THE INFLUENCE OF FOOD ON THE ORAL AND INTRAVENOUS PHARMACOKINETICS OF A HIGH CLEARANCE DRUG: A STUDY WITH LABETALOL

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- 1 The effects of food on the pharmacokinetics of orally and intravenously administered labetalol were assessed in six healthy volunteers.
- 2 Food caused a 38% increase in the mean systemic bioavailability of labetalol: from 0.26 ± 0.03 (mean $\pm$ s.e. mean) to 0.36 ± 0.05 ($P < 0.05$).
- 3 Food caused 20% increases in the volume of distribution of labetalol: (from 567 ± 63 to 685 ± 76) and in plasma clearance (from 1923 ± 417 to 2344 ± 566 ml/min. These changes did not reach statistical significance. Food did not alter the plasma half-life of labetalol after oral or intravenous dosing.
- 4 Food appears to increase labetalol bioavailability by decreasing its first pass metabolism. It is suggested that this change results from transient alteration of hepatic blood flow. The drug should therefore be taken at a standard time in relation to meals to minimise intraindividual variation in bioavailability.

Introduction

Recently it has been shown that food increases the plasma concentrations of certain drugs which are known to be completely absorbed in the fasting state, e.g. propranolol, metoprolol (Melander *et al.*, 1977b), labetalol (Mantyla *et al.*, 1980) and hydralazine (Melander *et al.*, 1977a). These drugs when given orally undergo significant first pass metabolism (pre-systemic elimination) and the higher plasma concentrations associated with food have been ascribed to a change in the proportion so metabolised (Melander, 1978). However, this hypothesis is based largely on changes observed after oral administration of these drugs. The absence of data following intravenous administration does not exclude changes in distribution volume, or clearance, or both to account for the elevated drug concentrations associated with food. Valid measurement of systemic bioavailability and thus first pass effect requires kinetic data following both modes of administration.

In the present study we have used labetalol as a model drug to investigate this phenomenon. Labetalol is a combined α - and β -adrenoceptor antagonist which is completely absorbed from the gut and undergoes first pass metabolism (Homeida *et al.*, 1978; Martin *et al.*, 1976).

Methods

Four male and two female healthy subjects took part in this study which was approved by the hospital ethics committee. They were aged between 20 and 24 years and none smoked or was on any medication. Each subject was randomly allocated to each of four treatments which were carried out at 1 week intervals. These were (i) labetalol 200 mg orally after an overnight fast, (ii) labetalol 0.5 mg/kg body weight by intravenous injection after an overnight fast, (iii) labetalol 200 mg orally immediately following a standard breakfast, and (iv) labetalol 0.5 mg/kg body weight by intravenous injection immediately following a standard breakfast.

The standard breakfast consisted of one 'Weetabix', 100 ml milk, one boiled egg, one slice of bread, 10 g marmalade, 7 g butter and 150 ml orange juice. The energy value was 1.7 mega-Joules (400 kcal). Coffee and tea were specifically avoided.

The subjects remained supine during the 6 h study period, except while eating or drinking. Venous blood samples (5 ml each) were collected into heparinised tubes via a forearm cannula before the dose of labetalol and 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 300 and 360 min after the dose. Plasma samples were frozen at -20°C for subsequent analysis.

of labetalol by a spectrofluorometric method (Martin *et al.*, 1976). This assay was sensitive down to 15 ng/ml of labetalol. Food related lipaemia did not interfere with the assay of labetalol. Heart rate and blood pressure were measured in the supine position before the dose and half-hourly for 4 h, then hourly for a further 2 h.

Calculations

The plasma half-life ($t_{1/2}$) of labetalol was calculated from least squares regression analysis of the terminal exponential log plasma concentration-time profile. The area under the plasma concentration-time profile (AUC) was calculated as follows: the area up to the end of sampling (X) was calculated using the trapezoidal rule; subsequent area extrapolated to infinity (Y) was calculated from regression analysis of the terminal log concentration-time slope. Total AUC was X plus Y.

The apparent volume of distribution of labetalol (V) and the clearance of labetalol were calculated as follows from data following intravenous administration:

$$\text{Clearance} = \frac{\text{dose i.v.}}{\text{AUC i.v.}}$$

$$V = \frac{\text{dose i.v.} \times t_{1/2}}{\text{AUC i.v.} \times 0.693}$$

where dose i.v. was dose given and 0.693 a constant, systemic (absolute) bioavailability was calculated as

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{dose i.v.}}{\text{dose oral}}$$

and expressed as a ratio.

