BIOAVAILABILITY OF CONVENTIONAL AND SLOW-RELEASE OXPRENOLOL IN FASTED AND NONFASTED INDIVIDUALS

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- 1 The influence of food on plasma levels of oxprenolol was examined in healthy female volunteers using both conventional and slow-release formulations.
- 2 There were no significant trends in plasma drug profiles due to food with either formulation. Elimination half-lives were longer after food with conventional tablets, presumably due to continued absorption. The opposite effect was seen with slow-release tablets.
- 3 Slow-release oxprenolol is, under the conditions of this study, a reliable and convenient dosage form, providing similar plasma-drug profiles in fasted and nonfasted individuals.

Introduction

The absorption of orally dosed drugs may be increased, reduced, delayed or unaffected when they are taken with food (Welling, 1977). The outcome depends partly on the drug but also on other factors including the nature of the food and the time elapsed between eating and drug ingestion. The influence of food depends also on the type of formulation used. This factor has been studied extensively with various erythromycin products, and the results indicate that absorption may be affected differently when drug is administered as a conventional tablet, coated preparation, capsule, or a suspension (Josselyn & Sylvester, 1952; Smith, Dyke & Griffith, 1953; Clapper, Mostyn & Meade, 1960; Griffith, Joiner & Kottowski, 1960).

One of the current developments in drug therapy, particularly for drugs taken over long periods, is directed towards once daily administration in the form of slow-release preparations. It is therefore of interest to know how food will affect the absorption of these and whether the influence of food on slow-release preparations is the same as on conventional dosage forms.

Slow-release oxprenolol (Slow Trasicor) is a preparation in which the active ingredient is embedded in a wax matrix from which it is slowly released to yield sustained plasma levels and a β -adrenoceptor blocking action which persists for 24 h (West, Kendall, Mitchard & Faragher, 1976). In the present study, plasma levels of oxprenolol were compared following single oral doses of slow-release (Slow Trasicor) and also conventional (Trasicor) oxprenolol

tablets to fasted subjects, or to the same subjects following a standard breakfast.

Methods

Subjects

The subjects were nine healthy female volunteers aged between 18 and 24 years (mean 20 years), weighing between 52 and 65 kg (mean 58 kg). All subjects were clinically well and had normal blood biochemistry. Details of the study, which had been approved by the Hospital ethical committee, were explained to each subject and written consent was obtained.

Protocol

Subjects were instructed to take no drugs other than required oxprenolol doses during the study. Drug was administered as the following treatments at intervals of at least 1 week using a single-blind crossover design:

1. One conventional tablet, 80 mg, with 100 ml water on an empty stomach.
2. One conventional tablet, 80 mg, with 100 ml water immediately following a standard breakfast.
3. One slow-release tablet, 160 mg, with 100 ml water on an empty stomach.
4. One slow-release tablet, 160 mg, with 100 ml water immediately following a standard breakfast.

Figure 1 Mean plasma levels of oxprenolol following ingestion of a) conventional (80 mg) and b) slow-release (160 mg) formulations after fasting (●) and after a standardized breakfast (○).

The standard breakfast consisted of one teacupful of cornflakes, two rounds of medium sliced toast, two pats of butter, two teaspoons of marmalade, 300 ml milk, two cups of tea, plus a small quantity of sugar if required.

Subjects fasted overnight before each treatment and ate no food, apart from test meals, until 3.5 h after dosing. Drinks were allowed at 2 and 5.5 h after dosing.

On the morning of a study, approximately 09.00 h, a cannula was inserted into a forearm vein and connected by a three-way tap to an intravenous infusion apparatus. Normal saline was slowly infused during the first 6 h postdosing. Blood samples (10 ml) were taken into lithium heparin tubes via the three-way tap, taking care not to dilute the samples with saline, immediately before at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 h after dosing.

Plasma was promptly separated and deep frozen until analyzed. Subjects rested supine during the first 6 h. Cannulae were then removed and the subjects allowed up. Subsequent blood samples were obtained by venepuncture.

Analysis of samples

The concentration of oxprenolol in plasma was determined by the method of Degen & Riess (1976). As indicated previously (Kendall, Brown & Yates, 1977), this method detects oxprenolol levels of 5 ng/ml and is accurate within $\pm 7\%$ at 10 ng/ml.

Statistical analysis

Plasma oxprenolol levels and also pharmacokinetic parameters obtained from the crossover study were

Table 1 Pharmacokinetic values (mean $\pm$ s.e. mean) for oxprenolol

Value	Conventional oxprenolol (80 mg)		Slow-release oxprenolol (160 mg)	
	Fasting	Food	Fasting	Food
C_{max} (ng/ml)	470 $\pm$ 46	462 $\pm$ 59	503 $\pm$ 126	490 $\pm$ 63
Range	250–739	204–684	241–1349	283–722
t_{max} (h)	1.6 $\pm$ 0.2	2.2 $\pm$ 0.3	2.6 $\pm$ 0.3	3.3 $\pm$ 0.4
Range	0.8–2.5	1.0–4.0	1.5–4.0	1.5–5.0
AUC (ng h ml) ¹	1590 $\pm$ 170	1630 $\pm$ 240	3110 $\pm$ 510	3130 $\pm$ 540
Range	880–2460	750–2870	1450–5330	1380–5810
$T_{1/2}$ (h) ²	1.4 $\pm$ 0.2	1.7 $\pm$ 0.2	3.3 $\pm$ 0.4	2.5 $\pm$ 0.4
Range	0.8–2.4	1.1–2.6	2.0–6.1	1.1–5.1

¹ Area under plasma oxprenolol curve from 0 to 24 h, calculated by trapezoidal rule.

