but it is possible that the hydrolysis of the parent compound in the body may not have been complete, in which case one would have probably expected the parent compound in the plasma or urine. However, our attempts to measure the PCP of CPIB in plasma or urine failed to detect any of this parent compound. We found that CPIB had a mean half-life of 26 h and therefore one would expect a major part of the drug to be eliminated in about 5 days time and completely in 7 days time. But in the present study we observed that only about 50% elimination occurred in 5 days time, thereby suggesting that the absorption of CPIB was incomplete. It may therefore be reasonably concluded that the absorption of CPIB was only 50–60% of the dose given. As a result, the V calculated assuming complete absorption would be an overestimate. In the study reported here V calculations made this way indicated no differences between the two experimental conditions.

The most important observation, however, made in this study is that the $C_{\max}$ of CPIB administered with food was significantly higher as compared to that of the fasting state. This is probably because of the high lipophilicity of the drug and the fatty nature of the breakfast provided to the volunteers. It has earlier been reported (Welling, 1977) that the rate of absorption of griseofulvin, another lipophilic drug, was accelerated by the presence of fat in the stomach. It has been hypothesized that dissolution of griseofulvin in the gastro-intestinal tract was greater due to the presence of fat, thereby aiding the absorption of this drug. A similar explanation could be offered for the increased absorption of CPIB in the present study.

The higher urinary excretion of CPIB in volunteers who ingested the drug with food, though not statistically significant because of large interindividual variations, supports the concept of an increased absorption as indicated by $C_{\max}$ concentrations.

Even though the differences in plasma concentrations of CPIB administered with and without food were not marked, it is most likely that these differences would be much greater during chronic administration. In fact, simulation studies that we carried out showed that when CPIB is administered on a long term basis with food, the steady plasma concentrations are two times higher than those seen when CPIB is administered in a fasting state.

The renal clearance of CPIB was found to be quite low and ranged from 7–10 ml/min. It is well documented for such low clearance drugs that the saturation of the plasma protein binding

mechanism has an important influence on the clearance and as a result the clearance may be observed to be non-linear at high plasma concentrations (Rowland *et al.*, 1973). CPIB is a drug mainly bound to serum albumin and therefore it may be assumed, taking into account the molecular weights of albumin and CPIB, that for concentrations higher than 50 mg/l the binding of CPIB to human serum albumin would be saturated (Tillement *et al.*, 1974). This, in fact, has been confirmed in studies with humans by Gugler *et al.* (1978). In the present study concentrations of CPIB never exceeded 25 mg/l thereby suggesting that the plasma protein binding may

not have been saturated. It may, therefore, be argued that the clearance of CPIB would be linear with the dosage employed and therefore simulation studies as carried out are justified.

The renal clearance calculated from the urinary excretion data also supports the concept of a linear elimination of CPIB as shown in Figure 2.

It may therefore be concluded, that the absorption of CPIB is greater when taken with a fatty meal because of the high lipophilicity of this drug and that the elimination of CPIB is linear with the dosage employed.

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