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Once Daily Beta-Blocker in Hypertension – Oxprenolol Slow-Release

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In a within-patient comparison of conventional oxprenolol administered twice daily with slow-release oxprenolol administered once daily in the treatment of hypertension, twenty patients previously responsive to beta-blockers took each formulation for 4 weeks, after wash-out periods off beta-blocker of 2 weeks' duration. The order of administration of the two forms was randomized, and sixteen patients continued medication with cyclopenthiazide 0·5 mg daily. Blood pressure levels at the end of the 4-week treatment periods were compared with levels at the end of the preceding 2-week wash-out periods.

Both formulations lowered blood pressure and pulse rate significantly. There was no difference in their effects on pulse rate or on blood pressure, whether measured by the doctors using standard sphygmomanometers or by the hypertension sister using a random-zero sphygmomanometer. In four patients who measured their own blood pressures at home each morning (before medications), afternoon and night, mean levels were similar with the two formulations. Both formulations were very well tolerated.

Introduction

The plasma half-life of beta-blockers varies from approximately 1 to 9 hours (Petrie *et al* 1976, McAinsh 1977), and their effect on heart rate (resting or stimulated) decreases significantly within 24 hours of administration. In spite of this, various beta-blockers have been administered with good effect once daily in the treatment of arterial hypertension (Gordon 1975, Gordon 1976, Frithz 1976, Douglas-Jones & Cruikshank 1976, Reybrouck *et al* 1978), with the advantages of ease of administration and improved patient compliance (Gatley 1968, Persoff, Rowbury & Mason 1978, Haynes *et al* 1976). If the patient is already receiving a thiazide diuretic once daily, both medications may conveniently be administered together.

The half-life of oxprenolol is 1·3 hours, while its pharmacological effects last for 8–12 hours (Brunner, Imhof & Jack 1975). A slow-

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release (S-R) formulation has been developed. The peak plasma concentration achieved by S-R in a dose of 160 mg is similar to that achieved by 80 mg of conventional oxprenolol (C-O), but high concentrations persist for much longer (West *et al* 1976). This paper describes a within-patient comparison of S-R once daily and C-O twice daily in the out-patient treatment of hypertension.

Methods

Throughout, diastolic pressure refers to Korotkoff phase V, disappearance of sound.

Patients were selected from among those attending an afternoon hospital out-patient hypertension clinic whose blood pressure had previously been well controlled by a beta-blocker, with or without a thiazide diuretic. Patients with past or present angina pectoris, heart failure, asthma, diabetes mellitus requiring insulin, clinical gout, cerebrovascular disease, plasma creatinine greater than 0·2 mmol/l or plasma potassium less than 3·0 mmol/l were excluded. Only patients with a good drug compliance record and untreated diastolic blood pressure less than 126 mm Hg were accepted. The beta-blocking drug which they were receiving was ceased for 2 weeks (first wash-out period). If diastolic blood pressure was then 100–125 mm Hg in the supine position after 5 minutes rest (mean of 4 readings on 2 consecutive occasions measured by MZ using a Hawkesley random-zero sphygmomanometer) they entered the trial, and were randomly allocated to one of two equal groups. This allocation determined whether they received C-O or S-R first. Twenty patients aged 26 to 71 years (mean, 56 years) entered and completed the study. Twelve were males. Sixteen were already receiving cyclopenthiazide 0·5 mg daily and this was continued.

Patients received either 80 mg C-O immediately before breakfast and immediately before the evening meal, or 160 mg S-R immediately before breakfast. After 4 weeks the oxprenolol was ceased, and after 2 weeks with no beta-blocker (second wash-out period) the alternative form was administered for 4 weeks (Table 1). Patients were seen each 2 weeks during medication periods, and each 4–7 days during wash-out periods.

Blood pressure was measured: (1) in twenty patients by a Hawkesley random-zero sphygmomanometer by one observer (MZ) after 5 minutes supine rest and again after 2 minutes standing. These measurements were repeated, and the results averaged; (2) in eighteen patients lying and standing by one of four doctors (RG, WR, CS, GR) using a standard mercury sphygmomanometer; and (3) in four patients by the patients themselves. They had been trained to use modified sphygmomanometers ('Autosfig' – Propper Manufacturing Company, New York, or 'Teru-Ace' Mark IV Home Blood Pressure Kit, Japan) with stethoscope diaphragm built into the cuff, and an aneroid gauge which was regularly checked against a mercury gauge. Blood pressure was measured after 5 minutes supine, and again after 2 minutes upright (a) on first awakening (b) on first arriving home from work (5–6.30 p.m.) and (c) immediately before retiring at night. These times correspond to 23, 10 and 14 hours after S-R and 12, 10 and 3 hours after C-O.

