A multiple dose comparative study of the pharmacodynamic and pharmacokinetic behaviour of polymer-matrix and Oros dosage forms of oxprenolol in healthy volunteers

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1 A new osmotic drug delivery system (Oros) has been evaluated in multiple-dose studies in young healthy volunteers as a sustained-release vehicle for once-daily administration of oxprenolol. Two Oros systems were examined in two separate studies, one containing 170 mg oxprenolol succinate with an initial zero-order release rate of 10 mg/h, and the other containing 260 mg oxprenolol succinate with an initial release rate of 16 mg/h. These were compared respectively with conventional oxprenolol hydrochloride (Trasicor®) 80 mg twice daily and polymer-matrix oxprenolol hydrochloride (Slow Trasicor®) 160 mg once daily.

2 Variations in mean plasma levels and β -adrenoceptor blockade (measured by inhibition of exercise tachycardia) were considerably reduced on the 10/170 Oros once-daily compared with the Trasicor 80 mg twice-daily regimen. With both formulations there was no significant change in mean plasma concentrations or areas under the curve after 8 days' treatment, and similar pre-dose plasma concentrations were obtained. There was significant inhibition of exercise tachycardia throughout 24 h after the 10/170 Oros on the eighth day.

3 The 16/260 Oros system gave smoother pharmacokinetic and pharmacodynamic profiles, and on repeated dosing a higher mean pre-dose plasma oxprenolol concentration than Slow Trasicor. Drug availability was similar for the two dose forms, suggesting an acceptable level of absorption of oxprenolol from most of the gastrointestinal tract. On the eighth day exercise heart rate was significantly reduced throughout 24 h with 16/260 oxprenolol Oros, but only between 1 and 15 h with Slow Trasicor.

Keywords oxprenolol Oros dosage form pharmacokinetics pharmacodynamics

Introduction

Oxprenolol is a non-selective β -adrenoceptor blocking drug with intrinsic sympathomimetic activity (McDevitt *et al.*, 1977) which has found wide application in the treatment of angina (Thadani *et al.*, 1979) and hypertension (Ferlinz *et al.*, 1980). In view of its short elimination half-life, however, effective treatment of these conditions requires either that several doses be taken daily (with consequent inconvenience to

the patient and possible decrease in compliance) or that a slow-release formulation be used. The currently available slow-release preparation of oxprenolol, Slow Trasicor®, is of the polymer-matrix type. Such formulations, while extending the effective half-life of the drug (West *et al.*, 1976), release the greater part of the incorporated dose fairly rapidly. The prospect of more favourable release characteristics has

recently been offered by the development of Oros drug delivery systems (Theeuwes *et al.*, 1985).

This paper reports two studies in normal volunteers designed to examine whether the improved *in vitro* release characteristics of the Oros system are reflected in improved pharmacodynamic and pharmacokinetic profiles for oxprenolol. In the first study (A) a 10/170 system containing 170 mg oxprenolol succinate (equivalent to approximately 160 mg oxprenolol hydrochloride) with an initial release rate of 10 mg/h, given once daily, was compared with conventional oxprenolol hydrochloride 80 mg twice daily. In study B, oxprenolol succinate 260 mg (equivalent to oxprenolol hydrochloride 240 mg) in a 16/260 Oros system with an initial release rate of 16 mg/h, given once daily, was compared with polymer-matrix oxprenolol hydrochloride (Slow Trasicor) 160 mg given in the same dosage regimen. In each study, pharmacokinetic and pharmacodynamic measurements were made on the first and eighth treatment day, using a within-subject, placebo-controlled, design.

Methods

In each study, tablets were administered in a double-blind, double-dummy manner according to a randomized crossover dosage schedule. Volunteers received oxprenolol in three different dosage regimens for periods of 8 days with at least 6 days between treatments. Both studies were given ethics committee approval.

In *study A* the treatment regimens were:

- 10/170 oxprenolol Oros: one 10/170 Oros plus one conventional placebo in the morning, and one conventional placebo in the evening.
- Twice-daily conventional Trasicor: one 80 mg conventional Trasicor plus one 10/170 Oros placebo in the morning, and one 80 mg conventional Trasicor in the evening.
- Placebo: one conventional plus one Oros placebo in the morning, and one conventional placebo in the evening.

