COMPARISON OF THE PHARMACODYNAMIC AND PHARMACOKINETIC PROFILES OF SINGLE AND MULTIPLE DOSES OF A COMMERCIAL SLOW-RELEASE METOPROLOL FORMULATION WITH A NEW OROS[®] DELIVERY SYSTEM

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- 1 A new osmotic pressure mediated delivery system for metoprolol (Lopresor Oros[®]) has been evaluated by measuring the haemodynamic effects and pharmacokinetics after single and multiple oral dosing in young healthy volunteers.
- 2 Similar studies have been carried out in the same group using equivalent single and multiple oral doses of the commercial slow-release preparation (Slow Lopresor[®]).
- 3 The new osmotic delivery system produces a more uniform haemodynamic response: a plateau metoprolol concentration in plasma is reached about 6 h after dosing and is maintained for 10 h.

Introduction

Metoprolol is a relatively cardioselective β -adrenoceptor antagonist (Kendall, 1981) effective in the treatment of hypertension and angina (Comerford & Besterman, 1976; Karlberg *et al.*, 1979). Because of its short elimination half-life, slow-release formulations have been developed to allow once-daily dosing while maintaining a clinical effect over a 24 h period. The prolongation of β -adrenoceptor blockade attainable with the 200 mg slow release formulation (Slow Lopresor[®]), has been demonstrated in a number of studies (Quarterman *et al.*, 1979; Kendall *et al.*, 1980).

The more conventional matrix type slow-release formulations suffer from the disadvantage that a substantial part of their total content is relatively rapidly released once the core surface is exposed: in the case of Slow metoprolol 50% of the drug is released from the formulation within the first 3 h (Regardh *et al.*, 1975). More recently, a new osmotic drug delivery system (Oros[®]) has been developed in which the drug is contained within a semi-permeable tablet shell. Water from the gastro-intestinal tract penetrates the shell by osmosis and forces the drug out through a single tiny exit hole. This system provides zero order drug delivery and, by selecting the appropriate manufacturing parameters, a variety of release rates can be obtained (Theeuwes, 1975; Eckenhoff *et al.*, 1981). In the case of the 19/190 Oros system which is currently being evaluated, the drug is slowly and continuously released at 19 mg/h over the first 8 h. Thereafter

release occurs at progressively slower rates over the next 8 h. The total duration of release for Oros is therefore 16 h compared with 10 h for Slow Lopresor.

Preliminary studies of this new system in a few healthy volunteers showed that higher plasma levels of metoprolol could be maintained over a longer period than with the conventional slow-release preparation. The amount of drug reaching the circulation was similar in both cases. The present study was carried out using six healthy young volunteers to compare in greater detail the pharmacodynamic and pharmacokinetic profiles of the two formulations after single and multiple dosing. The aim was to discover whether once-daily dosing with the new Oros formulation could provide consistent and adequate β -adrenoceptor blockade over 24 h.

Methods

Study design

The study used a double-blind within-subject comparative design with placebo treatment as control. On entry the volunteers were randomly allocated to three treatments: the commercially available slow-release preparation (Slow Lopresor), the Oros formulation and placebo. Each formulation was administered orally in the morning for 8 consecutive days with an

interval of at least 6 days between the different treatments.

Ethics

Before entry, the volunteers were given a full description of the nature and purpose of the study and were required to give their written informed consent before being allowed to participate. Approval for the study design was obtained from the Queen Elizabeth Hospital Research Ethical Committee.

Subjects

Six healthy young male volunteers, aged either 21 or 22 years and weighing between 60 and 78 kg (mean 69.9 kg) were examined before the study and found to be healthy and to have normal biochemical and haematological profiles. None had any history of asthma, allergy or respiratory disease and no known contraindications to the administration of β -adrenoceptor blocking drugs were present. At this preliminary visit the subjects exercised on a treadmill to determine the speed and gradient which would produce a heart rate greater than 150 beats/min over the last 15 s of a 3 min exercise period. None of the volunteers took any form of medication for at least 14 days before or during the trial.

