Relationship between the rate of appearance of oxprenolol in the systemic circulation and the location of an oxprenolol Oros 16/260 drug delivery system within the gastrointestinal tract as determined by scintigraphy

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1 The position in the gastrointestinal tract of an orally administered oxprenolol Oros drug delivery system labelled with technetium-99m DTPA was followed by gamma scintigraphy, and the corresponding plasma drug concentration-time profiles after oral and i.v. administration were used to relate pharmacokinetic and transit data.

2 Gastric emptying time (0.8 ± 0.4 h, mean $\pm$ s.d.), and the time to arrival in the colon (3.8 ± 0.7 h) were reasonably consistent after administration of the Oros system to fasted subjects, as were the calculated small intestine transit times (3.0 ± 0.7 h). As expected there were wide individual variations in colonic transit, so that recorded values for total transit ranged from 6 to 32 h (median, 24.7 h).

3 Absorption of oxprenolol occurred throughout the GI tract including the colon. Plasma drug concentration-time profiles and input functions (calculated by deconvolution) could be related to transit behaviour and *in vitro* release. Inflexions in the calculated rate of drug input when the Oros system was located in the colon corresponded with periods of stagnation at the hepatic and splenic flexures in two subjects and the ileocaecal junction in two others. The mechanism of these changes is unclear.

Keywords oxprenolol Oros gamma scintigraphy plasma concentration

Introduction

Oxprenolol is a non-selective β -adrenoceptor antagonist used for the treatment of angina, cardiac arrhythmias and hypertension. The drug has a short elimination half-life of 1–2 h (Brunner *et al.*, 1975; Mason & Winer, 1976; Russo & Covinsky, 1983; John & Smith, 1985a). Oxprenolol is well absorbed from the small and large intestines (Antonin *et al.*, 1985; Fara *et al.*, 1985; Langenbucher & Mysicka, 1985) and consequently therapeutic advantage can be gained if the drug is formulated as a controlled release

dosage form intended for once daily administration. One such system, Oros[®], is based upon an osmotic principle and has been described in detail (Theeuwes *et al.*, 1985).

The performance of a novel controlled release dosage form can be assessed by *in vitro* release studies combined with a pharmacokinetic evaluation that involves collection and analysis of suitably timed blood samples followed by mathematical deconvolution. The transit behaviour of a controlled release dosage form

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through the different regions of the gastrointestinal (GI) tract can often have an important bearing on the resultant blood drug concentration-time profiles. Consequently, in the present study a combination of gamma scintigraphy and a pharmacokinetic evaluation has been used to achieve the following objectives:

- i. To follow the GI transit of oxprenolol Oros, and in particular to measure gastric emptying and intestinal transit.
- ii. To determine the plasma concentration-time profile of oxprenolol.
- iii. To relate the pharmacokinetic data obtained from (ii) with the transit data from (i).

Methods

Subjects

The study was conducted in six healthy male volunteers aged 18–20 years (mean, 19 years), who weighed 63.0–94.5 kg (mean, 79.3 kg) with a height range of 1.75–1.93 m (mean, 1.83 m). They were normotensive with normal ECG recordings and no history of asthma, respiratory or GI disease. The subjects had no contraindications to the administration of β -adrenoceptor antagonists and had regular bowel movements. Clinical examination and standard biochemical and haematological tests prior to the study confirmed that values were in the normal range.

The study was approved by the University of Nottingham Ethics Committee and conformed with the guidelines laid down by the Declaration of Helsinki on biomedical research involving human subjects. The volunteers fasted overnight from 21.00 h. Light standardised meals were given 4 and 10 h post-dosing. No alcohol was permitted from 48 h before taking the study formulation until the end of the study. No drugs, including analgesics, vitamins and laxatives were allowed during the 7 days prior to, and during the study.

Dosage form and dosing

A single dose of 260 mg oxprenolol succinate (equivalent to 212.7 mg oxprenolol free base) was administered orally in an osmotic pump system (Oros). This was designed to release the drug after a small lag time, initially at a rate of 16 mg h⁻¹ (oxprenolol Oros 16/260) for about 9 h, and to have a total release time of approximately 24 h. The lag time is the time taken for the Oros system to equilibrate with water. The Oros system has been described in detail elsewhere (Theeuwes *et al.*, 1985). The *in vitro* performance of the

Oros systems was determined by the flow cell method (Langenbucher & Rettig, 1977) using simulated gastric juice (0–1 h) and simulated intestinal fluid (1–24 h). One litre of recycled medium was employed.

