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Evaluation of oxprenolol and metoprolol Oros systems in the dog: comparison of *in vivo* and *in vitro* drug release, and of drug absorption from duodenal and colonic infusion sites

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1 The performance of oxprenolol and metoprolol Oros® systems has been evaluated in the dog. One study compared *in vivo* and *in vitro* release from both systems over 2–14 h. The other compared the systemic availabilities of both drugs after 3 h infusion at a constant rate into the cephalic and hepatic portal veins, and into the lumen of the duodenum and colon.

2 In the *in vivo* release studies, Oros systems were recovered throughout the gut from the stomach to the colon. The amounts of drug remaining in the systems corresponded closely to those measured in a parallel *in vitro* release experiment. *In vitro* testing is thus a reliable indicator of *in vivo* system performance.

3 In the absorption studies, both metoprolol and oxprenolol were shown to be subject to substantial first-pass metabolism. Additionally, for metoprolol the data indicated a significant loss during transport from the gut lumen into the portal circulation. For both drugs the availability from the colon was equal to that from the duodenum.

4 These results provide some justification for the development of oral dosage forms with extended durations of release even for drugs which undergo significant first-pass metabolism.

Keywords oxprenolol metoprolol Oros systems dog

Introduction

Repeated twice-daily administration of the β-adrenoceptor antagonists, metoprolol and oxprenolol, in the form of rapid-release conventional tablets, produces considerable fluctuations in blood concentrations over 24 h. For both drugs, peak values are achieved 1–2 h after dosing but subsequent elimination is rapid, and near undetectable levels are present 12 h later (Kendall *et al.*, 1980; Regårdh *et al.*, 1975; Woods *et al.*, 1985).

Recent advances in drug delivery system design are directed towards once-daily dosing with rate-controlled dosage forms which deliver their total content over the greater part of the 24 h dosage interval. This raises new and important issues regarding both the *in vivo* release behaviour of such formulations and the extent of drug absorption from different segments of the gastrointestinal tract. *In vivo* release can only be evaluated if the dosage form can be recovered intact from the gut lumen at various times after dosing. Such studies obviously cannot be performed in man and the use of an appropriate animal model is required.

Absorption studies after oral dosing in man have mostly involved bolus administration of a solution or rapidly dissolving tablet into the stomach. There have been relatively few attempts to measure absorption in other gut segments such as the colon, or to characterize the relative contributions of gut-wall and hepatic metabolism to first-pass elimination of high clearance drugs.

For metoprolol and oxprenolol, elementary

osmotic pump (Oros) systems with the following characteristics have been designed for once-daily administration: (1) 19/190 metoprolol Oros with a total content of 190 mg metoprolol as the fumarate salt, an initial drug delivery rate of 19 mg/h and a total duration of release of 12–15 h; and (2) 16/260 oxprenolol Oros containing 260 mg oxprenolol as the succinate salt, with an initial delivery rate of 16 mg/h and a total release time of 20–24 h. With such extended delivery times, release should occur throughout the greater part of the gut and system performance needs to be evaluated in each segment, including the colon.

The studies reported here were performed in dogs and had the following objectives: (a) to ascertain the location of oxprenolol and metoprolol Oros systems within the gastrointestinal tract at various intervals after dosing, and to verify that the amount of drug delivered agreed with that predicted by *in vitro* testing; and (b) to investigate the absorption of metoprolol and oxprenolol in the upper and lower segments of the intestinal tract.

Methods

Animal selection and preparation

The dog is widely accepted as a suitable model for studying the physiological behaviour of the gastrointestinal tract in man. Indeed, much of our current information on motility and secretion/absorption has come from studies performed in dogs. Thus, for the purposes of evaluating the *in vivo* performance of Oros systems, and of comparing absorption from duodenum *vs* colon, the dog was considered the model of choice.

For all studies, male and female mongrel dogs, weighing 13–20 kg, were conditioned and kept in the animal facilities at least 2 weeks before the experimental period. All were housed indoors in individual concrete cages, and were fed standard meals of Purina Dog Meal with water *ad libitum*.

