A COMPARISON OF SLOW RELEASE WITH CONVENTIONAL OXPRENOLOL: PLASMA CONCENTRATIONS AND CLINICAL EFFECTS

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1 Plasma concentrations of oxprenolol have been compared in six healthy volunteers after 80 and 160 mg doses of a new slow release (SR) oxprenolol preparation, after an 80 mg dose of conventional oxprenolol (CO), and after the second of two 80 mg doses of conventional oxprenolol given 12 h apart. Basal pulse rates and blood pressures, and pulse rates before and after a standard exercise test have been compared after the four active treatments and after a placebo.

2 Peak plasma concentrations of oxprenolol attained after 160 mg of the slow release preparation were similar to the peak concentrations after the single 80 mg dose of conventional oxprenolol. Higher concentrations, however, persisted for much longer after the slow release preparations than after the conventional preparations.

3 Neither oxprenolol formulation had any effect on resting pulse rate or blood pressure in normotensive volunteers.

4 Comparison with placebo showed that the single dose of the conventional oxprenolol produced a significant reduction in exercise induced tachycardia for 8 h whereas the high dose of the slow release preparation produced a similar reduction which lasted for at least 14 hours.

Introduction

The β -adrenoreceptor blocking drugs are now widely used in the treatment of hypertension and angina. In both conditions, long term therapy is required and a simple treatment regime is not only desirable but necessary if reasonable patient compliance is to be attained (Gatley, 1968). Oxprenolol (Trasicor®) is an effective antihypertensive agent which is rapidly absorbed and which has pharmacological effects persisting for between 8 and 12 h (Taylor & Meeran, 1973; Brunner, Imhof & Jack, 1975). In order to simplify oxprenolol therapy, which is usually given twice or three times daily, a new slow release preparation has been developed to allow once daily administration.

This paper reports an investigation carried out to compare the plasma concentrations of oxprenolol attained at various times after each of two doses of slow release oxprenolol (SR 80 and SR 160 mg), after 80 mg of conventional oxprenolol (CO 80), after the second dose of

CO 80 in a twice daily dosage regime (CO 80 b.d.), and after placebo. Comparisons were also made of basal pulse rates and of blood pressure, and the pulse rates before and after a standard exercise test.

Methods

Subjects

The study was carried out in six healthy male volunteers aged between 21 and 25 years (mean 23 years) and weighing between 51.5 and 84.5 kg (mean 66.9 kg). The volunteers had given their written consent to the procedure after having the entire trial explained to them. No abnormalities were found on clinical examination, in the results of routine laboratory tests (haematological and biochemical profiles) nor in their electrocardiograms.

Trial design

The five different treatment regimes studied are shown in the table below. The first dose was taken at 22.00 h on the evening before the study and the second dose 12 h later (10.00 h) at the start of the study period.

Treatment	Dose 1	Dose 2
1	Placebo	CO 80 mg
2	CO 80 mg	CO 80 mg
3	Placebo	SR 80 mg
4	Placebo	SR 160 mg
5	Placebo	Placebo

The studies were carried out, double-blind, at weekly intervals and the order in which the subjects received the treatment was allocated randomly. Placebos were available for each preparation and the doses of each treatment were apparently identical.

The trials for each individual were carried out in a hospital side room at the same time of the day, on the same day of the week and according to a strict timetable. No food was taken after 19.00 h on the evening before the trial and at 22.00 h, the first dose was taken. The following morning, the volunteers, still fasting, came to the side room and a plastic intravenous cannula was inserted into a forearm vein. The cannula was connected to a drip set by a three way tap from which blood samples were obtained for the first 6 h of the study and patency of the cannula was assured by slow infusion of normal saline.

At the start of the study, the subject rested supine for 15 min, his pulse rate was counted over 30 s and his systolic and diastolic blood pressures were measured using a sphygmomanometer. The subject then stood for 2 min and his pulse rate was counted immediately before and after mounting two 9 in steps twenty-three times over a period of 1.5 min (Master, 1950). The aim of this test was to demonstrate any β -adrenoceptor blocking effect of the different treatments on exercise induced tachycardia. The subject then lay down and a basal blood sample was withdrawn from the cannula. When these baseline recordings had been obtained the volunteer took the second dose.

During the study the following regime was adopted:

(1) Blood samples were taken from the cannula at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 6 h after the second dose. The cannula was then removed and the subjects were allowed up. Further blood samples were taken by venepuncture at 8, 12, 14 and 24 h.

(2) Pulse rates were counted quarter-hourly and blood pressures measured half-hourly during the first 6 h and thereafter at the times of the venepunctures.

(3) The exercise test was performed at 1, 2, 4, 6, 8, 12, 14 and 24 h.

