Concentration-effect relationships for oxprenolol in patients with essential hypertension

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1 Plasma drug concentrations, and heart rate and blood pressure responses to exercise at a predetermined load were examined in twelve hypertensive patients following single and repeated doses of oxprenolol administered once daily as oral osmotic drug delivery systems (10/170 and 16/260 oxprenolol OROS).

2 Plasma oxprenolol concentration profiles after each preparation were consistent with the criteria for sustained drug release. Levels immediately after exercise were significantly higher than those prior to exercise ($P < 0.001$), but differences were slight.

3 Both OROS drug forms reduced exercise heart rate for 24 h after single and repeated doses; effects were greater for 16/260 OROS than for 10/170 OROS. Significant reductions in post-exercise systolic BP were observed 24 h after drug administration and after repeated doses there was little difference between the preparations. Effects on diastolic BP after exercise were slight.

4 The relationship between plasma oxprenolol concentrations and exercise heart rates fitted an exponential mathematical model which makes allowance for inter-individual variability. No such kinetic-dynamic relationship could be defined for post-exercise systolic or diastolic BP.

Keywords hypertension oxprenolol pharmacodynamics pharmacokinetics

Introduction

Relationships between the plasma concentrations of β -adrenoceptor antagonists and their therapeutic properties have proved difficult to establish (Chidsey *et al.*, 1976; Israili, 1979). Indeed, antihypertensive effects may persist when little or no circulating drug is detectable (Wilson *et al.*, 1976). In contrast, the duration of action of oxprenolol corresponds to its elimination half-life of only 1–2 h (Brunner *et al.*, 1975; Mason & Winer, 1976) and, even with the sustained release preparation (Slow Trasicor), antihypertensive efficacy is inconsistent 24 h after administration (Bobik *et al.*, 1979; Petrie *et al.*, 1980) often necessitating multiple daily dosing.

Oral osmotic (OROS) delivery systems

(Theeuwes, 1975) have been developed in an attempt to compensate for oxprenolol's short duration of action. Oxprenolol OROS systems deliver 90% of the drug in 20–24 h (approximately 60% at zero-order rates) regardless of the physiological environment of the gut (Theeuwes *et al.*, 1985). In healthy men, measurable plasma oxprenolol levels are obtained within 1 h of administration and substantial concentrations are sustained for 24 h (Bennett *et al.*, 1985). Furthermore, β -adrenoceptor blockade is maximal at 4 h and persists for 24 h (Bennett *et al.*, 1985).

This study examined oxprenolol pharmacokinetics, haemodynamic responses at the end

of a period of exercise and their relationships following single and repeated doses of two OROS preparations administered once daily to patients with essential hypertension. Since the heart rate response to submaximal exercise is a marker of endogenous sympathetic activity (Robinson *et al.*, 1966), reduction in exercise heart rate (EHR) is a valid measure of β -adrenoceptor blockade (Israili, 1979). Although systolic blood pressure (BP) on moderate exertion is also influenced by adrenergic tone, its modification during β -adrenoceptor blockade is less consistent (Collste *et al.*, 1976; Esler *et al.*, 1978; Israili, 1979; Martin *et al.*, 1978). Hitherto, plasma concentration-effect relationships for EHR and BP have been described mainly in terms of a log-linear model (Brunner *et al.*, 1975; Israili, 1979; McAinsh *et al.*, 1978; McDevitt, 1977; Martin *et al.*, 1978; Mason & Winer, 1976) but this approach has limitations (Holford & Sheiner, 1981), and as it depends on mean results, no allowance is made for variability in responses. The experimental model used here (Racine-Poon & Moppert, 1985) allows the inclusion of additional terms to account for drug and subject attributes and thus represents a more general description of the kinetic-dynamic relationship.

