Exercise and resting blood pressure and heart rate changes 24 h after dosing in patients with essential hypertension receiving 16/260 oxprenolol Oros once daily

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1 Nineteen patients receiving oxprenolol slow-release (SR) 160 mg (three patients) or 320 mg (16 patients) once daily for mild to moderate hypertension were treated with oxprenolol Oros 16/260 once daily for 3 weeks following a 2 week placebo wash-out period.

2 Repeated dosing with both Oros and SR oxprenolol preparations, in comparison with placebo, significantly reduced supine systolic and diastolic blood pressures, and pulse rate at 24 h after dosing. Single Oros doses also significantly reduced pulse rate and diastolic, but not systolic, blood pressure at 24 h. The reduction in supine systolic blood pressure was greater during repeated dosing with oxprenolol SR than after a single dose of the Oros preparation.

3 Control of supine diastolic blood pressure (≤ 90 mm Hg) at 24 h after dosing was achieved in 13 out of 18 patients with oxprenolol SR (two out of three patients given 160 mg, and 11 out of 15 given 320 mg). Similar control was achieved in 11 out of 18 patients after a single dose of oxprenolol Oros, and in 13 out of 17 patients treated for 3 weeks.

4 The mean percentage reduction in exercise heart rate (EHR) compared to placebo, at 24 h after dosing, was 16% following Oros treatment for 3 weeks, and 12% following SR administration. After a single dose of oxprenolol Oros EHR, was reduced by 9% at 24 h compared to placebo. At 3 weeks the Oros formulation was significantly better than the SR tablet at reducing EHR.

5 Oxprenolol Oros 16/260 was effective over 24 h and well tolerated. Once daily administration with this dosage form represents a useful treatment for mild to moderate hypertension.

Keywords oxprenolol hypertension Oros dosage systems

Introduction

The present slow-release formulation of oxprenolol (oxprenolol SR, Slow Trasacor®) was developed to enable convenient once-daily administration of this short elimination half-life β -adrenoceptor antagonist for the treatment of hypertension and angina. A rapid blockade of β -adrenoceptors, maintained for at least 14 h, is

produced by 160 mg oxprenolol SR, as indicated by the reduction of exercise-induced tachycardia measured in healthy volunteers (West *et al.*, 1976). In hypertensive patients, 4 weeks' treatment with oxprenolol SR once daily had a significant hypotensive effect in comparison to placebo at 24 h after dosing (Bühler *et al.*, 1976; Wilcox

& Hampton, 1981), although it has been argued that the magnitude of this effect may be insufficient to provide satisfactory control of blood pressure in all patients (Waal-Manning & Spears, 1978; Petrie *et al.*, 1980).

The new Oros delivery system of oxprenolol offers a potential therapeutic advantage over the SR formulation by reducing the peak plasma concentration, but providing higher levels at later times after dosing. The 16/260 Oros system contains 260 mg of oxprenolol succinate released at an initial rate of 16 mg/h.

The aim of this study was to assess the effect of oxprenolol Oros 16/260 on blood pressure and heart rate at rest and during exercise 24 h after dosing in patients with mild to moderate hypertension. The efficacy and tolerability of once-daily oxprenolol Oros 16/260 for 3 weeks were compared with the preceding oxprenolol SR 160 mg or 320 mg, or placebo treatments.

Methods

Patients

Eighteen patients with essential hypertension and one with renal hypertension, who were attending the Hypertension Clinic, Department of Medicine, University Hospital, Basle, entered the study. Their hypertension was classed as mild or moderate (WHO stage I and II) and had been present for between 1 and 17 years. Seventeen patients were male and two were female; their mean age was 43.4 (range 23–65) years and mean weight 77.6 (range 64–106) kg. All the patients had received either oxprenolol SR 160 mg (3 patients) or 320 mg (16 patients) once daily for at least 1 month before entering the trial. Any patients with angina, obstructive airway disease, contra-indications to β -adrenoceptor blockade, impaired renal or hepatic function or other severe concomitant illness were excluded from the trial. All the patients consented to taking part in the trial.