In *study B* treatment regimens were:

- Slow Trasicor: one 160 mg Slow Trasicor tablet plus one 16/260 Oros placebo in the morning.
- 16/260 oxprenolol Oros: one 16/260 Oros plus one Slow Trasicor placebo in the morning.
- Placebo: one 16/260 Oros placebo plus one Slow Trasicor placebo in the morning.

Tablets were taken with 100 ml water at 09.00 h and (study A) 21.00 h.

Subjects

In study A, the participants were one female and five male volunteers aged 19–31 years and weighing 52–97 (mean 71) kg. In study B there were eight male volunteers aged 21–24 years, weighing 58–86 (mean 69.4) kg. All had normal haematological and biochemical profiles, all gave informed consent and none had contraindications to β -adrenoceptor blockade. At a preliminary visit, each subject was exercised on a bicycle ergometer (study A) or treadmill (study B) to determine the workload necessary to produce a heart rate greater than 150 beats/min over the last 15 s of a 3-min exercise period. These individual workloads were used throughout the study. No medication other than test drugs was taken by the volunteers for at least 14 days before or during the trial.

On the first and eighth day of each treatment, the volunteers attended after an overnight fast of at least 12 h. They then took the appropriate test drugs under supervision. Non-alcoholic drinks were provided at 3 and 7 h, and light standardized meals were given at 5 and 10 h after dosing. Volunteers rested between exercise tests and stayed overnight in the investigation unit on the main study days.

Pharmacodynamic measurements

Study A Pulse rate and blood pressure were measured at rest and during the exercise tests at 0, 1, 2, 3, 4, 6, 9, 12, 14 and 24 h after dosing on the first and eighth treatment day.

Study B The assessments were as in study A except that measurements were made at 8 and 15 h rather than 9 and 14 h after dosing.

Exercise heart rate was taken as the mean rate over the last 15 s of exercise, measured on an electrocardiograph paper record.

Pharmacokinetic measurements

Study A Venous blood for oxprenolol assay was taken at 0, 1, 2, 3, 4, 6, 9, 12, 14, 20 and 24 h after dosing on the first and eighth day of each treatment.

Study B Blood samples on the first and eighth treatment days were taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 15 and 24 h after dosing.

All samples were heparinized, and plasma was immediately separated before being stored at -20°C until analysed. Plasma oxprenolol was measured by gas chromatography (Degen & Riess, 1976) and reported as the hydrochloride salt. The assay detection limit was 5 ng/ml with precision greater than $\pm 10\%$ above 20 ng/ml.

Data analysis

Overall differences in plasma level and haemodynamic profiles were examined statistically using the repeated-measures analysis of variance approach of Winer (1971). Where differences were significant, treatment means at individual assessments were compared using the generalized Student's *t*-test method of Welch (1947). Significance levels in each analysis were adjusted according to the total number of tests performed. Areas under the plasma concentration-time curve were calculated by the trapezoidal rule. Relative bioavailabilities of the oxprenolol formulations were assessed by comparing areas under the curve during one dosage interval on the eighth day.

Results

Plasma concentrations

Study A Mean plasma concentrations of oxprenolol on days 1 and 8 are summarized in Table 1 and illustrated in Figure 1. The plasma concentration profiles for 10/170 oxprenolol Oros once daily were flatter than those for conventional Trasacor 80 mg twice daily, the most notable difference being the virtual abolition by Oros of the peaks and troughs produced by the conventional regimen. Peak concentrations following Oros averaged 213 and 260 ng/ml on days 1 and 8, respectively, and were approximately one third of the corresponding values following the morning Trasacor dose (641 and 792 ng/ml, respectively). Times to peak were significantly delayed on both study days for the Oros preparation ($P = 0.03$), the median value being 4 h for 10/170 Oros and 1 h for conventional Trasacor.

Except for the higher pre-dose concentrations seen with both formulations, the profiles after repeated dosing were similar to those on the first day and there were no significant increases in areas under the curve with either formulation. Pre-dosing plasma concentrations averaged 100 ng/ml (range 8–343 ng/ml) on the Trasacor twice-daily compared with 75 ng/ml (range 16–180 ng/ml) for the Oros once-daily regimen. The availability of drug, as assessed by AUC measurement, was 63% (range 35.8–99.0%) for 10/170 Oros relative to the conventional Trasacor value.