Clinic blood pressures were measured between 1.30 p.m. and 3.00 p.m., 5·5 to 8·5 hours after the last dose of oxprenolol.

Table 1

Study protocol

Time (weeks)	*2*	*4*	*2*	*4*
Beta-blocker	Nil (wash-out)	Oxprenolol 80 mg twice daily or Oxprenolol S-R 160 mg once daily	Nil (wash-out)	Oxprenolol 80 mg twice daily or Oxprenolol S-R 160 mg once daily
± Cyclopenthiazide 0·5 mg mane				

Pulse rate lying and standing was measured by one observer (MZ) at the time of blood pressure measurement.

Biochemistry. Plasma creatinine, urea, uric acid, sodium, potassium and calcium were measured in the Hospital Biochemistry Department by routine methods at the conclusion of each wash-out and treatment period. Plasma glucose, cholesterol and triglycerides were measured in the Hospital Biochemistry Department at the conclusion of the first wash-out period and at the conclusion of each period of oxprenolol administration.

Other tests. Slit lamp examination of the eyes, ECG and ANF tests were performed before commencing oxprenolol and at the conclusion of each period of oxprenolol administration.

Tolerability of the drug was assessed at each visit by questionnaire and direct enquiry.

Statistics. Blood pressure levels at the end of the 4-week treatment periods were compared with levels at the end of preceding 'wash-out' periods. The effects of the two formulations (change from 'wash-out' period and also absolute level achieved) were compared by the Students' 't' test for paired data. Means and standard errors of the means are shown in the text and the Figures unless otherwise indicated.

Results

Blood pressure. Mean BP fell significantly by 21·5/15·7 mm Hg lying and 19·3/13 mm Hg standing during treatment with C-O and by 23·9/13 mm Hg lying and 20·4/12·6 mm Hg standing with S-R. There were no significant differences between the BP changes or levels achieved while receiving the two formulations, based on either the doctors' or the sister's measurements (Figure 1), which were themselves not significantly different. There were also no significant differences between mean BP levels at the end of wash-out periods.

Home blood pressures showed remarkably consistent patterns in individual patients (Figure 2). In one of the four patients, both systolic and diastolic pressures, lying and standing, were significantly higher in the morning while receiving the S-R formulation (lowest panel, Figure 2). In another patient (top panel), the lying diastolic and standing systolic pressures in the morning were significantly lower while receiving the S-R formulation. In the other two patients there was no difference in morning blood pressures while receiving the two formulations. In two patients, pressures later in the day were significantly lower while receiving the S-R formulation, and in one patient the last readings of the day were lower while receiving the C-O formulation. There was thus no consistent pattern for the four patients taken together, and mean levels for the group were almost identical in the morning (1), afternoon (2) and night (3); for lying blood pressure (1) C-O 134/83, S-R 134/83 (2) C-O 134/82, S-R 132/80 (3) C-O 135/84, S-R 134/82 and for standing blood pressure (1) C-O 130/93, S-R 131/94 (2) C-O 130/92, S-R 128/93 (3) C-O 131/91, S-R 131/89.

Other observations. Mean pulse rate fell significantly ($p < 0·01$) and equally with each formulation in both supine and upright positions.

There were no significant changes in body-weight, plasma urea, creatinine, uric acid, sodium, potassium, calcium, cholesterol, triglycerides, glucose, ECG or slit lamp examination of the eyes, and no appearance of positive ANF during the study.

Side-effects. Two patients complained of headache while taking oxprenolol (one receiving each formulation), two complained of nausea (both receiving S-R), and one each complained of dyspnoea (C-O), constipation (S-R) and urinary frequency (C-O). In each case the complaints were transient and in no case was it necessary to withdraw the oxprenolol.

Acceptance. Most patients said that they preferred the S-R formulation because of the convenience of once daily administration.