Procedure

The trial was single-blind and lasted for 7 weeks. Patients continued their current therapy with oxprenolol SR 160 mg or 320 mg once daily for 2 weeks, before entering a 2 week placebo wash-out period (sufficient time for the complete elimination of oxprenolol and cessation of β -adrenoceptor blockade; Bolli *et al.*, 1981). They then received oxprenolol Oros 16/260 once daily for 3 weeks. No concomitant medication was allowed except for one patient who received prednisolone 5 mg every other day throughout

the trial. Patients were assessed at the initial visit, at the end of the placebo and active treatment periods and also after administration of the first Oros dose. With the exception of the initial visit, all measurements were made at the same time of day between 23 and 25 h after dosing.

On entry into the trial, all patients had a physical examination, chest radiography and electrocardiography (ECG) performed. At each visit, the supine pulse rate was determined over 30 s, and systolic and diastolic blood pressures (Korotkoff phase I and V) were recorded using a standard mercury sphygmomanometer (13 cm cuff) after 5 min lying supine and again after 2 min standing. Patients were excluded from the trial if their supine diastolic blood pressure was below 95 or above 125 mm Hg at the end of the placebo period.

Standardized exercise testing on a bicycle ergometer was carried out at each visit. The exercise test at the initial visit served to familiarize subjects with the procedure. The workload was set at 50 watts for 3 min and then increased by 25 watts every 2 min. Patients exercised until they were exhausted, had reached a predetermined limit for submaximal exercise heart rate defined as: $215 - \text{age} \times 0.90$, or until signs or symptoms warranted premature discontinuation of the test. The workload and duration of exercising were recorded. Before the test, a resting 12-lead ECG was performed. Three ECG leads (V_5 and V_6 plus a limb or other chest lead) were monitored continuously throughout the exercise test and for 9 min after its completion. Heart rate (determined from the electrocardiogram) and systolic and diastolic blood pressure were recorded immediately before and at the end of the test, and 1, 2, 3, 6 and 9 min after test completion.

Adverse effects reported spontaneously by the patient, or observed by the clinician, were recorded throughout the trial. Standard laboratory investigations, including complete blood and urine analyses, were performed at the beginning and end of the trial.

Statistical analysis and calculations

Student's *t*-test for paired data was used to compare pulse or heart rates, and blood pressures between treatments (placebo, repeated administration of oxprenolol SR, single and repeated dosing with oxprenolol Oros). The Wilcoxon matched pairs signed ranks test was used to compare the effect of the different treatments on workload and duration of exercise tests. As multiple comparisons were performed, a *P* value of < 0.01 was taken as indicating statistical significance.

A comparison of exercise heart rates (EHR) attained during the active treatments was made by calculation of the mean percentage reduction in EHR compared to the placebo value:

$$\% \text{ EHR reduction} = \frac{\text{EHR}_{\text{placebo}} - \text{EHR}_{\text{active}}}{\text{EHR}_{\text{placebo}}} \times 100$$

Patients who did not reach 85% of their age-corrected maximum heart rate limit in the placebo exercise test, or who achieved a lower exercise workload on active treatment than on placebo, were excluded from the analysis.

Results

Resting blood pressure and pulse rate

Repeated administration of oxprenolol, either as an SR or an Oros formulation, significantly reduced the mean supine systolic and diastolic blood pressure and pulse rate 24 h after dosing, compared with placebo (Table 1). Supine pulse rate and diastolic, but not systolic, blood pressures were also significantly lower at 24 h after a single dose of oxprenolol Oros. A decrease in mean standing pulse rate, systolic and diastolic blood pressure was also observed following the active treatments (Figure 1), but the reduction was not as large as that in the supine position.

Repeated dosing with oxprenolol SR reduced the supine systolic blood pressure significantly more than did a single Oros dose (mean difference 7 mm Hg, $P < 0.01$). There were no other statistically significant differences between the efficacy of the active treatments in reducing resting blood pressures or pulse rates.