The procedure used at the assessment times was standardized so that the pulse and blood pressure were taken first while the subject was resting and relaxed, then the blood sample was taken and finally the exercise test was performed.

The subjects were allowed a drink (horlicks, milk or bovril) after 2 h and again in mid afternoon; they had a light lunch 3.5 h after taking the tablets.

Plasma oxprenolol concentrations

The analysis was based on a modified version of Jack & Riess (1974).

Metoprolol hydrochloride (100 ng), as internal standard, was shaken gently with plasma (1 ml) which was then made alkaline by the addition of 1N sodium hydroxide solution (0.4 ml). A saturated solution of sodium chloride (1 ml) was added to prevent emulsion formation during extraction into two successive 3 ml portions of methylene chloride : ether (1 : 4 v/v). After centrifugation the combined organic extracts were shaken with 0.1N hydrochloric acid (2 ml) and the organic phase was subsequently discarded. The acid phase was made alkaline by the addition of 1N sodium hydroxide (0.4 ml) and shaken with two successive 2 ml portions of the methylene chloride : ether mixture. The combined organic phases were washed with 5% sodium acetate solution (2 ml) and then evaporated to dryness under a stream of dry nitrogen on a water bath at 40°C. The dried extract was redissolved in dried benzene (500 μ l) and reacted with trifluoroacetic anhydride (100 μ l) for 90 min at room temperature. The reaction mixture was evaporated to dryness, the residue redissolved in toluene (500 μ l) and the derivatives of oxprenolol and internal standard were analysed by gas liquid chromatography.

A Hewlett Packard 5710 series gas chromatograph equipped with a ^{63}Ni electron capture detector was used for the analysis. The column was a glass coil (1.8 m long and 4 mm internal diameter), packed with 3% OV-1 on Gas Chrom Q (100-120 mesh) and operated at a temperature of 175°C. The injection port and detector temperature were 250°C and 300°C respectively and the carrier gas (95% Argon/5% Methane) flow rate was 60 ml/min.

Statistical analysis

The overall effects of the different treatment regimes were examined by the method of McHugh, Sivanich & Geisser (1961). For pulse rate, blood pressure and exercise test, treatment differences at each assessment time were examined using the Scheffé multiple comparison test (Scheffé, 1953). Statistical normality could not be assumed for the plasma concentration data, so treatment differences at each assessment time were analysed by the Friedman rank sum test (Friedman, 1937). The areas under the plasma concentration-time curves were estimated using the trapezoidal rule (Hildebrand, 1956).

Results

Plasma concentrations

The mean oxprenolol plasma concentrations during the trial period for each of the four treatments together with their standard errors and the areas under the curves are set out in Table 1. Separate analyses of this data at each assessment time revealed the following significant differences ($P \leq 0.05$):

(1) After CO 80 administration, absorption was rapid and the mean plasma level was higher than after SR 80 for the first 2 h of the study.

(2) After SR 160 the peak plasma level was reached in 2 h and the mean plasma level attained between 4 and 14 h was higher than the corresponding values after CO 80.

The ratios of the areas under the concentration-time curves after 24 h for CO 80 : CO 80 b.d. : SR 80 : SR 160 were 1 : 1 : 1 : 2.

Pulse and blood pressure

Pulse rate and systolic and diastolic blood pressure at rest after each of the treatments and after placebo did not differ significantly from each other.

Exercise test

Separate analyses were carried out for pre- and post-exercise pulse rates and showed no statistically significant differences between pre-exercise pulse rates after the five different treatments. The mean post-exercise pulse rate and its standard error for each treatment are set out in Table 2. Separate analyses of treatment differences

Table 1 Mean ($\pm$ s.e. mean) plasma oxprenolol concentration levels (ng/ml) and areas under plasma level curves (AUC) at 24 h in six subjects.

Treatment	Time									
	0	1	2	4	6	8	12	14	24	AUC
Conventional oxprenolol (80 mg)	0	592 (± 114)	628 (± 66)	281 (± 50)	120 (± 27)	55 (± 27)	25 (± 20)	8 (± 8)	0	2703 (± 450)
Conventional oxprenolol (80 mg b.d.)	2 (± 2)	749 (± 116)	637 (± 85)	315 (± 49)	151 (± 36)	82 (± 25)	37 (± 15)	12 (± 7)	2 (± 2)	3091 (± 445)
Slow release oxprenolol (80 mg)	0	91 (± 21)	276 (± 28)	360 (± 75)	234 (± 72)	195 (± 66)	74 (± 24)	47 (± 18)	4 (± 3)	2821 (± 709)
Slow release oxprenolol (160 mg)	0	488 (± 123)	682 (± 167)	609 (± 184)	474 (± 128)	397 (± 144)	181 (± 73)	125 (± 45)	18 (± 13)	6193 (± 1913)

in post exercise pulse rates at each assessment time revealed the following significant differences ($P \leq 0.05$):

- (1) At the start of the study, the mean pulse rate of those who had received CO 80 the previous evening was lower than the mean pulse rates of those who had taken a placebo.
- (2) One hour after CO 80 the mean pulse rate was lower than the mean pulse rate after placebo and this significant difference lasted for 8 h.
- (3) The mean pulse rate 1 h after SR 160 was lower than the mean pulse rate after placebo and this difference persisted for 14 h following treatment.