In vivo *release rate studies*

The relationship between *in vitro* and *in vivo* release can be examined for Oros preparations because the system can be recovered intact from the gut lumen. The semipermeable membrane surrounding the Oros core is not susceptible to degradation by digestive fluids or to contractile forces encountered within the gut, and the integrity of the system is maintained during its transit through the body. In the present study, two groups of four mongrel dogs were fasted overnight and during the study, but were allowed water *ad libitum*. Individually labelled oxprenolol or metoprolol Oros systems were then administered to each dog at 0, 2, 4, 6, 10 and 12 h after the start of the oxprenolol study, and at 0, 2, 4, 6, 8, 10 and 11 h after the start of the metoprolol study. The dogs were then sacrificed at 12–14 h and the systems recovered from their gastrointestinal tracts. By analysing the residual drug in these systems, the amount released was calculated as the difference between initial and residual content.

At the same times as the dogs were dosed, equal numbers of systems were placed in the *in vitro* release apparatus (Theeuwes *et al.*, 1985). These systems were removed at the time the dogs were sacrificed, and assayed for residual drug content using an identical analytical procedure. These results were then compared with those obtained in the *in vivo* experiment. Theoretical curves for release rate or cumulative amounts released were also calculated from the known physicochemical properties of the drug, the physical dimensions of the system, and the permeability characteristics of the membrane (Theeuwes *et al.*, 1985). *In vivo* and *in vitro* performance was evaluated against this predicted behaviour of the system.

Absorption studies

Each dog was surgically prepared with five indwelling catheters inserted into a cephalic vein, the portal vein (via the splenic vein), the mid-duodenum, the mid-colon, and a saphenous vein in a leg. Access by the dogs to the abdominal catheters was prevented by tunnelling the tubes under the skin to emerge in the lower back region, where they were bandaged. At least 7 and usually 10 days were allowed between the surgical procedure and the start of the absorption experiments. Drug was infused by the four routes in each dog in random order at intervals of at least 1 week.

On each of the study days, the dogs were brought to the laboratory in the morning after an 18–24 h fast. Drug was then infused into one of the sites, using the Harvard Infusion Pump, Model 975, which delivered solution at 0.1 ml/min. In all cases the infusion lasted 3 h and the rate was identical to the initial release values for the metoprolol (19 mg/h) or oxprenolol (16 mg/h) Oros systems. The volume delivered from the infusor was considerably greater than that from the Oros preparation, and as such represents an extreme case with respect to drug distribution within the gut relative to mass output.

Blood samples from the saphenous vein were collected in heparinized containers, centrifuged, and the plasma separated. These samples were then stored frozen until analysed.

Drug assays for the *in vitro/in vivo* release comparison and for the absorption studies were performed by a sensitive and specific gas-chromatographic technique based on the published method of Degen & Riess (1976).

Results and discussion

In vivo *release rate studies*

The cumulative amounts of drug released *in vivo* and *in vitro* from the 16/260 oxprenolol Oros systems, together with the site of system recovery in the dog gut, are reported in Table 1. The theoretical amounts released are also given in this table for comparative purposes.

As expected for residence times of 2–14 h, Oros systems were located throughout the gastrointestinal tract from the stomach to the colon. It was therefore possible to assess the performance of the dosage form under all physiological conditions likely to be encountered in the gut. In the zero-order portion (up to 60% of the drug released) the data were within experimental error of the theoretical value. Beyond 60%, additional scatter occurred *in vivo*, possibly due to colonic contractile forces in the lower bowel region. However, the overall agreement of the data suggests that the Oros system functioned *in vivo* in a manner similar to its *in vitro* release behaviour.

A similar comparison was made for 19/190 metoprolol Oros, and the results are given in Table 2. Again *in vivo* and *in vitro* performance agreed closely with the theoretical response. The deviations of individual data points were somewhat larger than in the oxprenolol study during the zero-order phase (0–60% released), but did not increase in the remaining non-zero-order portion. The general agreement between theory and both sets of experimental data shows that the amounts released *in vitro* were again an accurate reflection of *in vivo* performance.

Absorption studies

Mean plasma concentration of oxprenolol succinate after infusion into the cephalic and hepatic portal veins, and into the lumen of the duodenum and colon in four dogs, are shown in Figure 1. All four mean profiles followed the same time course in that levels increased during the infusion period, were maximal at 3 h when the infusion was stopped, and declined rapidly thereafter.