Blood pressure control, defined as a supine diastolic blood pressure ≤ 90 mm Hg, was achieved at 24 h after dosing in 13/18 patients with oxprenolol SR (2/3 patients given 160 mg and 11/15 patients given 320 mg). A similar response was seen in 11/18 patients after a single dose, and 13/17 patients after repeated doses of oxprenolol Oros. All but one patient had a dia-

stolic blood pressure > 95 mm Hg at the end of the placebo period and data from this individual were excluded from the analysis of blood pressure changes.

In a follow-up period, 13 patients received oxprenolol Oros for between 1 and 7 months. The mean blood pressure values at the end of the first 3 months averaged 140/90 mm Hg and the mean pulse rates were between 68 and 71 beats/min. The patients who continued oxprenolol Oros for longer than 3 months showed similar blood pressure and pulse rate responses at the end of each further follow-up month.

Exercise testing

Data from one patient were excluded from the analysis following his withdrawal from the exercise testing due to dyspnoea and premature ventricular beats. All other patients exercised until they were exhausted (64 occasions) or had reached their submaximal heart rate limit (eight occasions).

At the end of exercising, at 24 h after dosing, the patients achieved the same median workload and duration of test under each treatment condition (Table 2). In comparison with placebo, a higher workload was achieved at the end of exercise testing in five patients who had received repeated doses of oxprenolol SR, in five patients after repeated administration of oxprenolol Oros, and in one patient after a single dose of oxprenolol Oros.

The mean heart rate at the end of the exercise test (Table 2) was lower after both single and repeated administration of oxprenolol Oros than after placebo (mean difference: 12.3 beats/min, $P < 0.005$; 18.1 beats/min, $P < 0.001$, respectively). By contrast, the difference during repeated doses of oxprenolol SR was not statistically significant. Repeated administration of oxprenolol Oros reduced EHR more than did oxprenolol SR (mean difference: 10.3 beats/min, $P < 0.01$) but there were no other statistically significant differences between the efficacy of

Table 1 Mean reduction relative to placebo in supine blood pressure (mm Hg) and pulse rate (beats/min) by oxprenolol SR and oxprenolol Oros in 18 patients 24 h after dosing

Oxprenolol	Systolic blood pressure	Diastolic blood pressure	Pulse rate
SR repeated	15.3***	13.3***	7.1***
Oros acute	8.3	11.8***	6.3*
Oros repeated†	11.7*	13.7***	6.4**

* $P < 0.01$; ** $P \leq 0.001$; *** $P \leq 0.0001$

† $n = 17$

Figure 1 Effects of placebo, oxprenolol SR, and oxprenolol Oros, on supine $\square$, and standing ▨ blood pressure and pulse rate at 24 h after dosing. Means $\pm$ s.d. for 18 patients. (* $n = 17$ due to missing value).

the active treatments in reducing EHR. During the 9 min recovery period, the mean heart rate decreased progressively under all treatment conditions but did not reach pre-test values.

The mean percentage reduction in EHR, relative to placebo, was greater after repeated administration of oxprenolol Oros than oxprenolol SR, which in turn was more effective than a single dose of oxprenolol Oros (Table 3). The values are based on data from 13 patients who reached 85% of their age-corrected maximum EHR in the placebo exercise and 1 patient who

reached to within 2 beats/min of his 85% maximum value. Data from four patients who did not reach 85% of their maximum limit in the placebo exercise test, and from one patient who achieved a lower exercise workload on active treatment than on placebo, were excluded from the analysis. On the 11 occasions when patients achieved a higher exercise workload on active treatment than on placebo, the EHR at the same workload as the final placebo value was used in the analysis.

