Influence of food on the absorption of metoprolol administered as an Oros drug delivery system to man

J. B. LECAILLON¹, P. MASSIAS², J. P. SCHOELLER¹ & F. ABADIE¹

¹Biopharmaceutical Research Centre, Ciba-Geigy, BP 308, 92506 Rueil Malmaison Cedex, France, and ²Hôpital de Bicêtre, 94270 Le Kremlin Bicêtre, France

1 The influence of food on the release, absorption and metabolism of metoprolol has been studied after single administration of a 19/190 Oros system to eight healthy volunteers on four occasions, once after an overnight fast, and just before each of three daily meals (breakfast, lunch and dinner).

2 The plasma concentration-time profiles under the four test conditions were virtually identical, and no statistically significant differences in mean areas under the curves between 0 and 32 h, peak concentrations, or times to peak, were detected.

3 The absorption of metoprolol was unaffected by food intake, with 80–90% of the amount absorbed reaching the systemic circulation within 10 h.

4 The ratios of areas under the curve for α -hydroxymetoprolol to its parent drug were in the same range for the four treatments, and similar to those reported after conventional tablets.

5 The *in vivo* release and absorption of drug from the Oros system, and its systemic availability, were not influenced by concomitant ingestion of food.

Keywords metoprolol 19/190 Oros formulation food drug absorption

Introduction

Food intake may have a profound influence on the systemic concentrations of orally administered drugs. Changes in, for example, the rate of gastric emptying, intestinal motility and intraluminal pH may affect not only the dissolution of the drug from the dosage form, but also its rate and extent of absorption. Food may increase the systemic availability of high clearance drugs by reducing their first-pass metabolism. This effect appears to result from a transient, food-induced increase in splanchnic and hepatic blood flow during the time when the drug is being absorbed. However, since blood flow is elevated for only a relatively short period after food (Svensson *et al.*, 1983), its influence on drug absorption from dosage forms with extended durations of release may be negligible. The bioavailability of metoprolol was enhanced by roughly 40% when a conventional tablet was given after a meal (Melander *et al.*, 1977). However, the influence of food on the *in vivo* perfor-

mance of, and extent of drug absorption from, an Oros system has not previously been assessed.

Metoprolol is totally absorbed after oral administration but is subject to significant first-pass metabolism (Regårdh & Johnsson, 1980). The extent of this first-pass loss varies with size of the administered dose, indicating possible saturation of hepatic and gut-wall metabolism by high drug concentrations (Kendall *et al.*, 1977). Any change in the extent of metabolism should be reflected in an altered ratio of areas under the curve for the parent drug to its principal plasma metabolite, α -hydroxymetoprolol (Hoffman *et al.*, 1980). The influence of the reduced rate of delivery from the Oros preparation on the metabolism of metoprolol has also not been previously measured.

This study had three distinct aims: (1) to assess the influence of food administered on the *in vivo* performance of the metoprolol Oros system; (2) to ascertain if the systemic availability of meto-

prolol from the Oros system was enhanced by food intake; and (3) to determine whether or not the reduced rate of drug delivery from Oros, compared with that of the conventional formulation, altered the degree of conversion of metoprolol to its α -hydroxy metabolite.

Methods

Procedure

Eight healthy volunteers (one female, seven males) aged 21–36 (mean 26) years participated in a four-period crossover experiment. One Oros tablet containing 190 mg metoprolol fumarate (equivalent to 200 mg metoprolol tartrate) with a constant initial release rate of 19 mg/h *in vitro* was administered with 100 ml of mineral water on four separate occasions: in the morning following an overnight fast, or at different times during the day just before one of three meals (breakfast, lunch and dinner). The timing of meals, as well as food and liquid intake, were carefully standardized for 32 h after dosing; the interval between breakfast and lunch was 4 h, between lunch and dinner 7 h, and between dinner and breakfast the following morning 13 h. The energy equivalent of the food given over the study period was roughly 3000 calories/day. The four Oros treatments were each separated by a 2-week drug-free period, and the subjects were asked to take no drug besides metoprolol during the investigation.

Venous blood samples (6 ml) were collected before, and at specified times after drug administration over a 32 h period; the same sampling regimen was followed on each of the four occasions irrespective of the time of day when the Oros system was administered. The samples were placed into heparinized tubes, centrifuged and the plasma stored at -20°C until analysed.