Discussion

This study has shown that the 160 mg slow release tablet (SR 160) produces maximum blood levels comparable to those of conventional oxprenolol (80 mg) almost as quickly. High concentrations persist for much longer with SR 160 than with CO 80 and these high levels are associated with a prolonged β -adrenoceptor blocking effect.

The figures for the areas under the curve at 24 h show that the amounts absorbed from the 80 mg preparations are comparable with each other and that twice the amount is absorbed when a double dose is given in the form of SR 160. This shows there is a direct relationship between the dose given and the amount reaching the systemic circulation which suggests that over the dose range studied the proportion of drug metabolized remains constant and confirms the results of Brunner *et al.*, (1975). This is of interest since a significant proportion of other β -adrenoceptor blocking drugs such as alprenolol, metoprolol and

propranolol are lost prior to entering the systemic circulation (Perrier, Gibaldi & Boyes, 1973; Regardh, Borg, Johansson, Johansson & Palmer, 1974): thus, for example, when metoprolol is given in increasing doses, there is a disproportionate increase in the area under the curve, presumably indicating that the amount removed during the initial passage through the gut wall and liver is a smaller proportion of the larger dose (Johansson, Regardh & Solvell, 1975). On the other hand, the direct relationship between dose and area under the curve demonstrated for oxprenolol suggests that either appreciable amounts of this drug are not lost by the 'first pass effect' or that the rate of metabolism is first order; this needs to be investigated further.

In an earlier study, Brunner *et al.*, (1975) determined plasma oxprenolol concentrations over an 8 h period after which concentrations were too low to be detected. On the basis of their study, the plasma half life was found to be 1.5 h, though the pharmacological effects of the drugs were still observed 8 h after ingestion. In this investigation, using a sensitive method, we have shown that oxprenolol is still detectable 14 h after a single dose and 24 h after the second of two 80 mg doses of conventional oxprenolol. After a single dose, 80 mg, of the slow release preparation, oxprenolol was easily detected at 24 h and when the larger dose was used, the blood level was still 17.6 ng/ml. This suggests that the half-life of oxprenolol is longer than 1.5 h and that the long lasting pharmacological effects are related to the persistence of the drug in the plasma.

The β -adrenoceptor blocking effect on exercise-induced tachycardia would have been better demonstrated if heart rate increments of 40-50% had been induced by standardized exercise on a treadmill or bicycle ergometer. However, we

Table 2 Mean ($\pm$ s.e. mean) post-exercise pulse rates (beats/min) in six subjects

Treatment	Time								
	0	1	2	4	6	8	12	14	24
Conventional oxprenolol (80 mg)	123 (± 6)	95* (± 7)	94* (± 5)	94* (± 6)	97* (± 5)	103* (± 6)	108 (± 8)	106 (± 9)	118 (± 3)
Conventional oxprenolol (80 mg b.d.)	105* (± 3)	92* (± 5)	91* (± 6)	97* (± 5)	100* (± 5)	108* (± 6)	104 (± 9)	108 (± 9)	119 (± 5)
Slow release oxprenolol (80 mg)	120 (± 7)	106 (± 6)	98 (± 6)	99* (± 4)	99* (± 3)	100* (± 5)	102 (± 7)	104 (± 8)	109 (± 6)
Slow release oxprenolol (160 mg)	120 (± 7)	97* (± 6)	100 (± 5)	100* (± 5)	98* (± 4)	95* (± 7)	93* (± 8)	95* (± 7)	121 (± 7)
Placebo	121 (± 4)	119 (± 11)	110 (± 7)	118 (± 5)	119 (± 6)	123 (± 7)	112 (± 8)	109 (± 8)	119 (± 7)

* Results significantly different from the corresponding placebo values $P < 0.05$.

chose to use a simplified two-step technique (Master, 1950) since we wished to obtain multiple blood samples from an i.v. cannula, to continue this study until after midnight and to perform the study close to a medical ward. In healthy volunteers, this step test probably does not provoke sufficient stress to outweigh completely the effects of factors such as food, emotion and activity during the previous hour. This may explain the considerable variability seen in the results of this test. Nevertheless, the overall

conclusion must be that both oxprenolol formulations achieved a satisfactory β -adrenoceptor blocking effect rapidly and that with the slow release preparation this was still marked at 14 hours.

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