Discussion

The adequacy of a single daily dose of beta-blocker in the treatment of hypertension is best assessed by repeated measurements spaced throughout the 24-hour period during chronic administration. In the present study, measurements in the clinic, 5·5 to 8·5 hours following the last dose of oxprenolol, showed the slow-release formulation to be equally effective with the conventional formulation. The use by the hypertension sister of a random-zero sphygmomanometer in order to

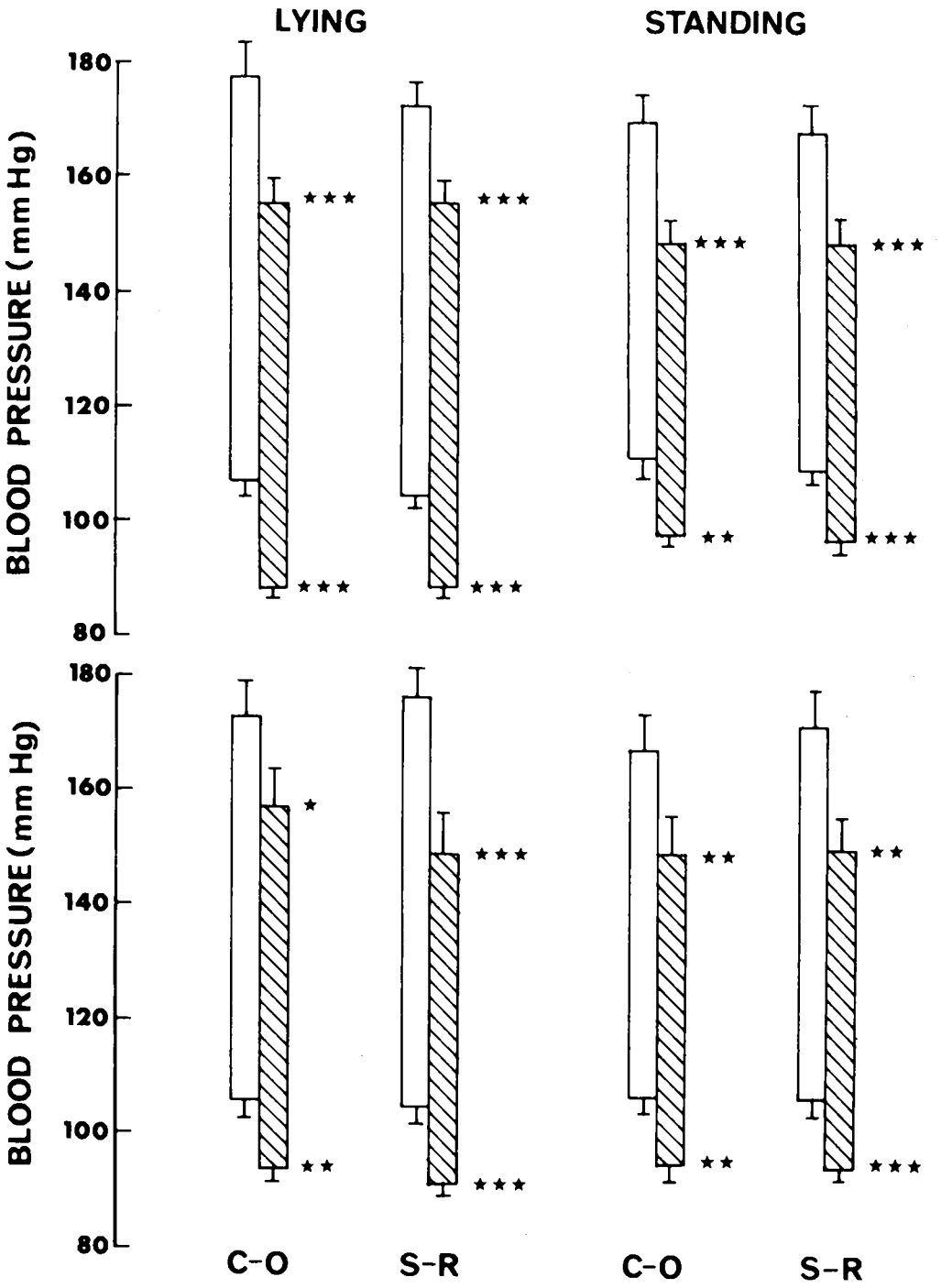

Fig 1 *Blood pressure levels measured by standard mercury sphygmomanometer (lower panel) or by random-zero sphygmomanometer (upper panel) after 2 weeks without beta-blocker therapy (open bars) and again after 4 weeks' therapy with oxprenolol in conventional (C-O) or slow-release (S-R) formulation (hatched bars).*