Analytical procedure

Plasma concentrations of metoprolol and α -hydroxymetoprolol were determined by high-performance liquid chromatography (Lecaillon *et al.*, 1984). The determinations were performed in duplicate, the limit of quantitation being 10 ng/ml for each component.

Results and discussion

Plasma metoprolol concentrations

The mean concentration-time profiles obtained under each treatment condition are shown in

Figure 1 Mean plasma metoprolol concentrations (expressed as metoprolol tartrate) after administration of an Oros system fasting (●—●), before breakfast (■—■), before lunch (□—□), and before dinner (△—△), to eight healthy volunteers.

Figure 1. The profiles followed the expected time course for an Oros system with an extended duration of drug release, in that plasma concentrations increased gradually for around 10 h before decreasing at a rate which was slower than the normal elimination rate for metoprolol. Under all four conditions measurable plasma concentrations were still observed 32 h after dosing with the Oros system.

No marked influence of food on the time course or magnitude of the metoprolol concentration profiles could be detected. There was no evidence to suggest that longer gastric retention of the system, which could have occurred after food, had any influence on the onset of initial rate of drug absorption. This result was not unexpected since drug release from Oros should occur at the normal rate in the stomach (Theeuwes *et al.*, 1985), and gastric emptying of drug solutions appears to be little affected by food. Similarly, administration of the Oros system at different times during the day had no effect on the plasma profile, suggesting the absence of any diurnal variation in the pharmacokinetic behaviour of metoprolol given in this dosage form.

The calculated pharmacokinetic parameters for each subject are given in Tables 1 and 2. No significant differences were detected between treatments for peak concentrations or times to peak. A comparison of the AUC (0–32 h) values following each treatment regimen, using the Westlake test for bioequivalency (Westlake, 1972), indicated a maximum difference of less than 20% (95% confidence limits) between fed and fasting subjects. The amount of drug reaching the circulation after Oros was thus little altered by food, in contrast with the marked increase noted by Melander *et al.* (1977) for the conventional tablet. This discrepancy is probably

Table 1 Maximal plasma metoprolol concentrations ($C_{\max}$) and times to peak ($t_{\max}$) after administration of 19/190 metoprolol Oros with different meals. All concentrations are expressed in terms of metoprolol tartrate.

Subject	Without food		With breakfast		With lunch		With dinner	
	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)
1	39.0	4.0	24.2	12	20.7	3	19.5	8
2	129	8.0	132	6	125	10	95.1	8
3	120	10.0	107	8	116	10	105	10
4	81.7	10.0	87.2	6	82.8	8	85.5	6
5	127	6.0	141	12	137	8	192	10
6	33.5	6.0	46.5	6	38.6	10	35.2	8
7	58.5	10.0	62.2	8	44.5	8	53.7	6
8	70.5	10.2	90.3	8	83.4	8	113	10
Mean	82.4		86.3		81		87.4	
s.d.	38.8		40.6		43.2		54.0	
Median		9		8		8		8

a consequence of the transient nature of the food-induced increase in splanchnic and hepatic blood flow (< 4 h; Svensson *et al.*, 1983), and its relationship to total absorption times for the conventional and Oros preparations (2.5 h and 14 h for 90% absorption, respectively; Godbillon *et al.*, 1985).

Drug absorption kinetics

The absorption kinetics of metoprolol were investigated using the method of Gerardin *et al.* (1983) which assumes that disposition kinetics can be described by an open two-compartment model, as reported for metoprolol by Jordö *et al.* (1980). The results are expressed as cumulative percentages of the total amount absorbed, and thus indicate the rate, but not the extent, of absorption. In the present study the absorption profiles after Oros administration (Figure 2) were similar for each test condition. The profiles

showed that metoprolol was continuously absorbed, with 80–90% of the total fraction reaching the systemic circulation within 10 h, irrespective of whether the system was taken fasting or with food.

The absorption rate was virtually constant between 1 and 10 h after dosing, although a slight increase in rate occurred in response to the meal given several hours after administration of the Oros system, as indicated in Figure 2. When no meal was taken during the absorption phase, for example, when the Oros system was administered with dinner and the next meal (breakfast) was not given until 13 h later, no inflexion in the curve was observed (Figure 2d).