The Oros systems were administered to the subjects with 100 ml water. On a separate occasion subjects received intravenously (i.v.) 20 mg oxprenolol hydrochloride (equivalent to 17.66 mg oxprenolol free base) dissolved in 20 ml of physiological saline and administered at a constant rate over 2 min. The two treatments were given according to a balanced cross-over design.

Drug assay

Blood was taken at selected times over 0–36 h after oral administration and 0–12 h after i.v. administration of the drug. Plasma samples were frozen at –20°C until analysed for oxprenolol using a modification of the gas chromatographic method with electron capture detection described by Degen & Riess (1976). Metoprolol tartrate was used as internal standard. All values are expressed as ng ml⁻¹ of oxprenolol free base. With one exception, the Oros systems were recovered from the faeces and assayed for residual drug content.

Data analysis

Deconvolution analysis of the individual plasma profiles obtained after Oros dosing was carried out using the programme CONVOL (Langenbucher, 1982). The i.v. data for each subject were used as the weighting function. The area under the plasma drug concentration-time curve (AUC) was estimated by the trapezoidal rule. The AUC for oxprenolol is proportional to the dose administered (Kendall *et al.*, 1976; Mason & Winer, 1976). Consequently, the absolute bioavailability of oxprenolol following administration of the 16/260 Oros system was calculated from the ratio of the dose normalised AUC values following the Oros system and i.v. administration in each subject.

Mean body residence times (MRT) for oxprenolol were calculated by dividing the area under the first moment of the plasma drug concentration-time curve (AUMC) by the AUC. The mean absorption time (MAT) for oxprenolol from the Oros delivery system was then estimated by subtracting the MRT_{i.v.} from the corresponding MRT after administration of the Oros system. The MAT is itself the sum of the mean dissolution time (MDT) *in vivo* for the Oros system and the mean residence time at the site of

absorption. Oxprenolol is rapidly absorbed from an oral solution (Kendall *et al.*, 1976), and for the present study MAT can be taken as an approximation of MDT.

Labelling of Oros systems and gamma scintigraphy

Oros systems do not disintegrate in the gut lumen. In order to follow the position of the system as it moved through the different regions of the GI tract, it was labelled by the incorporation of a small quantity of technetium-99m DTPA (diethylenetriaminepentaacetic acid) into an adhesive (Dow-Corning, silicone rubber) which was coated onto a small area around the equator of the system. The integrity of the system was checked by appropriate *in vitro* tests under relevant conditions of temperature and pH, as well as by the recovery of the systems from the faeces during the actual study. The amount of radioactivity administered was about 4 MBq.

The transit of the osmotic pump in the GI tract was followed by placing the subjects in front of a gamma camera (MaxiCamera-GEC 40 cm field of view) and taking scintiphotos at intervals over the period of the study. The position of the Oros system was determined by three independent observers by reference to external anatomical markers. These markers took the form of technetium-99m labelled adhesive patches attached to the subjects (Davis *et al.*, 1988).

Results

In vitro dissolution

The mean *in vitro* dissolution profile of the Oros system is given in Figure 1. The mean values for

Figure 1 Mean *in vitro* dissolution profile for the oxprenolol Oros 16/260 system ($\pm$ s.d., $n = 6$).

the percentage of drug released at selected times were: 1.7% at 1 h, 53.9% at 10 h and 85.7% at 24 h ($n = 6$, s.e. mean $< 1\%$).

Gastrointestinal transit

The transit behaviour of the Oros systems in each of the 6 subjects is demonstrated in the individual diagrams prepared from the scintigraphic images (Figure 2). Estimates of gastric emptying time, the time to arrival in the colon, small intestine, colonic and total transit time are given in Table 1. It will be noted that the values for the first three parameters were reasonably consistent. There were, however, wide individual variations in colonic transit. Consequently, recorded values for total transit time ranged from 6–32 h. The total transit for the Oros system in subject 4 was rapid (6.0 h), and this was confirmed by repeating the investigation in this subject; total transit time 6.5 h. Although colonic transport was rapid, the gastric emptying and small intestine transit times for subject 4 were similar to those recorded for the other

Table 1 Individual GI transit data after oral administration of an oxprenolol Oros 16/260 system as determined by gamma scintigraphy.

Subject	Gastric emptying (h)	Colon arrival (h)	Small intestine transit (h)	Colonic transit (h)	Total transit (h)
1	1.0	4.0	3.0	20.5	24.5
2	1.0	3.5	2.5	8.0	11.5
3	0.5	3.6	3.1	21.2	24.8
4	1.2	3.5	2.3	2.5	6.0
5	0.6	5.0	4.4	26.8	31.8
6	0.3	3.0	2.7	27.5	30.5
Mean	0.8	3.8	3.0		
s.d.	0.4	0.7	0.7		
median				20.9	24.7

Figure 2 Position of the Oros system in the GI tract at various times post-dosing. Subjects 1-6. Each position is labelled with the time post-dosing (h) that this was recorded.

subjects. Subject 2 also had a short transit time (<12 h) on the one occasion he was studied. Total transit times recorded for the other four subjects corresponded with the expected norm.