Methods

Subjects

Twelve patients (five males and seven females) with essential hypertension gave written consent to participate in the study after full explanation of its purposes and risks. Mean age was 47.3 years (range 25–59), weight 64.5 kg (40–97.3) and height 163 cm (152–182). In all patients, resting BP prior to study was controlled by a β -adrenoceptor antagonist (atenolol 50–100 mg in six; propranolol 80–320 mg in four, oxprenolol 240 mg in one and pindolol 5 mg in one). None of the patients had clinically significant renal, hepatic or gastrointestinal impairment. The protocol was approved by the hospital ethics committee.

Design

The study was a randomised, balanced, crossover comparison of 10/170 oxprenolol OROS and 16/260 oxprenolol OROS. Treatment sequence was placebo, active therapy, placebo, active therapy. Each treatment phase was of 2 weeks' duration. The study was carried out under patient-blind conditions by means of the double-dummy technique.

Drugs

10/170 oxprenolol OROS + 16/260 oxprenolol OROS placebo
16/260 oxprenolol OROS + 10/170 oxprenolol OROS placebo
Double placebo

10/170 oxprenolol OROS contains oxprenolol succinate 170 mg released at an initial zero-order rate of 10 mg h⁻¹ and 16/260 oxprenolol OROS contains oxprenolol succinate 260 mg released at a rate of 16 mg h⁻¹. Oxprenolol succinate is used instead of the hydrochloride (in other commercial formulations) because it is less soluble in water. Succinate 170 mg is equivalent to hydrochloride 160 mg and succinate 260 mg to hydrochloride 240 mg.

Drugs were administered once daily at 09.00 h.

Procedure

Patients were admitted to the investigation unit after 2 weeks' treatment with placebo (day 1) and 2 weeks treatment with oxprenolol OROS (day 15). Heart rate and blood pressure were measured after 3 min constant exercise immediately prior to administration of oxprenolol OROS i.e. day 1–24 h after placebo; day 15–24 h after previous dose of oxprenolol OROS. Thereafter drug was administered and pharmacodynamic measurements were repeated 4, 8, 12 and 24 h later. Venous blood samples for plasma oxprenolol concentrations were obtained immediately before and after exercise tests and also approximately 1, 2, 3, 6, 10, 14 and 22 h after drug administration. Blood samples were centrifuged without delay and plasma fractions stored at -20° C until analysis. Patients remained ambulant on study days and diet was uncontrolled.

Measurements

- Plasma oxprenolol concentrations were assayed using a specific high performance liquid chromatography method (Degan & Riess, 1976) and reported as the hydrochloride salt.
- Exercise testing was conducted using a speed-independent bicycle ergometer (Ergomed 740, Siemens Aktiengesellschaft). The workload employed was that necessary to produce a heart rate of 120–130 beats min⁻¹ after 3 min constant exercise while the patient was taking pre-trial β -adrenoceptor antagonist (mean 100 watts, range 50–250).
- Heart rate was measured from a standard ECG trace (modified lead II) using beat frequency (mean R-R interval) during the last 10 s of exercise.

(d) BP in the erect position was measured using a Bosomat II semi automatic BP recorder (Bosch & Sohn).

ECG tapes and BP recordings were assessed by two independent observers.

Data analysis

(a) *Pharmacokinetic parameters* Peak plasma oxprenolol concentrations ($C_{\max}$), time to reach $C_{\max}$ ($t_{\max}$) and plasma concentrations at 24 h after drug administrations (C_{24h}) were measured directly. Areas under the plasma concentration-time curves (AUC_{0-24h}) were calculated by the trapezoidal rule.

(b) *Plasma concentration-effect relationships* Plasma oxprenolol concentrations and post-exercise heart rates were fitted to the mathematical model of Racine-Poon & Moppert (1985) using a computerised non-linear least-squares regression method, NONLIN (SAS, 1982). The equation defining the relationship is given by:

$$R_{(c)} = R_0 - R_{\max} (1 - e^{-\alpha C})$$

where $R_{(c)}$ = exercise heart rate (EHR) at concentration C
 R_0 = EHR in absence of drug
 α = a proportionality constant reflecting the overall sensitivity of the responses
 $R_{\max}$ = the maximum achievable effect and is given by $R_0 - R_{\min}$

Data from days 1 and 15 were pooled, since chronic dosing does not appear to modify the dynamic response to oxprenolol (Racine-Poon & Moppert, 1985).