Materials

The following formulations were used in the study:

1. Slow Lopresor® tablets containing 200 mg metoprolol tartrate.
2. Lopresor Oros® tablets containing 190 mg metoprolol fumarate (equivalent to 200 mg tartrate) with a 19 mg/h zero-order release rate.
3. Placebo tablets to match both formulations.

Procedure

On the first and eighth days of each treatment volunteers came to a hospital side-room at 07.30 h after a 12 h overnight fast. An intravenous cannula was inserted into a forearm vein and kept patent by a slow infusion of 0.9% w/v saline. Tablets were administered at 08.00 h with 100 ml water. Non-alcoholic drinks were permitted 3 and 7 h later and food was given at 5 and 10 h after dosing. Haemodynamic parameters were measured immediately before drug administration and at 1, 2, 3, 4, 6, 8, 12, 15 and 24 h thereafter. At each assessment volunteers rested for 10 min before pulse rate and blood pressure were measured. They then exercised on the treadmill and their heart rates were calculated over the last 15 s of the test using an electrocardiographic recording. Blood pressures were measured manually using a mercury sphygmomanometer, measurements being made within 15 s of

completing the test since blood pressure recording during exercise proved unreliable. The volunteers rested between assessments but were discouraged from sleeping during the day. All were required to remain in hospital overnight on the first and eighth day of each treatment.

In order to measure metoprolol concentrations, blood specimens were withdrawn immediately before and 1, 2, 3, 4, 6, 8, 12, 15 and 24 h after dosing on the first and eighth day. The specimens were heparinized, centrifuged immediately and the separated plasma stored in plain tubes at -20°C until required for analysis.

Metoprolol assay

Plasma metoprolol concentrations were measured using a gas chromatographic method with propranolol as the internal standard (Degen & Riess, 1976). Drug concentrations were reported as free metoprolol base because of the difference in chemical composition of the two formulations. Quality control specimens were included in each assay run and all values were within acceptable limits ($\pm 10\%$). The assay detected drug at a minimum concentration of 5 ng/ml and had a precision greater than $\pm 10\%$ at levels above 20 ng/ml.

Figure 1 Mean exercise heart rate during placebo (●), Slow Lopresor (○) and Lopresor Oros (□) treatments on day 1 (a) and day 8 (b). Both formulations differed significantly from placebo at 1–24 h on day 1 and 0–24 h on day 8, and from each other at 1, 2 and 24 h on day 1.

Data analysis

Overall differences in plasma concentration and haemodynamic profiles were examined by n-factor repeated measures variance analysis. Where differences were detected, a more detailed analysis based on the generalized Student's *t*-test was used (Welch, 1947). The significance level of each test was adjusted to insure against detection of spurious positive results. Areas under the curve (AUC), peak concentration ($C_{\max}$) and time to peak ($T_{\max}$) were also examined by repeated measures variance analysis as were overall differences in resting pulse rates, exercise heart rates and exercise systolic blood pressures. Areas under the plasma concentration curves between 0 and 24 h (AUC_{0-24}) were estimated by the trapezoidal rule. The total areas, $AUC_{0-\infty}$ were estimated using the expression: $AUC_{0-\infty} = AUC_{0-24} + C_{24}/\beta$ where C_{24} is the plasma concentration at 24 h and β is the terminal slope of the plasma elimination curve. Only approximate values of β were obtained since estimates were based on 2 or 3 data points but, generally, the contribution of C_{24}/β was small.

Results

Exercise heart rates

The exercise heart rates (Figure 1) on placebo did not vary significantly over the 24 h period on either study day indicating a consistent and reproducible response to the exercise procedure. Both drug formulations significantly reduced exercise heart rates, greater effects being observed on the eighth day. The maximum reductions were similar for the two formulations although the profile slopes were different. The time of maximum reduction occurred later for Oros than for the commercial slow-release preparation and the effects persisted for a longer period after dosing. On the first day analysis of the treatment means revealed statistically significant differences ($P < 0.05$) between drug and placebo values at each assessment between 1 and 24 h for both formulations. Differences between formulations were significant ($P < 0.05$) at 1, 2 and 24 h, the Oros formulation producing the greater effect at 24 h.