Pharmacokinetic data

Plasma concentrations of oxprenolol 36 h after administration of the Oros system were below the limit of quantitation (9 ng ml^{-1}) for most (4/6) subjects, and the remaining two subjects had very low plasma drug concentrations at this time.

The total area under the plasma concentration-time curve (AUC) was therefore estimated from 0–36 h post-dosing for each subject. The extrapolated AUC from 36 h to infinity accounted for approximately 0.3% of the total AUC in each individual. The AUC after oral and i.v. dosing, and peak drug concentrations (ng ml^{-1}) and the time to reach peak drug concentration (h) for each subject after oral dosing are given in Table 2. Dose normalised AUC values (AUC/dose) for both treatments are given in Table 3. As expected the calculated bioavailability of

Table 2 Individual pharmacokinetic parameters derived from the plasma drug concentration/time data after oral administration of oxprenolol Oros 16/260 and intravenous (i.v.) administration of 20 mg oxprenolol hydrochloride. Plasma concentrations of oxprenolol are all expressed in ng ml^{-1} of oxprenolol free base.

Subject	Area under curve ($\text{ng ml}^{-1} \text{ h}$)		Peak concentration (ng ml^{-1})	Time to peak (h)	MRT (h)	
	16/260 Oros	i.v.	16/260 Oros	16/260 Oros	16/260 Oros	i.v.
1	1476	487	105	6.0	13.0	1.8
2	1079	545	178	6.0	7.9	1.8
3	7218	1336	344	4.0	14.8	2.0
4	1381	825	223	6.0	5.8	2.0
5	4926	1011	265	12.0	14.5	1.9
6	4559	694	299	12.0	13.8	1.9
Mean	3440	816	236		11.6	1.9
s.d.	2506	318	86		3.8	0.1
median				6.0		

MRT – mean body residence time.

Table 3 Individual dose-normalised pharmacokinetic parameters and percentage of the dose in recovered systems.

Subject	Dose normalised AUC ($\text{ng ml}^{-1} \text{ h mg}^{-1}$)		Absolute bioavailability (F) (%)	MAT (h)	% of dose in recovered systems
	16/260 Oros	i.v.	16/260 Oros	16/260 Oros	
1	6.10	24.35	25.1	11.2	17.4
2	4.46	27.25	16.4	6.1	56.5
3	35.12	66.80	44.7	12.8	21.2
4	5.70	41.23	13.8	3.8	79.3
5	20.37	50.54	40.3	12.6	*
6	18.85	34.68	54.3	11.9	14.3
Mean	15.10	40.81	32.4	9.7	37.7
s.d.	12.04	15.89	16.4	3.8	28.8

* – data not available; AUC – area under the curve; MAT – mean absorption time. Dose normalised AUC values calculated from plasma drug concentrations expressed in ng ml^{-1} oxprenolol free base.

oxprenolol from the Oros system ($AUC_{oral}/AUC_{i.v.}$) agreed with the percentage of the dose reaching the circulation, calculated by deconvolution analysis, for each subject.

The mean plasma drug concentration profile following i.v. dosing with oxprenolol is shown in Figure 3, and individual plasma concentrations of oxprenolol following oral administration are illustrated in Figure 4. Individual *in vivo* input functions, generated by deconvolution analysis of the plasma drug concentration profiles following the Oros system, are shown in Figure 5. The position of the Oros system in the GI tract, as determined by scintigraphy, has also been plotted for each subject in Figures 4 and 5.

The percentage of the dose present as unreleased drug in the recovered system (Table 3) was consistent with *in vitro* release (Figure 1) and total transit time (Table 1). The difference between the calculated bioavailability and residual amount of drug in the recovered system was used to estimate loss of the drug, by processes

such as metabolism, degradation and non-absorption. As expected, rapid transit of the Oros system and high residual drug in the recovered system provide less opportunity for loss. When the loss was normalised to the amount

Figure 3 Mean plasma drug concentration profile ($ng\ ml^{-1}$ oxprenolol free base) following i.v. administration of 20 mg oxprenolol hydrochloride ($\pm$ s.d., $n = 6$).

Figure 4 Concentration of oxprenolol ($ng\ ml^{-1}$ oxprenolol free base) in the systemic circulation and the location of the Oros delivery system in the GI tract. Subjects 1–6. ST – stomach, SI – small intestine.

