Single-dose pharmacokinetic and pharmacodynamic comparison of polymer-matrix (Slow Trasicor) and Oros dosage forms of oxprenolol in healthy volunteers

P. N. BENNETT¹, J. BENNETT², I. BRADBROOK³, J. FRANCIS³, V. A. JOHN⁴, H. ROGERS³, P. TURNER² & S. J. WARRINGTON²

¹Clinical Pharmacology Unit, Royal United Hospital, Bath; ²Department of Clinical Pharmacology, St Bartholomew's Hospital, London; ³Department of Clinical Pharmacology, Guy's Hospital, London, and

⁴Clinical Research Department, Ciba-Geigy Pharmaceuticals, Horsham, West Sussex, UK

1 Oxprenolol was administered in single doses by mouth to healthy volunteers either in a polymer-matrix slow-release formulation (Slow Trasicor®) or in osmotic drug-delivery systems (oxprenolol Oros). Plasma oxprenolol concentrations and heart rates after exercise were measured.

2 Plasma concentrations of the drug were maximal at 3 h but negligible at 24 h after administration of Slow Trasicor. Following ingestion of the Oros systems measurable concentrations were maintained throughout 24 h.

3 Significant reduction of exercise-induced tachycardia persisted for 24 h after administration of oxprenolol Oros. With Slow Trasicor heart rate responses had returned to baseline values by this time.

4 The osmotic drug-delivery systems appear to sustain significant β -adrenoceptor blockade for 24 h after a single oral dose.

Keywords oxprenolol Oros dosage form plasma concentrations β -adrenoceptor blockade

Introduction

Pharmaceutical systems that control drug release within the body have long been the subject of study and innovation. For oral dose forms, micro-encapsulation or incorporation of drug into an inert polymer-matrix are frequently used. Elsewhere in this issue is a description of the Oros system (Theeuwes *et al.*, 1985), which depends on osmotic pumping of drug from its dose form to achieve controlled delivery. Oxprenolol is a β -adrenoceptor antagonist which is widely used for treatment of hypertension and angina. Its short elimination half-life of 1–2 h (Brunner *et al.*, 1975) is a disadvantage in these indications and the drug has been made available in a polymer-matrix formulation (Slow Trasicor) which delays its release in the alimentary tract. Incorporation of oxprenolol into an Oros system has significantly extended the duration of this release process, offering the

prospect of an improved preparation for once daily use. This paper reports plasma oxprenolol concentrations and exercise heart rates in healthy volunteers who took single doses of oxprenolol by mouth either as Slow Trasicor or as three different Oros systems.

Methods

Materials consisted of oxprenolol as:

1. Slow Trasicor tablets (each containing 160 mg of the hydrochloride salt)
2. Oxprenolol Oros systems containing:
 - (a) 170 mg of the succinate salt released at an initial rate of 10 mg/h ('10/170 Oros'),
 - (b) 170 mg succinate released at an initial rate of 16 mg/h ('16/170 Oros'), and

(c) 260 mg succinate released at an initial rate of 16 mg/h ('16/260 Oros'), and

3. Matching placebo tablets.

Subjects were healthy male and female volunteers, the ranges of whose ages and weights were as follows: study I ($n = 8$) 21–22 years, 72–84 kg; study II ($n = 6$) 23–30 years, 58–73 kg; study III ($n = 6$) 21–24 years, 49–70 kg. Blood was taken from each volunteer for haematological and biochemical examination and normal results were obtained. The experimental procedures were approved by the ethics committee of each centre at which the work was undertaken.

The investigation was conducted in three parts, each of which took place in a different centre. The trials were designed to be double-blind, and the formulations tested were administered in random order. In study I, two Slow Trasicor tablets, one 16/260 Oros system and placebo were compared; in study II, one Slow Trasicor tablet, one 10/170 Oros, one 16/260 Oros and placebo were compared; in study III, one 10/170 Oros, one 16/170 Oros and placebo were compared.

The formulations were administered as single doses, there being at least 7 days between doses. Each formulation was taken with 100 ml of water at about 9 a.m. after volunteers had fasted for at least 12 h. Volunteers were permitted non-alcoholic drinks at 2 and 7 h, and given light meals at 4 and 10 h after dosing. Heart rates were measured at rest and during sub-maximal exercise on a bicycle ergometer. The workload required to produce a heart rate above 150 beats/min during the last 15 seconds of a 3 min exercise test on the ergometer was established for each volunteer before the study was begun, and this workload was used at each assessment.

Blood samples for measurement of oxprenolol concentrations were taken at intervals after dosing.

Assay of oxprenolol in plasma was performed by gas-liquid chromatography (Degen & Riess, 1976) and concentrations were reported as the hydrochloride salt. The technique has a precision of better than $\pm 10\%$ at concentrations in excess of 20 $\mu\text{g/l}$.

Statistical analysis was based on the generalised Student's *t*-test approach of Welch (1947), and on the non-parametric Friedman and Wilcoxon signed rank sum tests.

Results

Mean plasma oxprenolol concentration and heart rate changes in the three studies are shown in Table 1.