Interestingly the rate of decline appeared to be slower after colonic compared with the other infusion routes, suggesting that absorption continued for some time after stopping drug delivery to this segment of the gut. However, the number of animals investigated was small and this observation needs to be confirmed in a more detailed study before any definite conclusions can be reached concerning the relative absorption rates at the different sites within the gut.

Plasma concentrations were highest after intravenous infusion, progressively lower levels being reached after duodenal, portal vein and colonic drug administration. The mean ± s.e. mean systemic availabilities of oxprenolol succinate (intravenous = 100%), calculated from the areas under the curve between 0 and 12 h, were: duodenum, 50.2 ± 16.9%; colon, 45.1 ± 15.8%; and portal vein, 37.1 ± 13 5%. The similarities in values for the duodenum and colon indicate that oxprenolol is absorbed to the same relative extent at these two sites.

Table 1 Comparison of oxprenolol succinate release *in vivo* and *in vitro* from a 16/260 oxprenolol Oros system. Mean data from four dogs.

	In vivo		In vitro		*Theoretical*	
Residence time (h)	*Location*	*% Release*	*Residence time (h)*	*% Release*	*Residence time (h)*	*% Release*
2.5 ± 0.2	D,I,D,D	12.8 ± 0.6	2	10.0 ± 1.1	2	12.5
4.4 ± 0.2	C,C,S,C	27.4 ± 0.6	4	22.2 ± 2.0	4	25.8
8.8 ± 0.4	C,C,D,C	62.6 ± 20.6†	8	45.8 ± 1.0	8	53.3
10.5 ± 0.2	C,C,D,C	65.0 ± 15.0	10	55.4 ± 3.1	10	66.7
12.6 ± 0.3*	C,*,S,C	86.1 ± 1.5	12	67.4 ± 2.6	12	72.9
14.5 ± 0.3	C,C,C,C	86.9 ± 2.0	14	76.9 ± 5.0	14	77.0

S, stomach; I, ileum; D, duodenum; C, colon.
*, mean of three animals, as in one animal system was recovered shortly after dosing.
†, system administered to animal was cracked (bitten) during dosing procedures.

Table 2 Comparison of metoprolol fumarate release *in vivo* and *in vitro* from a 19/190 metoprolol Oros system. Mean data from four dogs.

In vivo			In vitro		*Theoretical*	
Residence time (h)	*Location*	*% Release*	*Residence time (h)*	*% Release*	*Residence time (h)*	*% Release*
1.2 ± 0.1	S,S,S,S	10.8 ± 1.3	1	7.4 ± 0.5	1	10.0
2.2 ± 0.1	S,S,J,I	21.4 ± 1.9	2	17.5 ± 0.5	2	19.0
4.3 ± 0.2	I,S,C,Ce	43.9 ± 5.6	4	41.4 ± 1.6	4	39.0
6.3 ± 0.2	Ce,S,C,C	55.0 ± 8.1	6	58.6 ± 1.7	6	59.0
7.9 ± 0.7	C,S,C,St	72.1 ± 15.0	8	68.3 ± 2.6	8	69.0
9.9 ± 0.7	C,C,C,St	78.6 ± 9.7	10	81.9 ± 3.9	10	76.0
11.9 ± 0.7	C,C,C,St	83.5 ± 9.5	12	88.8 ± 3.1	12	82.0

S. stomach; J, jejunum; I, ileum; Ce, caecum; C, colon; St, stool.

There is no apparent explanation for the greater availability from duodenum, compared with portal vein, and the result may simply have been a consequence of the small number of animals involved. Further investigation in a larger number of animals is required to confirm this observation and to allow a statistical analysis to be performed.

For metoprolol fumarate, the mean plasma concentration curves obtained in the infusion experiments with four dogs are given in Figure 2. Similar results were obtained with metoprolol