Student's *t*-test for paired data was used for statistical analysis.

Results

Labetalol caused transient scalp tingling in three subjects after both routes of administration. There were no other adverse effects.

Composite drug concentration *v* time plots are shown in Figures 1 and 2. The biexponential decay in plasma labetalol concentration after intravenous administration was similar in the fasting state and after food.

The pharmacokinetic measurements are summarised in Table 1. There was a significant 11% increase in the mean AUC oral after food. The mean AUC i.v. was less after food than in the fasting state. Mean *aVd* increased by 21% and mean plasma clearance increased 20% after food though these did not achieve statistical significance. There was no change in the oral and intravenous $t_{1/2}$ of labetalol following food.

Figure 1 Plasma labetalol levels (mean $\pm$ s.e. mean) in six healthy volunteers following administration of 200 mg orally (●) and 0.5 mg/kg body weight intravenously (○) in the fasting state.

Figure 2 Plasma labetalol levels (mean $\pm$ s.e. mean) in six healthy subjects following administration of 200 mg orally (●) and 0.5 mg/kg body weight intravenously (○) after a standard meal.

The mean systemic bioavailability increased 38% compared to the mean fasting value.

The mean ($\pm$ s.e. mean) time to peak concentration of labetalol ($t_{\max}$) after oral dosing was 85 ± 17 min in the fasting state and 125 ± 9 min when

Table 1 The influence of food on the pharmacokinetics of labetalol in six normal subjects (mean $\pm$ s.e. mean)

	Half-life (min)		Volume of distribution (l)	Plasma clearance (ml/min)	AUC (ng ml ⁻¹ min)		Systemic bioavailability
	oral	i.v.			oral	i.v.	
Fasting	184 $\pm$ 28	214 $\pm$ 28	567 $\pm$ 63	1923 $\pm$ 417	36032 $\pm$ 10480	23986 $\pm$ 4307	0.26 $\pm$ 0.03
After food	182 $\pm$ 34	217 $\pm$ 29	685 $\pm$ 76	2344 $\pm$ 566	40085 $\pm$ 11448	19887 $\pm$ 1412	0.36 $\pm$ 0.05
Significance (<i>P</i> value)	NS	NS	0.08	0.16	< 0.05	0.02	< 0.05

labetalol was taken after food ($P = 0.1$). The mean ($\pm$ s.e. mean) peak concentrations of labetalol ($C_{\max}$) after oral dosing were 182 ± 57 ng/ml and 180 ± 33 ng/ml in the fasting state and after food respectively.

Supine heart rate and blood pressure were only slightly lower following oral dosing after food and returned to baseline values by 6 h. There were no statistically significant differences in absolute systolic and diastolic blood pressure and heart rate when labetalol was given after food compared to the fasting state. However when changes in these parameters

were examined, there was a greater reduction in systolic blood pressure and heart rate when labetalol was given following food. Food did not appear to influence the reductions in diastolic blood pressure associated with labetalol (Figures 3 and 4).

Discussion

We have confirmed the food associated increase in oral AUC previously reported by Mantyla *et al.*

Figure 3 Mean ($\pm$ s.e. mean) fall in supine systolic and diastolic BP and pulse rate in six healthy subjects following labetalol 200 mg orally in the fasting state ($\square$) and following a standard meal ($\blacksquare$).

Figure 4 Mean ($\pm$ s.e. mean) fall in supine systolic and diastolic BP and pulse rate in six healthy subjects following labetalol 0.5 mg per kg body weight intravenously in the fasting state ($\square$) and following a standard meal ($\blacksquare$).

(1980) and also the prolongation in $t_{\max}$ noted by these workers. However, the present study does not confirm the decrease in $C_{\max}$ reported by Mantyla and colleagues (1980). They showed a food associated fall in mean $C_{\max}$ from 134 ng/ml to 105 ng/ml, though it was not statistically significant. The present study clearly shows that food increases the absolute systemic bioavailability of labetalol. In addition it shows that a food related change occurs in the pharmacokinetics of labetalol given intravenously, i.e. a significant decrease in $AUC_{i.v.}$ with a trend towards an increase in V and plasma clearance.