In study I, maximum plasma oxprenolol concentrations attained after 16/260 Oros was significantly lower ($P = 0.008$) than those attained after 2×160 mg Slow Trasicor tablets. However, the rate of decline from the maximum was slower for the former preparation, so that at 20 and 24 h after Slow Trasicor plasma oxprenolol concentrations were negligible or zero, whereas after Oros the mean concentrations were 80 and 62 $\mu\text{g/l}$, respectively. Exercise heart rate fell after administration of both oxprenolol formulations; 24 h after dosing, heart rate had returned to the baseline value when Slow Trasicor tablets were taken, but remained significantly below the baseline value when 16/260 Oros was administered ($P = 0.002$).

In study II the mean plasma oxprenolol concentrations reached a higher maximum value after Slow Trasicor than after either the 10/170 or 16/260 Oros systems ($P = 0.006$). By 20 h and 24 h after Slow Trasicor, plasma oxprenolol concentrations were negligible, whereas after the Oros forms they were well maintained, and heart rates were significantly lower than the baseline values at both assessment times ($P = 0.002$). Plasma oxprenolol concentrations recorded at 24 h after dosing with 16/260 Oros were significantly higher than those observed after 10/170 Oros ($P = 0.001$). Exercise heart rates were also lower with the former preparation at this time point.

In study III the mean maximum plasma oxprenolol concentration was significantly higher for 16/170 than for 10/170 Oros ($P = 0.031$) but at 24 h after dosing the mean concentration was considerably higher for the 10/170 Oros form. The differences in exercise heart rates after administration of the two Oros systems were less pronounced, and similar maximum effects were observed. At 24 h after dosing, heart rates were lower for the 10/170 compared with the 16/170 Oros dosage form.

For comparison, the mean values for all subjects in the three studies are given in Figure 1. The lowest maximum concentrations were recorded with the 10/170 and 16/260 Oros systems, and the highest with 2×160 mg Slow Trasicor. At 24 h after dosing with Oros, mean plasma oxprenolol concentrations ranged between 47 and 93 $\mu\text{g/l}$, and heart rate responses to exercise were significantly attenuated.

Discussion

Studies I and II show that plasma oxprenolol concentrations were more evenly maintained throughout the period of the study if 10/170 or 16/260 Oros were taken. Maximum plasma

Table 1 Plasma oxprenolol concentrations and exercise heart rates in healthy volunteers after single oral doses of Slow Trasicor and Oros systems in Studies I, II and III

		Time after dosing (h)											AUC ($\mu\text{g l}^{-1}\text{h}$)
		0	1	2	3	4	6	9	12	14	20	24	
Study I (n = 8)													
Plasma oxprenolol ($\mu\text{g/l}$)													
Slow Trasicor	mean	0	461	560	619	553	376	226	123	72	15	0	4767
2 $\times$ 160 mg	$\pm$ s.e. mean	0	90	60	70	70	54	39	14	9	1	0	24
16/260 Oros	mean	0	17	86	172	204	174	159	148	124	80	62	2893
	$\pm$ s.e. mean	0	9	15	18	30	29	37	21	21	17	19	426
Exercise heart rates (beats/min)													
Placebo	mean	180	—	175	—	185	185	181	181	186	—	179	
	$\pm$ s.e. mean	5	—	3	—	3	3	4	3	2	—	4	
Slow Trasicor	mean	179	—	129	—	127	136	139	151	156	—	171	
	$\pm$ s.e. mean	2	—	3	—	3	3	2	3	4	—	3	
16/260 Oros	mean	180	—	153	—	147	149	148	153	152	—	156	
	$\pm$ s.e. mean	7	—	3	—	4	3	4	6	5	—	6	
Study II (n = 6)													
Plasma oxprenolol ($\mu\text{g/l}$)													
Slow Trasicor	mean	0	228	336	356	355	253	136	120	66	18	8	3202
160 mg	$\pm$ s.e. mean	0	15	61	44	34	21	17	26	11	9	3	318
10/170 Oros	mean	0	30	121	143	178	163	123	121	104	52	45	2418
	$\pm$ s.e. mean	0	10	17	19	14	18	22	19	13	12	11	639
16/260 Oros	mean	0	23	98	206	210	187	157	176	166	127	133	3627
	$\pm$ s.e. mean	0	9	20	37	32	14	34	35	30	13	21	526
Exercise heart rate (beats/min)													
Placebo	mean	163	—	158	—	161	161	153	156	158	—	161	
	$\pm$ s.e. mean	6	—	6	—	5	5	5	5	5	—	5	
Slow Trasicor	mean	163	—	126	—	128	133	135	137	141	—	160	
	$\pm$ s.e. mean	5	—	2	—	4	4	4	5	2	—	4	
10/170 Oros	mean	159	—	135	—	127	129	131	133	132	—	143	
	$\pm$ s.e. mean	4	—	1	—	2	3	2	2	1	—	1	
16/260 Oros	mean	167	—	140	—	128	130	124	126	127	—	134	
	$\pm$ s.e. mean	3	—	6	—	4	4	2	3	4	—	4	
Study III (n = 6)													
Plasma oxprenolol ($\mu\text{g/l}$)													
10/170 Oros	mean	0	40	227	297	312	301	203	192	184	95	95	4280
	$\pm$ s.e. mean	0	13	27	29	48	58	17	24	22	12	22	367
16/170 Oros	mean	0	121	273	425	437	332	236	209	154	66	47	4585
	$\pm$ s.e. mean	0	35	18	60	51	50	24	33	30	13	13	466
Exercise heart rate (beats/min)													
Placebo	mean	168	—	166	—	169	167	168	—	162	—	163	
	$\pm$ s.e. mean	5	—	4	—	3	4	3	—	5	—	6	
10/170 Oros	mean	164	—	130	—	130	132	132	—	132	—	144	
	$\pm$ s.e. mean	5	—	4	—	5	5	5	—	5	—	6	
16/170 Oros	mean	163	—	131	—	128	133	135	—	138	—	151	
	$\pm$ s.e. mean	5	—	4	—	5	5	4	—	5	—	6	