These results indicate that *in vivo* performance of the Oros system was little affected by the ingestion of food.

Extent of drug metabolism

The plasma concentration/time profiles for the α -hydroxy metabolite of metoprolol are shown in Figure 3, and the pharmacokinetic constants calculated from the plasma level data are given in Tables 3 and 4. The profiles under each treatment condition exhibited no obvious differences, and the amounts of metabolite in plasma as judged from the AUCs were similar, and comparable to those recorded for the parent drug (see Tables 2 and 4). The mean total AUC for the α -hydroxy metabolite was 1.1 times that for metoprolol, which is similar to the value of 0.9 recorded in subjects of the same age given the conventional tablet formulation (Quarterman *et al.*, 1981).

Thus, the considerable difference in the rate of drug release from an Oros system, compared with that from a standard tablet, does not appear to influence the extent of conversion of metoprolol to its α -hydroxy metabolite.

Table 2 Area under the plasma concentration-time curve from 0–32 h (AUC) for metoprolol after administration of 19/190 metoprolol Oros with different meals.

Subject	AUC (ng ml ⁻¹ h)			
	Without food	With breakfast	With lunch	With dinner
1	306	390	285	302
2	2001	1720	1843	1553
3	1522	1320	1344	1279
4	1183	1142	1033	1070
5	2073	2216	2038	2004
6	506	557	575	380
7	763	728	292	523
8	1077	1176	1070	1368
Mean	1179	1156	1060	1060
s.d.	654	609	663	610

Figure 2 *In vivo* absorption profiles, plotted as the percentage of the total amount absorbed vs time after administration of the Oros system fasting (a; ●), before breakfast (b; ■), before lunch (c; □), and before dinner (d; △) to eight healthy volunteers. The timings of meals after dosing are indicated by arrows.

Figure 3 Plasma α -hydroxymetoprolol concentrations (expressed in terms of metoprolol tartrate concentration) after administration of an Oros system fasting (●—●), before breakfast (■—■), before lunch (□—□), and before dinner (△—△), to eight healthy volunteers.

Oros system performance

The results of this study indicate that the *in vivo* performance of the Oros system was not modified by the time of subsequent food intake, and that Oros preparations administered to subjects either fasting or concomitantly with food exhibited the same systemic availability. The performance of the Oros system, which releases drug over an extended time interval, is influenced less than a conventional tablet by the transient physiological changes associated with the ingestion of food, and no special dosage recommendations would appear to be necessary with this preparation. The results for the main plasma metabolite also show that metabolism during absorption appears to be unaffected by the slow delivery of the drug from the Oros dosage form.

Table 3 Maximal α -hydroxymetoprolol plasma concentrations ($C_{\max}$) and times to peak ($t_{\max}$) after administration of 19/190 metoprolol Oros with different meals. All concentrations are expressed in terms of metoprolol tartrate.

Subject	Without food		With breakfast		With lunch		With dinner	
	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)	$C_{\max}$ (ng/ml)	$t_{\max}$ (h)
1	70.8	4	66.7	12	71.1	12	88.2	10
2	71.8	12	82.1	10	74.9	10	67.0	15
3	48.6	10	48.9	12	57.8	12	60.2	10
4	40.7	12	43.8	12	44.1	10	51.3	8
5	66.7	8	82.1	12	73.9	15	94.1	10
6	70.1	10	56.4	6	68.7	12	57.1	10
7	67.0	10	52.7	10	31.3	8	62.9	6
8	64.3	15	67.0	12	73.2	10	83.4	10
Mean	62.5		62.5		61.9		70.5	
s.d.	11.5		14.5		16.2		15.9	
Median		10		12		11		10

Table 4 Area under the plasma concentration-time curve from 0–32 h (AUC) for α -hydroxymetoprolol after administration of 19/190 metoprolol Oros with different meals. All values refer to metoprolol tartrate.

Subject	AUC (ng ml ⁻¹ h)			
	Without food	With breakfast	With lunch	With dinner
1	1347	1330	1402	1638
2	1447	1457	1300	1265
3	732	855	834	845
4	735	657	732	828
5	1365	1474	1419	1286
6	1200	1118	1207	838
7	732	838	245	728
8	1221	1183	1064	1361
Mean	1097	1114	1025	1099
s.d.	312	305	403	331

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