Figure 5 Cumulative input (% of dose) *in vivo* (calculated by deconvolution) and the location of the Oros delivery system in the GI tract. Subjects 1–6. ST – stomach, SI – small intestine.

released from the system, metabolic and other losses accounted for about 50% of the delivered drug.

Discussion

Transit of the Oros system through the stomach and small intestine was relatively rapid and reasonably consistent. The short gastric emptying time (0.8 ± 0.4 h) reflects the known physiology of the fasted stomach. Indigestible material, such as a single unit dosage form, will be cleared by the powerful contractions arising from phase 3 of the migrating myoelectric complex (MMC), the so-called 'housekeeper wave' (Szurszewski, 1969; Minami & McCallum, 1984; Davis *et al.*, 1986). The system will then be moved through the small intestine to arrive at the ileocaecal junction approximately 2–4 h later. The value obtained for the mean transit time in the small intestine was 3.0 ± 0.7 h. This was very close to

that reported by Hardy *et al.* (1985) and Davis *et al.* (1986) for the GI transit of various dosage forms administered to a large group of patients and volunteers. It will be noted that the first meal (light lunch) was provided after 4 h when the system had reached or was past the ileocaecal junction for all subjects except number 5. In this study the system was administered to fasting individuals. During routine treatment systems would be taken with food and transit times would probably be longer (Hirtz, 1985).

By contrast, transit through the colon was more variable but in general was the major determinant of total transit. The total transit for subject 4 was rapid (6.0 h), although similar values have been reported by John *et al.* (1985b) for the transit of Oros systems in a small number of subjects. Subject 4 was a vegetarian and his diet may have played a role in reducing colonic transit time. Small deviations from the predicted delivery rate were more apparent in the colon and were often associated with periods of system

stagnation in the flexures. It is not known whether this apparent fall in drug absorption rate was due to local changes in osmolality of the luminal contents, the presence of stagnant diffusion layers affecting the performance of the system, poorer absorption at these sites, or the presence in these regions of muscular sphincters (Didio & Anderson, 1968).

For zero-order delivery of a compound the MAT will be one half the total delivery time, and this was observed experimentally. Where total transit time was not limiting, MAT for the Oros system ranged from 11.2 to 12.8 h, and for the two subjects who had total transit times less than 24 h MAT was approximately one half the total transit time. These data are thus consistent with zero-order delivery of oxprenolol from the Oros system throughout the GI tract.

Mason & Winer (1976) have reported that after oral administration of oxprenolol a substantial loss of the drug occurs before it reaches the general circulation. They suggested that this loss might be due to incomplete absorption or metabolism. However, recent studies by Vidon *et al.* (1986) demonstrated that oxprenolol given orally was totally absorbed from the intestine. These authors commented that under well-controlled conditions of oxprenolol delivery to the intestine, absorption rates exhibited rather small inter-subject variations. In contrast, the pharmacokinetic parameters derived from plasma data were more variable between subjects. Thus, the large differences recorded for AUC values may not necessarily be related to the actual amounts absorbed from the GI tract but result from important inter-subject differences in hepatic drug metabolism (first-pass effect). The data obtained in the present study appear to be consistent with this. Subjects 1 and 2 not only showed high losses for orally administered

oxprenolol but also had a lower AUC after i.v. administration than other subjects.

The semi-permeable membrane of the Oros dosage form permits only the passage of water into the system. Thus dissolution of the core and subsequent delivery of the drug should not be influenced by factors such as pH, ionic strength or luminal environment. This has been demonstrated by *in vitro* measurement under different conditions (Theeuwes *et al.*, 1985). Other than system characteristics, drug delivery should be influenced only by intra-luminal osmolality and temperature, both of which show little physiological variability throughout the gut (Theeuwes *et al.*, 1985). In this study small changes in drug delivery to the circulation were observed particularly during periods of apparent stagnation in the colonic flexures. The mechanism underlying this effect remains unclear, and it is not possible on the basis of the present data to distinguish between reduced delivery from the system and reduced absorption into the systemic circulation. The observed changes in the rate of absorption were small compared to the inter-subject differences in pharmacokinetic parameters and are unlikely to have any clinical significance.

This study illustrates the value of combining a classical pharmacokinetic interpretation of controlled release drug delivery systems with a knowledge of the position of the system within the GI tract. Changes in the rate of absorption could be correlated with the location of the system within the GI tract and with the transit behaviour of the system. For oxprenolol, drug release from the Oros system and absorption across the intestine appeared to take place throughout the GI tract for up to 32 h; although in some cases premature expulsion of the system occurred with a consequent reduction in bio-availability.

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