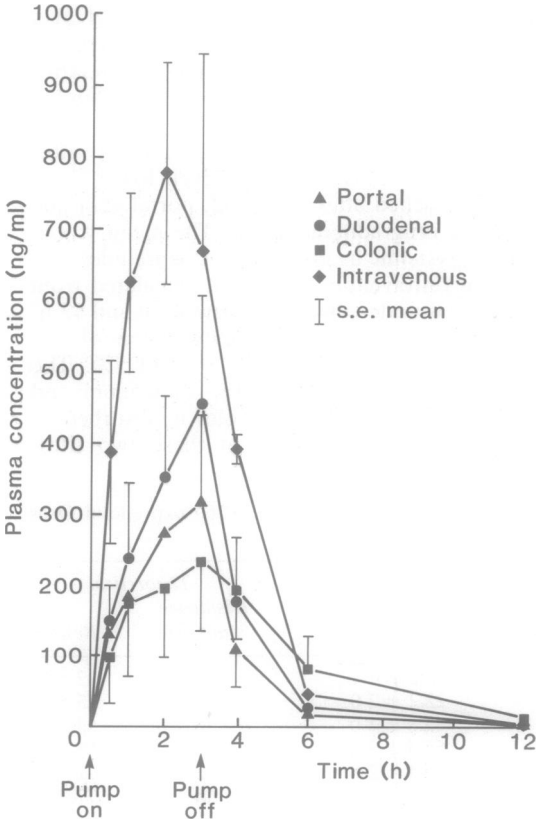

Figure 1 Average plasma concentrations of oxprenolol succinate following continuous 3 h infusions at 16 mg/h in four dogs.

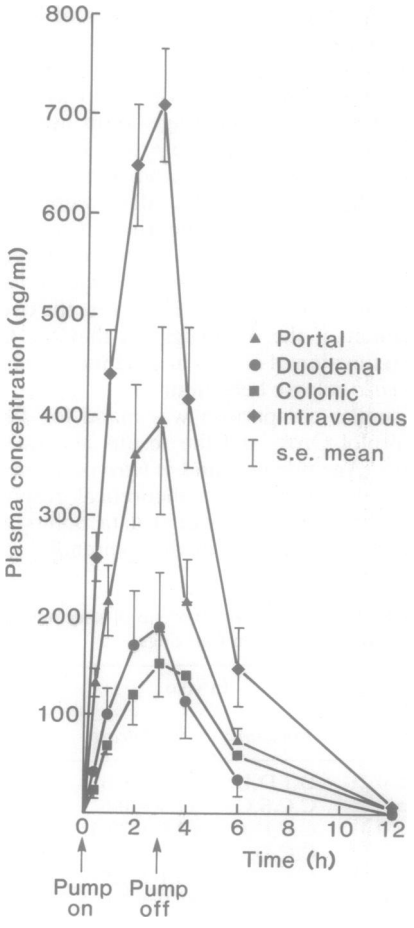

Figure 2 Average plasma concentrations of metoprolol fumarate following continuous 3 h infusions at 19 mg/h in four dogs.

as with oxprenolol, except that higher concentrations were obtained after portal compared with duodenal infusion. For this drug also colonic infusion produced the lowest concentrations and the elimination rate was again slower than for the other routes of administration. The mean ± s.e. mean systemic availabilities of metoprolol fumarate, as determined from area under the plasma concentration curves (intravenous = 100%) were: duodenum, 24.3 ± 5.3%; colon, 25.8 ± 8.6% and portal vein, 53.7 ± 7.6%. These results indicate that metoprolol undergoes substantial first-pass hepatic metabolism in the dog. Additionally, as with oxprenolol, metoprolol is absorbed to the same degree from the duodenum and colon. However, a comparison of the systemic availabilities after portal vein and gut infusion indicates a sizeable loss during the transfer of the drug from the lumen (duodenal and colonic values were only 50% of those after portal administration). Whether this loss is due to gut metabolism of the drug or to other rate-limiting absorption phenomena is not known. Here too, data were averaged from only four dogs.

Rate-controlled dosage forms with total release times approaching 24 h will deliver drug throughout most of the gastrointestinal tract. This study has shown that, regardless of their position within the gut, the 16/260 oxprenolol and 19/190 metoprolol Oros systems function identically *in vivo* as they do *in vitro* in the dissolution apparatus. Thus, *in vitro* release rate testing is a direct and reliable demonstration of systems performance *in vivo*.

The results also indicated that both oxprenolol and metoprolol are subject to a substantial hepatic first-pass metabolism in the dog. Additionally, significant drug loss occurs across the gut wall with metoprolol, but not apparently with oxprenolol. The systemic availability of drug from the duodenum and colon are similar for both drugs although there is some suggestion of a difference in the rate of absorption.

If these results can be extrapolated to man, they provide some justification for the development of dosage forms with sufficiently long durations of release to permit once-daily dosing, even for drugs which exhibit significant first-pass metabolism.

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