Study B Mean plasma oxprenolol concentrations on days 1 and 8 are shown in Table 1 and Figure 2. On day 1 the 160 mg Slow Trasacor and 16/260 oxprenolol Oros preparations pro-

duced similar plasma profiles though the mean peak level was lower and time to peak significantly delayed with the Oros dosage form. On day 8, however, the 16/260 Oros profile was characterized by an extended plateau during the second half of the 24 h period. Mean pre-dosing oxprenolol concentrations at 0 and 24 h on day 8 were 93 and 89 ng/ml, respectively, for 16/260 oxprenolol Oros compared with significantly lower concentrations of 8 and 7 ng/ml for Slow Trasacor. On day 8 there was no significant difference between the two formulations with respect to area under the curve (0–24 h), peak plasma concentration, or time to peak.

There was an average increase of 37% in area under the curve (0–24 h) for 16/260 oxprenolol Oros on day 8 compared with day 1. No such effect with chronic dosing was observed for Slow Trasacor, in keeping with the negligible 24 h level after single dosing with this formulation. The relative bioavailabilities of Slow Trasacor and 16/260 Oros on day 8 did not differ significantly after correction for differences in dose.

Haemodynamic results

Although the active treatments produced small reductions in resting pulse rate and in blood pressure at rest and during exercise, these did not at any time reach statistical significance relative to placebo, and will not be considered further.

In both studies, exercise heart rate on placebo did not vary significantly during 24 h on either study day (range 153–161 beats/min), confirming that the exercise test produced a consistent and reproducible response. Exercise heart rate, however, revealed highly significant treatment effects.

Study A Mean heart rate reductions during near-maximal exercise are shown in Table 2 and Figure 1. The response was significantly attenuated from 1–24 h on day 1, and from 0–24 h on day 8 after 10/170 oxprenolol Oros. On both study days, however, the conventional formulation given twice daily failed to maintain significant levels of β -adrenoceptor blockade throughout the 12 h between doses; inhibition of exercise tachycardia was significant from 1–6 and 14–24 h on day 1, and from 0–9 and 14–24 h on day 8. Pre-dosing reductions in heart rate, relative to the placebo response, averaged 9.9% (range 0.9–18.9%) for the Oros, compared with 10.6% (range 3.4–19.3%) for the conventional Trasacor regimen; these differences were not statistically significant.

Table 1 Mean (1 s.d.) plasma oxprenolol concentrations (ng/ml) and area under the concentration-time curve (ng ml⁻¹ h)

Treatment	0	1	2	3	Time after dosing (h)					12	14	20	24	Area under curve
					4	6	9							
Study A														
Conventional Trasacor, day 1	0	559 (389)	590 (411)	365 (235)	239 (172)	89 (84)	21 (14)	10 (9)	435 (441)	78 (67)	22 (20)	2172 ^a (1495)		
Conventional Trasacor, day 8	100 (134)	543 (316)	709 (442)	527 (393)	307 (242)	121 (100)	33 (26)	13 (6)	412 (249)	86 (87)	28 (22)	2717 ^a (1530)		
Oxprenolol Oros, 10/170, day 1	0	18 (10)	114 (66)	188 (84)	210 (105)	186 (102)	147 (85)	48 (70)	113 (75)	78 (67)	59 (47)	2830 ^b (1629)		
Oxprenolol Oros, 10/170, day 8	75 (58)	66 (32)	121 (47)	200 (80)	257 (146)	189 (74)	157 (58)	141 (59)	101 (52)	69 (59)	58 (49)	2985 ^b (1371)		
Study B														
Slow Trasacor, day 1	0	68 (114)	129 (76)	213 (96)	266 (119)	321 (208)	284 (237)	253 (192)	207 (137)	154 (147)	110 (145)	5 (8)	3554 ^b (2607)	
Slow Trasacor, day 8	8 (24)	41 (26)	179 (88)	255 (149)	327 (246)	297 (182)	290 (206)	269 (141)	182 (140)	99 (107)	60 (62)	7 (17)	3072 ^b (2272)	
Oxprenolol Oros, 16/260, day 1	0	0	35 (54)	89 (44)	146 (47)	226 (88)	210 (63)	224 (70)	159 (65)	183 (120)	102 (75)	26 (28)	3015 ^b (1040)	
Oxprenolol Oros, 16/260, day 8	93 (65)	90 (69)	178 (105)	202 (104)	240 (117)	302 (102)	279 (99)	258 (69)	175 (53)	174 (73)	165 (87)	89 (67)	4139 ^b (1340)	