A similar approach was used in an attempt to correlate plasma oxprenolol concentrations with effects on post-exercise BP.

(c) *Statistical analysis* Pharmacokinetic data were analysed using the Wilcoxon's matched pairs signed rank test. For each formulation, pharmacodynamic results on the first day of

treatment were compared using analysis of variance. A similar analysis was carried out on the day 15 results. Results 24 h after final dose of placebo (09.00 h day 1) and 24 h after repeated doses oxprenolol OROS (09.00 h day 15) were compared using Student's t -test. The results at 4, 8, 12 and 24 h after the first dose and after repeated dosing with each formulation were compared by analysis of variance. In the absence of time $\times$ drug interaction, an F test was performed to determine if the days differed at all time points. The effects of 10/170 OROS and of 16/260 OROS both after single and repeated doses were compared using a similar approach. No carryover effects were found indicating that the formulation differences did not depend on order of administration.

Results

Plasma oxprenolol concentrations

Pharmacokinetic parameters on days 1 and 15 of treatment with 10/170 and 16/260 OROS systems are presented in Table 1. Mean plasma oxprenolol concentration profiles are illustrated in Figure 1.

After single and repeated administrations of both drug forms, $t_{\max}$ was 5 to 6 h, and was earlier for the 16/260 OROS system than for the 10/170 system particularly after the first dose. $C_{\max}$ and AUC after both drug delivery systems were higher after repeated doses than following single administrations but the increases were significant only for 16/260 OROS. On both study days, $C_{\max}$, C_{24h} and AUC were higher after the 16/260 system than after the 10/170 system although the difference in $C_{\max}$ after single doses failed to achieve statistical significance. The post peak decline in mean plasma oxprenolol concentrations was gradual, such that considerable amounts of oxprenolol were still detectable 24 h after drug administration. Levels at 24 h after repeated administration were similar to those after single doses.

Table 1 Median (range) for pharmacokinetic parameters derived from plasma oxprenolol concentrations in 12 hypertensive patients after once daily administration of 10/170 and 16/260 OROS systems

Parameter	Day 1		Day 15	
	10/170 OROS	16/260 OROS	10/170 OROS (n = 11)	16/260 OROS
$C_{\max}$ (ng ml ⁻¹)	351 (110-557)	360 (179-837)	364 (232-827)	463 (278-818)**††
$t_{\max}$ (h)	6.07 (3.82-11.62)	4.97 (2.88-8.47)†	6.10 (3.87-11.97)	5.52 (3.83-12.05)
C_{24h} (ng ml ⁻¹)	101 (46-300)	195 (70-510)††	148 (65-308)	206 (93-471)††
AUC_{0-24h} (ng ml ⁻¹ h)	4293 (1687-9193)	5417 (2478-14371)†	5361 (3088-10000)	7001 (3824-12808)**††

Statistical significance vs day 1 * $P = 0.05$ ** $P < 0.01$
vs 10/170 OROS † $P < 0.05$ †† $P < 0.01$

Figure 1 a) Plasma oxprenolol concentrations after single (●) and repeated (○) once daily doses administered by an oral osmotic delivery system (10/170 OROS). Mean (vertical bars s.e. mean) results. b) Plasma oxprenolol concentrations after single (●) and repeated (○) once daily doses administered by an oral osmotic delivery system (16/260 OROS). Mean (vertical bars s.e. mean) results.