On the eighth day the reductions in exercise heart rates were greater than on the first, the main differences occurring at the beginning and end of the dosage interval. Variations in heart rate response over 24 h were considerably reduced on the eighth day and particularly striking for the Oros formulation where individual values only varied between 118 and 130 beats/min. Not surprisingly, differences between drug and placebo values were significant throughout the 24 h for both formulations.

The differences between the formulations did not

Figure 2 Mean post-exercise systolic blood pressure during placebo (●), Slow Lopresor (○) and Lopresor Oros (□) treatments on day 1 (a) and day 8 (b).

attain the 13 beats/min level required for statistical significance at any of the assessment times. The Oros formulation clearly exerted a greater pre-dosing effect during chronic dosing, the differences between formulations averaging 9 beats/min at the beginning and end of the dosage interval. The pre-dosing reductions in heart rate expressed relative to the placebo value increased from a mean of 12.5% for Slow Lopresor and to 18% for the Oros formulation.

Resting pulse rates

Both formulations produced qualitatively similar effects on resting pulse rates as on exercise heart rates. On the eighth day the effects were generally greater and maximum reductions coincided approximately with peak plasma concentrations of metoprolol.

Blood pressure

Systolic blood pressure increased on exercise, the smaller effects for the active treatments providing a further indication of the extent of β -adrenoceptor blockade. The effects of the two active preparations on Days 1 and 8 are presented in Figure 2. The Oros preparation produced a relatively uniform and constant reduction in the exercise systolic pressure over the 24 h on Day 8 with values between 133–145 mmHg compared with the more variable reduction on the slow-release formulation of 125–153 mmHg.

Table 1 Mean plasma metoprolol concentrations and pharmacokinetic parameters

			Time (h)										Area under curve (ng ml ⁻¹ h)	Peak concentration (ng ml ⁻¹)	Median time to peak (h)
			0	1	2	3	4	6	8	12	15	24			
Slow Lopresor	Mean	0	18	48	89	94	110	112	121	85	61	16	1603	123	7.0
	s.d.	0	6	17	41	42	53	60	67	63	25	25	1104	65	
Slow Lopresor	Mean	43	89	126	146	170	179	175	134	110	47	56	2870	202	5.5
	s.d.	48	62	72	89	85	36	62	72	72	56	37	1519	69	
Lopresor Oros	Mean	0	2	17	47	66	102	121	113	95	37	35	1878	138	8.0
	s.d.	0	2	9	24	29	66	84	94	65	35	71	1295	101	
Lopresor Oros	Mean	86	82	94	132	155	170	180	167	169	71	48	3372	202	12.0
	s.d.	56	43	41	40	44	79	65	82	90	48	73	1516	73	

Pharmacokinetic data

The mean plasma concentrations together with AUC values and peak concentrations on dosing with the slow-release and Oros formulations are given in Table 1 and the mean plasma profiles for both formulations on Days 1 and 8 are illustrated in Figure 3. The two plasma concentration curves reached similar $C_{\max}$ values on both study days and no statistically significant difference in $C_{\max}$ was seen. However, for the Oros formulation, time to peak $T_{\max}$ was longer, and the plasma levels were higher in the period 8–24 h post dosing. The onset of absorption on Day 1 was also delayed for the Oros formulation and clear differences in initial plasma levels were seen. Similar lag phases have been reported in other studies and have been attributed to a delay in attaining the required osmotic pressure to initiate the drug release process. During chronic dosing this initial period will be covered by the drug still present from the tablet given 24 h earlier as can be seen in Figure 3. At 24 h post-dosing on both study days, metoprolol was readily detected in plasma, the Oros values being higher than those resulting from the commercial slow-release preparation in all volunteers.