^a—0 to 12 h, ^b—0 to 24 h

Figure 1 Study A: Plasma oxprenolol concentrations (top panel) and reductions in exercise heart rate (lower panel) on the first and eighth day of treatment with conventional Trasicor 80 mg twice daily (●—●), and 10/170 oxprenolol Oros once-daily (□—□).

Figure 2 Study B: Plasma oxprenolol concentrations (top panel) and reductions in exercise heart rate (lower panel) on the first and eighth day of treatment with Slow Trasicor 160 mg (○—○) and 16/260 oxprenolol Oros (■—■) administered once daily.

Table 2 Mean (1 s.d.) heart rates during submaximal exercise (beats/min) on placebo and active treatments

Treatment	Time after dosing (h)									
	0	1	2	4	6	9	12	14	24	
Study A										
Placebo, day 1	155 (4)	150 (7)	151 (9)	152 (8)	158 (7)	152 (6)	157 (4)	155 (2)	153 (6)	
Placebo, day 8	149 (7)	148 (6)	149 (7)	148 (7)	158 (6)	154 (4)	157 (5)	157 (5)	151 (8)	
Conventional Trasacor, day 1	150 (7)	116 (6)	118 (5)	126 (9)	139 (10)	147 (10)	149 (9)	120 (5)	140 (15)	
Conventional Trasacor, day 8	133 (11)	116 (10)	116 (4)	123 (5)	136 (11)	144 (9)	149 (7)	120 (3)	140 (6)	
Oxprenolol Oros 10/170, day 1	148 (6)	136 (7)	127 (4)	123 (4)	128 (4)	127 (6)	131 (5)	131 (6)	135 (9)	
Oxprenolol Oros 10/170, day 8	135 (12)	131 (9)	127 (4)	122 (5)	127 (5)	127 (3)	132 (5)	132 (8)	136 (9)	
	0	1	2	3	4	6	8	12	15	24
Study B										
Placebo, day 1	155 (9)	156 (9)	157 (8)	158 (8)	158 (10)	161 (7)	156 (8)	160 (9)	156 (8)	155 (8)
Placebo, day 2	154 (7)	155 (7)	157 (8)	158 (7)	158 (7)	159 (5)	157 (7)	158 (7)	156 (5)	153 (7)
Slow Trasacor, day 1	151 (5)	130 (7)	126 (7)	125 (8)	125 (8)	128 (7)	129 (6)	137 (6)	139 (6)	147 (6)
Slow Trasacor, day 8	145 (13)	126 (8)	125 (9)	125 (11)	125 (10)	125 (8)	128 (10)	135 (9)	135 (12)	147 (12)
Oxprenolol Oros 16/260, day 1	154 (5)	142 (9)	133 (7)	129 (6)	128 (6)	129 (4)	130 (6)	133 (7)	134 (6)	141 (10)
Oxprenolol Oros 16/260, day 8	133 (11)	135 (12)	131 (8)	129 (9)	128 (8)	128 (6)	128 (6)	131 (10)	130 (8)	135 (12)

Overall β -adrenoceptor blocking activity, as assessed by the areas between drug and placebo profiles over 24 h, were similar for the two dosage forms, and there was no evidence of an enhanced pharmacological response after repeated dosing. For both formulations on the two study days there was a linear relationship between the logarithm of the plasma oxprenolol concentration and the percentage reduction in exercise heart rate.