Mean plasma oxprenolol concentrations were generally greater following exercise than immediately prior to exercise (Figure 1). Using only results obtained during the declining phase in plasma concentrations for each individual (i.e. after t_{max}), the differences were statistically significant for both preparations but the overall difference was slight (mean $\pm$ s.d. $245.5 \text{ ng ml}^{-1} \pm 144.3$ vs 239.5 ± 142.5 , $P < 0.001$).

Pharmacodynamic responses

The results are summarised in Table 2. Compared with placebo, reductions in EHR persisted for 24 h after single and repeated administrations of 10/170 and 16/260 OROS. EHRs after repeated administrations were consistently greater than those following the first doses ($P = 0.009$ for 10/170 OROS and $P = 0.014$ for 16/260 OROS). Mean EHRs across 24 h were significantly lower during treatment with 16/260 OROS than during treatment with 10/170 OROS, both after single ($P = 0.001$) and repeated daily administrations ($P < 0.001$).

Post-exercise systolic BP was reduced 24 h after the first dose of each OROS preparation. After 14 days treatment, there were no significant changes in systolic pressure during the day after 10/170 OROS but significant variations persisted after 16/260 OROS ($P = 0.007$). Compared with levels after 2 weeks' treatment with placebo, both formulations produced similar decreases in systolic pressure but only the reduction following 10/170 OROS reached statistical significance. BP profiles after 14 days' treatment were reduced significantly compared with those after single doses ($P < 0.001$ for 10/170 OROS and $P =$

Table 2 Mean $\pm$ s.d. results for heart rate (EHR, beats min^{-1}), systolic BP (SBP, mm Hg) and diastolic BP (DBP, mm Hg) after constant exercise in hypertensive patients following placebo and during treatment with oxprenolol administered once daily (09.00 h) as 10/170 and 16/260 OROS

Response	OROS	Placebo	Day 1				0h	Day 15			
			4h	8h	12h	24h		4h	8h	12h	24h
EHR	10/170	148.2 ± 14.2	116.7 ± 8.5	120.9 ± 8.7	120.6 ± 9.6	126.6** ± 12.1	127.1*** ± 15.1	120.8 ± 15.9	123.3 ± 15.0	124.0 ± 14.9	129.6 ± 16.5
	16/260	150.5 ± 16.3	112.8 ± 9.5	115.4 ± 10.6	119.8 ± 10.0	118.6** ± 11.6	124.9*** ± 13.6	115.2 ± 9.3	118.1 ± 9.9	119.8 ± 9.1	122.7 ± 11.2
SBP	10/170	175.4 ± 15.4	160.3 ± 15.5	166.3 ± 15.3	162.1 ± 12.8	159.7** ± 20.7	159.5* ± 17.6	149.9 ± 24.1	149.8 ± 23.5	152.0 ± 22.1	150.8 ± 25.2
	16/260	178.2 ± 18.4	157.2 ± 22.3	156.6 ± 16.3	160.3 ± 14.5	151.2** ± 17.8	161.8 ± 23.8	152.7 ± 18.4	148.1 ± 18.7	149.7 ± 23.9	146.9†† ± 22.8
DBP	10/170	92.6 ± 14.7	97.3 ± 11.1	89.9 ± 12.0	93.7 ± 9.4	89.3 ± 9.8	88.9 ± 6.3	88.9 ± 10.3	89.8 ± 10.7	87.0 ± 13.1	81.6† ± 9.4
	16/260	95.3 ± 15.0	95.8 ± 12.6	91.3 ± 10.6	90.8 ± 9.6	83.9** ± 10.0	89.0 ± 13.9	88.0 ± 12.1	87.5 ± 12.3	85.7 ± 12.6	84.0 ± 9.2

Statistical significance vs placebo * $P < 0.05$ ** $P < 0.01$ *** $P < 0.005$
vs 0900h Day 15† $P < 0.05$ †† $P < 0.01$

0.002 for 16/260 OROS). Lower pressures were attained with the first dose of 16/260 OROS than with the first dose of 10/170 OROS ($P = 0.02$) but there were no differences after repeated administrations.