Ingestion of food is known to cause a rise in splanchnic and hepatic blood flow, which is in part determined by the type of food consumed (Brandt *et al.*, 1955). Food related changes in hepatic blood flow have not been demonstrated in man later than 1 h after a meal. In dogs and primates hepatic blood flow may remain raised for 3–7 h (Vatner *et al.*, 1970, 1974).

In man, estimated hepatic blood flow in the supine position at rest is about 1 l/min (Daneshmend *et al.*, 1981) and hepatic plasma flow about 600 ml/min. However, in the present study in normals and other studies in patients with hypertension (McNeil *et al.*, 1979) and in cirrhotics (Homeida *et al.*, 1978) the plasma clearance of labetalol has been noted to be at least twice as much as hepatic plasma flow. This suggests that in man there is considerable extra hepatic clearance of labetalol. Very little (< 5%) labetalol is excreted unchanged in the urine in man (Mantyla *et al.*, 1980; Martin *et al.*, 1976), therefore the kidney is probably not a major site of extra hepatic labetalol clearance. The major metabolites of labetalol in man are glucuronides (Martin *et al.*, 1976; Richards & Prichard, 1979) and are devoid of pharmacological activity. The site(s) of extra hepatic and extra renal labetalol clearance in man are not known though animal work suggests the gut wall may probably be the most important (Hopkins *et al.*,

1976). It is known that total splanchnic blood flow (of which hepatic blood flow is a component) increases with food (Vatner *et al.*, 1970, 1974; Rowell, 1974) and this may account for the food related increase in total labetalol plasma clearance noted in the present study.

Labetalol, like metoprolol and propranolol is a high clearance drug and its clearance is in part dependent on hepatic blood flow. It has been suggested (Kornhauser *et al.*, 1978) that changes in hepatic blood flow would not, in theory, be expected to alter the bioavailability of high clearance drugs. In contrast, McLean *et al.* (1978) have explained the observed increase in propranolol and metoprolol bioavailability with food in terms of transient increases in hepatic blood flow caused by food. However, their evidence was based on computer simulations of such changes in hepatic blood flow. Recently these workers (Elvin *et al.*, 1981) have shown the validity of their concepts by demonstrating a food related increase in the clearance of intravenously administered lignocaine in normal subjects. Elvin *et al.* (1981) also found that the meal did not influence lignocaine serum protein binding.

Data from the present study support the hypothesis of McLean *et al.* (1978) of a transient increase in hepatic blood flow with food as the mechanism underlying increased bioavailability. A transient increase in hepatic blood flow caused by food would tend to decrease the extraction ratio and result in decreased first pass metabolism and increased systemic bioavailability of orally administered labetalol. Return to the hepatic blood flow to normal would prevent a sustained increase in systemic clearance and result in AUC_{oral} being greater with food but without a change in $t_{1/2}$. Similarly, a transient increase in hepatic blood flow would result in a food related decrease in initial $AUC_{i.v.}$. Return of the hepatic blood flow to normal would result in no

alteration of $t_{1/2}$ but a smaller total $AUC_{i.v.}$ with food.

Changes in supine blood pressure and heart rate following oral labetalol have been shown not to correlate with plasma labetalol concentrations (McNeil *et al.*, 1979), though Richards *et al.* (1977) found a linear correlation between plasma concentrations and the degree of inhibition of exercise tachycardia 2 h after an oral dose. In the present study food did not significantly alter the effects of labetalol on heart rate and blood pressure despite the observed changes in labetalol pharmacokinetics. We may have noted greater changes had we assessed β -adrenoceptor antagonism by attenuation of exercise induced tachycardia, and in view of the α -adrenoceptor blocking property of labetalol examined the effect on blood pressure in the erect posture. However our study was designed to minimise changes in hepatic blood flow except those caused by food. Changes in exercise and posture both cause alterations in hepatic blood flow (Daneshmend *et al.*, 1981) and would have been confounding variables in the present study. Such incidental changes in hepatic blood flow were minimised by keeping the subjects supine throughout the study period and avoiding coffee, tea and tobacco.

It is of interest that a number of drugs used in the treatment of hypertension undergo first pass metabolism, e.g. alprenolol, labetalol, metoprolol, propranolol and hydralazine. There is considerable interindividual variability in first pass metabolism which therefore increases the need for individualisation of the dosage of such drugs in clinical practice. Our study has shown that food may also increase this variability. On the basis of the findings of the present study we would recommend that labetalol should be taken in a standard relation to meals so as to lessen variability within the same individual in terms of bioavailability and, possibly, therapeutic efficacy.

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