Study B Mean exercise heart rates are shown in Figure 2 and Table 2. On day 1, heart rates were significantly reduced from 1–15 h after dosing with Slow Trasacor compared with 1–24 h after 16/260 oxprenolol Oros. The only significant difference between formulations was seen at 1 h, when Slow Trasacor produced the greater effect. On the eighth day a greater pre-dosing effect with 16/260 Oros was observed, giving a reduction in mean exercise heart rate,

relative to placebo, of 12.3% compared with 4.7% for Slow Trasacor. The differences between Oros and Slow Trasacor regimens were significant at 0 and 24 h after dosing ($P = 0.0017$). On day 8 the mean exercise heart rates over the 24 h period did not differ by more than 7 beats/min after 16/260 Oros, whereas after Slow Trasacor this value was 22 beats/min.

'Haemodynamic' areas between drug and placebo curves were similar for the two formulations on both study days. A linear relationship between the logarithm of plasma oxprenolol concentration and percentage reduction in exercise heart rate was again observed for both formulations on both days.

Discussion

The 10/170 oxprenolol Oros system given once daily provided a considerably smoother plasma

oxprenolol curve than did conventional Trasacor 80 mg given 12 hourly. Peak plasma oxprenolol levels after the former were lower by a factor of three than after the latter formulation. Despite these differences, the pre-dosing plasma oxprenolol concentrations for the two treatment regimens were similar. The pharmacodynamic profile of the 10/170 Oros was likewise smoother (as assessed by inhibition of exercise tachycardia) than that of conventional Trasacor 80 mg 12 hourly and, in contrast to the latter, maintained significant β -adrenoceptor blockade for 24 h. It is notable that the peak effects of the two formulations on exercise tachycardia were more similar than their peak plasma oxprenolol values. This reflects the fact that inhibition of exercise tachycardia is related to the logarithm of plasma concentration rather than to the plasma concentration itself (Davidson *et al.*, 1976; McAinsh *et al.*, 1978; Woods *et al.*, 1979).

The 16/260 oxprenolol Oros system performed *in vivo* in a similar manner to the 10/170 Oros preparation. By the eighth day, 16/260 Oros was producing a significantly higher plasma oxprenolol concentration during the second half of the 24-h dosage interval than did Slow Trasacor, with more sustained inhibition of exercise tachycardia in consequence. Between 1 and 24 h on the eighth day, mean exercise heart rates after 16/260 Oros also varied within a considerably narrower range than after Slow Trasacor (7 as opposed to 22 beats/min).

The maximum haemodynamic effects produced by 80 mg conventional Trasacor, 160 mg Slow Trasacor, 10/170 Oros and 16/260 Oros regimens were similar, suggesting that all treatments would be equally well tolerated. However, both Oros systems extended the duration of significant β -adrenoceptor blockade to 24 h which, if translated into a comparable clinical response, would permit once-daily administration without loss in efficacy towards the end of the dosage interval. Not surprisingly, the pre-

dosing effect was greatest with the 16/260 Oros, and the variation in response over the 24 h was least with this form.

Areas under the curve were not increased after repeated dosing with the conventional and polymer-matrix slow-release formulations; the increases observed with both Oros systems were also consistent with simple accumulation following multiple dosing with an extended-release preparation. No evidence for a change in drug clearance on repeated dosing, as has been described for metoprolol (Kendall *et al.*, 1980), propranolol (Wood *et al.*, 1978) and acebutolol (Meffin *et al.*, 1978), was obtained.

The results of study A suggest that the availability of drug from the 10/170 Oros system is reduced in relation to the conventional tablet form. Despite this possible limitation, pre-dosing plasma concentrations for the conventional twice-daily and 10/170 Oros once-daily regimens were similar. In study B the amounts of drug reaching the circulation from Slow Trasacor and the 16/260 Oros were in proportion to the doses administered. Since the Oros system continues to release drug for longer than 20 h the equivalence of the two dosage forms suggests that oxprenolol is well absorbed throughout most of the gastrointestinal tract, and that colonic absorption is not subject to a significantly different first-pass effect.

These studies indicate that the *in vitro* release characteristics of oxprenolol Oros result in prolonged, steady drug delivery *in vivo* in healthy volunteers. It remains to be seen whether this dosage form will confer a measurable advantage over Slow Trasacor in the treatment of conditions such as angina pectoris and hypertension, where sustained β -adrenoceptor blockade is sought.

We thank Sister Ruth Gibson and Mrs Doreen Bradley for their technical skills in the conduct of this study.

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