Although the areas under the plasma curves over 24 h were greater for the Oros formulation, the differences were not statistically significant ($P = 0.276$). The amount of drug reaching the circulation from the two formulations can therefore be considered to be equivalent.

Figure 3 Mean plasma profiles of metoprolol during Slow Lopresor (○) and Lopresor Oros (□) treatments, day 1 (a) and day 8 (b).

Discussion

A detailed comparison of the haemodynamic and pharmacokinetic effects of the two formulations following single and multiple dosing has shown that the Oros formulation elicited a more uniform haemodynamic response and a greater pre-dosing effect when administered once daily. The results on Day 8 are of particular interest. The exercise heart rate was reduced by 30 and 27 beats/min at time 0 and 24 h after taking the Oros formulation and the maximum reduction was 38 beats/min.

The extent of β -adrenoceptor blockade at the beginning and end of the dosage interval (19 and 17% respectively) was comparable to that reported for other β -adrenoceptor blockers with long half-lives such as sotalol (Leahy *et al.*, 1980) and pindolol (Aellig, 1976) or those administered in special slow release forms for example propranolol, Inderal LA[®] (Leahy *et al.*, 1980). The corresponding values for Slow Lopresor were smaller than those for the Oros system (12 and 13% respectively) but the maximum effects were similar.

The relationship between antihypertensive effect and β -adrenoceptor blockade is not well established. However Krediet and colleagues (1980) have recently demonstrated a weak correlation between the reduction in exercise heart rate and the reduction in blood pressure. If, as would be anticipated, a similar relationship exists for metoprolol then the Oros preparation would be expected to offer a more even and sustained antihypertensive effect than the commercial slow release preparation, itself an improvement on the conventional form of metoprolol. This, however, needs to be verified by appropriate clinical trials.

Inspection of the post-exercise systolic blood pressure data revealed comparable results with a marked and obvious effect at 0 and 24 h and a fairly sustained and even response throughout the day. By comparison Slow Lopresor on Day 8, whilst achieving a significant reduction in exercise heart rate and systolic blood pressure, produced a less uniform response, though it was a marked improvement on the results which would have been obtained after a

dose of the conventional preparation (Quarterman *et al.*, 1979; Kendall *et al.*, 1980). Although diastolic blood pressure results were not reduced on Day 1, by Day 8 there was an average reduction of 8 mmHg over 24 h (range 3 to 13 mmHg). The maximum effects coincided with the occurrence of peak concentrations in plasma although overall the correlation between these parameters was not strong.

The pharmacokinetic behaviour of the Oros system was consistent with its *in vitro* release profile, in that the formulation produced constant plasma levels over longer periods compared with the commercial slow-release formulation. Although both produced measurable pre-dosing plasma levels following chronic dosing, Oros produced consistently higher levels. Despite the considerably slower rate and longer duration of drug release from the Oros system the same total amount of drug reached the circulation from the two formulations as shown by the similarity of the AUC values. This result suggests that metoprolol is efficiently absorbed over a considerable length of the gastro-intestinal tract. It is also consistent with the findings of a study in dogs which showed that the drug was rapidly and extensively absorbed from the proximal and distal colon (Hess *et al.*, 1980).

Plasma levels and resulting AUCs on the eighth day were higher than predicted from the first day data for both formulations. This effect has been reported previously for metoprolol (Kendall *et al.*, 1980), propranolol (Evans & Shand, 1973; Wood *et al.*, 1978) and acebutolol (Meffin *et al.*, 1978). It has generally been attributed to changes in both bioavailability and clearance during chronic dosing although this has not been specifically demonstrated for metoprolol.

In conclusion, when administered once daily, the Oros system produces a more uniform response and a greater pre-dosing effect than the commercial slow-release form. The significance of these improvements in the clinical management of hypertensive and anginal patients remains to be determined.

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