In comparison with placebo, the mean systolic

Table 2 Median exercise workload and duration and mean post-exercise heart rate and systolic blood pressure at 24 h after dosing in 18 patients

Treatment	Workload (watts) Median (range)	Duration (min) Median (range)	Heart rate (beats/min) Mean $\pm$ s.d.	Systolic blood pressure (mm Hg) Mean $\pm$ s.d.
Placebo	175 (150–225)	13 (11–17)	151 $\pm$ 18	199 $\pm$ 19
Oxprenolol SR repeated	175 (150–225)	13 (11–17)	143 $\pm$ 19	192 $\pm$ 16
Oxprenolol Oros acute	175 (100–225)	13 (10–17)	139 $\pm$ 18	184 $\pm$ 18
Oxprenolol Oros repeated	175 (150–225)	13 (11–17)	133 $\pm$ 17	199 $\pm$ 12

Table 3 Percentage reduction in placebo EHR by oxprenolol SR and Oros 24 h after dosing in 14 patients

<i>Oxprenolol</i>	<i>Mean</i>	<i>Median</i>	<i>Minimum</i>	<i>Maximum</i>
SR repeated	11.9	13.2	-0.7	25.0
Oros acute	9.2	5.8	-3.4	25.0
Oros repeated	16.4	15.9	8.6	25.3

blood pressure at the end of the exercise test was lowered by repeated administration of oxprenolol SR and single doses of oxprenolol Oros (Table 2), but the mean reductions of 6.6 mm Hg and 14.4 mm Hg, respectively, were not statistically significant. During the 9 min recovery period, mean systolic and diastolic blood pressures decreased to pre-test values, although diastolic blood pressure increased from the third minute onwards under both placebo and active conditions.

Tolerability

One patient receiving oxprenolol SR 320 mg felt weak for 1 day. One patient receiving oxprenolol Oros had ventricular extrasystoles in the resting ECG which were probably not treatment-related, and another patient had tinnitus and palpitations of moderate severity. There were no abnormal laboratory findings of clinical significance. Good tolerability was maintained in 13 patients who continued oxprenolol Oros treatment for between 1 and 7 months after the trial.

Discussion

Repeated administration of both the Oros and SR formulations of oxprenolol caused a significant reduction, compared with placebo, in resting systolic and diastolic blood pressure and pulse rate at 24 h after dosing in patients with mild to moderate hypertension. Single doses of oxprenolol Oros also significantly reduced resting diastolic blood pressure and pulse rate at 24 h, but not systolic blood pressure. Repeated doses of both the Oros and SR formulations controlled blood pressure in a similar number of

patients. Overall, the results suggested that the resting antihypertensive effect 24 h after the dose of oxprenolol Oros 16/260 (containing the equivalent of 242 mg oxprenolol hydrochloride) following 3 weeks of treatment was very similar to that following chronic treatment with oxprenolol SR 320 mg in 15 patients and 160 mg in three patients.

Although patients achieved the same median workload and duration of exercise testing under placebo and active treatments, exercise was accompanied by a significantly lower heart rate after single and repeated doses of oxprenolol Oros. Oxprenolol SR also reduced EHR but to a significantly lesser extent than did repeated doses of oxprenolol Oros.

β -adrenoceptor blockade, as assessed by the degree of EHR reduction (McDevitt, 1977), was greater at 24 h after dosing following repeated administration of oxprenolol Oros than after single dosing with Oros or repeated dosing with the SR formulation. The average reduction in EHR of 16% at 24 h after dosing, during repeated administration of oxprenolol Oros, is similar to values reported for β -adrenoceptor-blocking drugs with long elimination half-lives, for example sotalol (Leahey *et al.*, 1980), or those administered in slow-release formulations, for example, propranolol (McAinsh *et al.*, 1978).

In conclusion, once-daily dosing with oxprenolol Oros 16/260 provided effective control of hypertension over 24 h for the majority of the patients in this study, and was achieved with a lower dose of oxprenolol than required to produce a similar degree of control with the SR formulation. This suggests that 16/260 oxprenolol Oros can provide an acceptable, well-tolerated, once-daily monotherapy of hypertension which is effective over 24 h.

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