No change in erect diastolic BP was seen after the first dose of 10/170 OROS but the 16/260 system produced significant reduction at 24 h. After 14 days treatment with 10/170 OROS, values at 24 h were significantly less than at 0 h ($P < 0.05$); no such variability in response was seen after 14 days' treatment with 16/260 OROS. Repeated doses of both drug formulations caused a reduction in mean erect diastolic BP when compared with the placebo responses but changes were not statistically significant. For both formulations, the mean values after 14 days' treatment were consistently below those after the first dose at all time points ($P < 0.001$ in each case). There were no differences between the dosage forms after single or repeated administration.

In this short term study, both OROS preparations were well tolerated.

Plasma concentration-effect relationships

The relationship between plasma oxprenolol concentration and EHR in a representative patient is shown in Figure 2. The computer derived parameter estimates for EHR in individual subjects are presented in Table 3. The mean values of R_0 ($149.1 \text{ beats min}^{-1} \pm 14.4$ and 154.5 ± 18.1 for the 10/170 and 16/260 systems, respectively) indicate that a baseline workload producing an EHR of approximately $150 \text{ beats min}^{-1}$ was achieved effectively in most patients. With the

Figure 2 Percentage reduction in EHR after single and repeated doses of oxprenolol administered as oral osmotic delivery systems. ● – 10/170 OROS single doses, □ – 10/170 OROS repeated doses, ▲ – 16/260 OROS single doses, ○ – 16/260 repeated doses. Example of correlation with plasma oxprenolol concentration in one subject.

exceptions of subjects 2 and 8, $R_{\min}$ values were similar after both treatments.

An attempt was made to fit the post-exercise BP responses using the same programme. However, in some subjects convergence of the fitting process was not achieved, and in others the fit was very poor, with negative values estimated in many cases. Thus concentration-effect modelling was precluded.

Discussion

Although there was marked inter-patient variability, administration of 10/170 and 16/260 oxprenolol OROS systems gave rise to plasma profiles characteristic of satisfactory controlled

Table 3 Derived parameter estimates for concentration-effect relationships in hypertensive patients treated with oxprenolol administered by oral osmotic delivery systems (10/170 OROS and 16/260 OROS) where R_0 = exercise heart rate in the absence of drug (beats min^{-1}), $R_{\min}$ = minimum achievable exercise heart rate (beats min^{-1}) and α = constant reflecting sensitivity of response

Subject	R_0		$R_{\min}$		α	
	10/170 OROS	16/260 OROS	10/170 OROS	16/260 OROS	10/170 OROS	16/260 OROS
1	*	162.0	*	107.1	*	0.0019
2	164.1	161.9	71.9	114.1	0.0042	0.0112
3	150.0	156.0	116.0	116.8	*	*
4	*	*	*	*	*	*
5	165.6	174.3	114.9	116.9	0.0079	0.0077
6	149.9	150.0	114.5	117.4	0.0044	0.0096
7	150.0	162.3	111.9	100.5	0.0041	0.0032
8	121.2	129.0	101.7	117.7	0.0013	0.0212
9	140.6	*	125.8	*	0.0126	*
10	168.0	168.0	130.0	126.1	0.0438	0.0221
11	144.3	137.8	115.0	108.2	0.0065	0.0025
12	137.8	143.5	109.7	108.1	0.0131	0.0143
Mean	149.1	154.5	111.1	113.3	0.0109	0.0104
s.d.	14.4	14.2	15.8	7.3	0.0130	0.0076

* Data unable to be fitted.

drug release. Peak concentrations were considerably lower than those generally observed after conventional oxprenolol or the existing slow-release formulation at similar doses (Bobik *et al.*, 1979). In addition, substantial plasma levels were maintained throughout a 24 h dosage interval. Mean plasma oxprenolol concentrations 24 h after dosing were 100–250 ng ml⁻¹, and in all subjects terminal plasma concentrations exceeded 50 ng ml⁻¹, levels at which adequate β -adrenoceptor blockade can be maintained (Theeuwes *et al.*, 1985).