² Elimination half-life of oxprenolol calculated from linear portion of plasma curve, up to 24 h.

compared between treatments using the Wilcoxon Matched Pairs Signed-Rank test (Von Fraunhofer & Murray, 1976), and also by paired *t*-test. The paired *t*-test produced essentially identical results to the Wilcoxon test, and only the latter values are reported.

Results

Mean plasma levels of oxprenolol resulting from the four dosages are shown in Figure 1. Mean values of maximum drug concentrations in plasma, $C_{\max}$, observed times of maximum concentrations, $t_{\max}$, areas under plasma oxprenolol profiles from zero to 24 h after dosing, AUC, and elimination half-lives, $T_{1/2}$, are given in Table 1. Although it has been possible to describe the pharmacokinetics of oxprenolol in terms of a three-compartment model after rapid intravenous doses (Kendall, Mitchard, West, John & Ebbutt, 1976) with both intermediate and terminal elimination phases, only a single elimination phase could be calculated from the relatively few data points in the post-absorptive phase in this study.

Plasma levels from both the conventional and slow-release formulations were similar in fasted and nonfasted subjects. Following the conventional dose, food caused a significant ($P < 0.05$) decrease in plasma drug levels at 3 h and a significant increase at 12 h. Following the slow-release dose, food caused a significant decrease in levels at 2 h only.

No significant differences were observed in $C_{\max}$ or AUC values between fasting and nonfasting doses. Although $t_{\max}$ values tended to be larger after nonfasted doses, the differences were not significant. The elimination half-life from conventional doses was slightly but significantly ($P < 0.05$) increased by food, presumably because of continued drug absorption. Elimination half-lives of oxprenolol were prolonged following the slow-release dosages, but more so in fasted than in nonfasted individuals.

Discussion

The above results indicate that the absorption of oxprenolol from both conventional and slow-release formulations is essentially unchanged by the presence of food. The negligible effect of food with conventional tablets is consistent with observations of Shand, Nuckolls & Oates (1970) with propranolol, but not with those of Melander, Danielson, Schersten & Wahlin (1977) with propranolol and metoprolol. The latter authors reported increased absorption of both compounds in the presence of food. However, it is difficult to compare the results from these studies as the standard meal used by Melander *et al.* (1977)

differed from that used by us, while the type of meal used by Shand *et al.* (1970) was not described. Different types of meals are known to have varied effects on the absorption of some drugs (Welling, 1977).

The apparent slower elimination of oxprenolol from plasma following the slow-release formulation compared to the conventional preparation, is clearly due to prolonged drug absorption.

In the case of the slow-release preparation, the faster elimination of oxprenolol from plasma in nonfasted subjects may be related to delayed stomach emptying. Prolonged residence in the acidic environment of the stomach will facilitate dissolution of the basic oxprenolol molecule, although the dissolved drug will be ionized and poorly absorbed. Stomach emptying will be delayed by food but, when it occurs, a large proportion of the drug will be in solution so that absorption from the relatively alkaline small intestine will occur more readily than in fasted individuals.

The combined effect of delayed stomach emptying, and the passage of predominantly dissolved drug from the stomach into the intestine in the presence of food will tend to delay the $t_{\max}$ and shorten the apparent elimination half-life. The $t_{\max}$ was delayed somewhat by food, but differences in this value between fasted and nonfasted subjects were not significant.

The above argument appears not to apply in the case of conventional tablets, where food caused a small but significant relative increase in the apparent drug half-life. It is probable that, with the conventional formulation, drug dissolution is sufficiently rapid in both fasted and nonfasted individuals that the only observed effect is that of delayed stomach emptying reducing the rate of drug absorption, this causing a small artifactual increase in the drug half-life in nonfasted subjects.

The plasma levels of oxprenolol in this study are generally lower than those obtained earlier in healthy male volunteers (West *et al.*, 1976). However the possibility of a sex linked difference in oxprenolol pharmacokinetics is thought to be unlikely as the levels obtained from the conventional dosage form here are comparable to those obtained in studies in male (Kendall *et al.*, 1976) and mixed female and male (Mason & Winer, 1976) volunteers.

The results obtained in this study, together with those described earlier in fasted subjects (West *et al.*, 1976) indicate that the presence of food does not materially influence the bioavailability of oxprenolol from conventional and slow-release formulations. The latter dosage form would be convenient to use, particularly when chronic oxprenolol therapy is indicated.

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