(AUC—area under the plasma concentration-time curve between 0 and 24 h).

Figure 1 Mean plasma oxprenolol concentration and reduction of exercise-induced heart rate in healthy volunteers after Slow Trasicor 160 mg ($n = 6$; $\circ$ --- $\circ$), Slow Trasicor 2×160 mg ($n = 8$; $\blacktriangle$ --- $\blacktriangle$), 10/170 Oros ($n = 12$; $\square$ --- $\square$), 16/170 Oros ($n = 6$; $\triangle$ --- $\triangle$) and 16/260 Oros ($n = 14$; $\bullet$ --- $\bullet$) systems by mouth in single doses.

oxprenolol concentrations were highest after Slow Trasicor, but 24 h after dosing concentrations were negligible or zero. Changes in plasma oxprenolol concentration are reflected in the heart rate responses during exercise. Following Slow Trasicor maximum depression of exercise heart rate occurred at 2–4 h but by 24 h the rate had returned to its baseline value. With 10/170 and 16/260 Oros, maximum reductions occurred at 4 h and were still significant 24 h after dosing.

When the characteristics of the different Oros systems are compared, it is evident from study II (Table 1) that 10/170 and 16/260 Oros gave rise to similar plasma drug-concentration/time profiles—the higher concentrations following 16/260 Oros reflecting the higher release rate and greater total content of this system. The plasma profiles for both Oros forms appear to meet the objective of prolonged, controlled drug delivery. Furthermore the release rates and drug content of each system seem to be such that reasonably stable β -adrenoceptor blockade can be maintained throughout 24 h after a single dose. It is also evident from study III (Table 1) that the design of the 16/170 system provides too rapid a rate of delivery, in

relation to its content, to be a satisfactory prolonged-release preparation. Plasma concentrations of oxprenolol with 16/170 Oros were initially greater but subsequently less than those obtained with 10/170 Oros.

The areas under the plasma concentration curves between 0 and 24 h (AUC), corrected for the size of the administered dose, were not significantly different when the results for the Oros systems in studies II and III were compared. However, in study I, the dose-corrected AUCs after Slow Trasicor were substantially greater than the corresponding values obtained with 16/260 Oros in at least two of the eight subjects. In study II, the AUCs after Slow Trasicor also tended to be greater than those obtained after the 10/170 Oros system.

Oxprenolol administered by the oral route undergoes presystemic elimination. Studies by Mason & Winer (1976) in normal volunteers indicated that the systemic availability of oxprenolol was 24–60%. These authors also found that in the dose range 20–160 mg there was no evidence of saturation of first-pass elimination when single conventional doses were taken. The reduced oxprenolol availability from Oros

suggests that slow delivery may be associated with increased presystemic metabolism of the drug. Alternatively, *in vivo* drug release from Oros may have terminated prematurely, or gut wall metabolism of oxprenolol may have been greater in the lower compared with the upper segments of the gastrointestinal tract. These

possibilities cannot be distinguished in the present study. Despite the reduced drug availability from Oros, however, the systems maintained measurable plasma concentrations and significant levels of β -adrenoceptor blockade throughout 24 h after single dosing.

References

- Brunner, L., Imhof, P. & Jack, D. (1975). Relation between plasma concentrations and cardiovascular effects of oral oxprenolol in man. *Eur. J. clin. Pharmac.*, **8**, 3–9.
- Degen, P. H. & Riess, W. (1976). Simplified method for the determination of oxprenolol and other β -receptor blocking agents in biological fluids by gas-liquid chromatography. *J. Chromatogr.*, **121**, 72–75.
- Mason, W. D. & Winer, N. (1976). Pharmacokinetics of oxprenolol in normal subjects. *Clin. Pharmac. Ther.*, **20**, 401–412.
- Theeuwes, F., Swanson, D. R., Guittard, G., Ayer, A. & Khanna, S. (1985). Osmotic delivery systems for the β -adrenoceptor antagonists, metoprolol and oxprenolol: design and evaluation of systems for once-daily administration. *Br. J. clin. Pharmac.*, **19**, 69S–76S.
- Welch, B. L. (1947). The generalization of Student's problem when several different population variances are involved. *Biometrika*, **34**, 28–35.