Transient exercise induced increases in plasma levels of lipophilic β -adrenoceptor antagonists have been reported in animals (Powis & Snow, 1978) and in normal human subjects (Hurwitz *et al.*, 1983). These changes may reflect redistribution of β -adrenoceptor antagonists at site(s) of action (evidence cited by Hurwitz *et al.*, 1983). The increases in plasma oxprenolol concentrations (mean 2.5%) were smaller than those reported for propranolol (13–14%) by Hurwitz *et al.* (1983), although these may represent only a fraction of the changes at receptor sites. It is uncertain whether this phenomenon contributes to the therapeutic actions of β -adrenoceptor antagonists but it may represent an additional factor in evaluating plasma concentration-effect relationships.

Both OROS dose forms caused a significant reduction in exercise tachycardia throughout the once daily dosage interval after single doses and repeated administrations. The mathematical concentration-effect model employed described an exponential relationship between plasma oxprenolol concentrations and submaximal EHR consistent with the 'law of diminishing returns' (Holford & Sheiner, 1981). It appears to be established instantaneously indicating rapid equilibrium between drug in plasma and at the receptor as reported previously for oxprenolol (Silke *et al.*, 1983) and propranolol (McDevitt & Shand, 1975). EHR fell as plasma concentration rose; the degree of change with plasma concentration was greatest at low concentrations and negligible at high concentrations; a constant minimum was approached with increasing concentrations; and the relationship with plasma concentrations displayed neither an S-shaped pattern nor changes at plasma concentrations close to zero.

Although the plasma oxprenolol concentrations in our hypertensive population were approxi-

mately two-fold greater than those in healthy young subjects (Bennett *et al.*, 1985), analysis of the relationship between oxprenolol concentrations and reduction in exercise induced tachycardia gave similar parameter values in the two groups (Racine-Poon & Moppert, 1985). This suggests that sensitivity to oxprenolol does not differ greatly between hypertensives and normals.

Compared with placebo, both dosage forms caused substantial reductions in mean systolic BP immediately after exercise, for 24 h after single and repeated doses. Corresponding changes in mean diastolic pressure, which generally falls on exercise, were slight. Post-exercise BP after 2 weeks' treatment was significantly lower than that after single doses at all time points indicating a greater antihypertensive effect of oxprenolol on repeated administration in contrast to the amelioration of the effect on exercise induced tachycardia, emphasising differences in the pharmacokinetic-pharmacodynamic relationships for these cardiovascular responses.

Our inability to define the relationship between plasma oxprenolol concentrations and post exercise BP is likely to reflect the multiplicity of mechanisms which control BP and the complexity of the overall response to β -adrenoceptor antagonism (Israili, 1979). Although correlation between reduction in BP and plasma concentrations of β -adrenoceptor antagonists have been reported occasionally in acute studies uncomplicated by adaptive changes (Martin *et al.*, 1978), in chronic studies, relationships are much less clear (Collste *et al.*, 1976; Esler *et al.*, 1978). Furthermore, during exercise the reduction in systolic BP induced by β -adrenoceptor antagonists is not enhanced while their action on diastolic BP may actually be reversed (Leenen *et al.*, 1980) indicating that the sympathetic nervous system may not play a major role in controlling BP during exercise and/or that it can be easily overcome. Any relationship may be further complicated by the partial agonist properties of oxprenolol (Frishman & Silverman, 1979).

In conclusion, administration of both oxprenolol OROS formulations to hypertensive patients gave rise to well maintained plasma drug concentrations and correspondingly prolonged pharmacological effects. Plasma oxprenolol concentration-effect relationships were apparent for heart rate but not for blood pressure after exercise.

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