*p < 0·02
**p < 0·01
***p < 0·001
} beta-blocker vs no beta-blocker

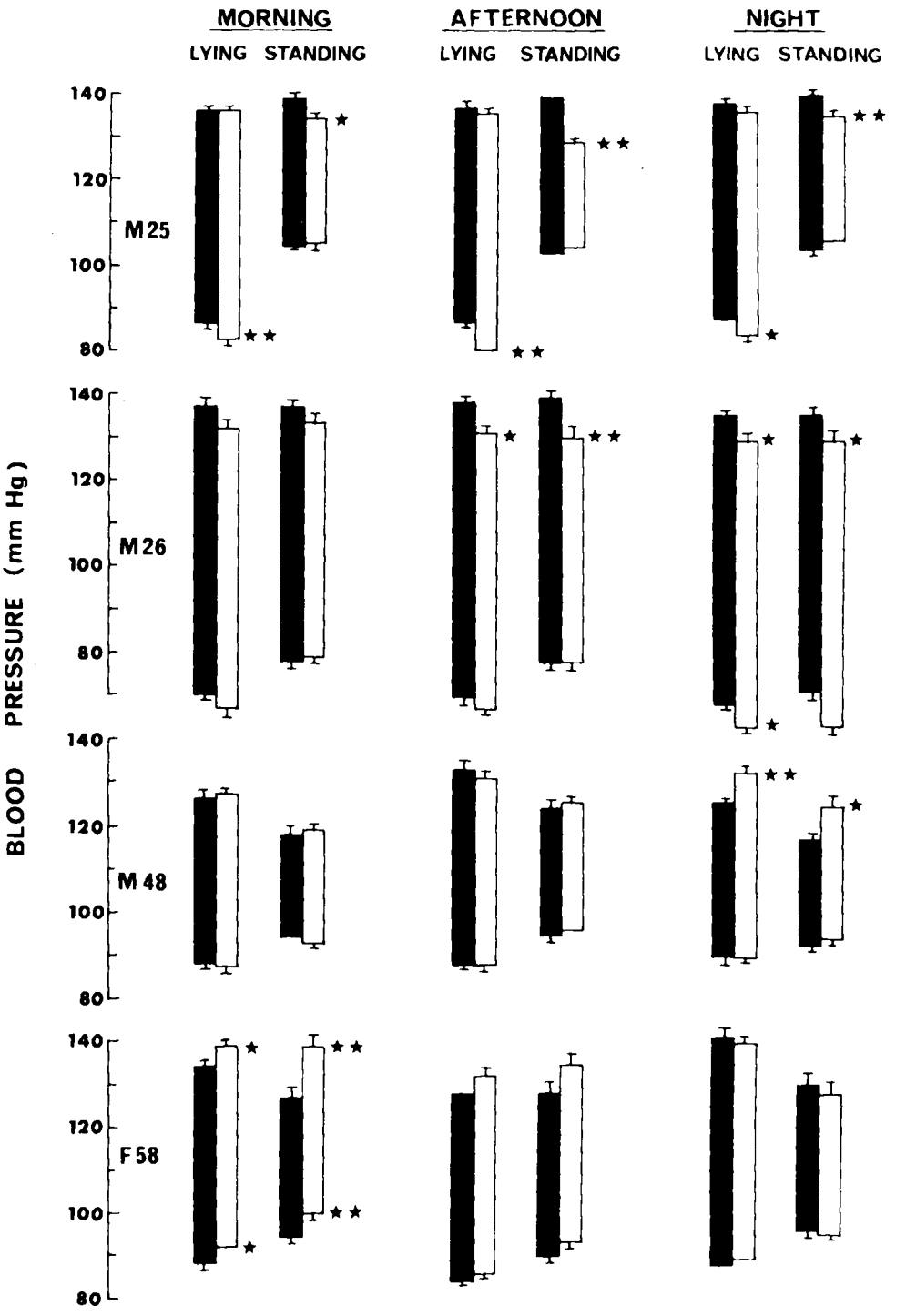

Fig 2 *Home blood pressure levels (means of 14 observations, S.E. of mean less than 1 mm Hg not shown) during the last 2 weeks' treatment with either conventional oxprenolol twice daily (solid bars) or slow-release oxprenolol once daily (open bars), in three males aged 25, 26 and 48 years, and one female aged 58 years.*

*p < 0·05
**p < 0·01
} S-R vs C-O

remove observer bias confirmed the findings based on doctor's readings.

Home blood pressure measurement in four patients permitted comparison of efficacy 23, 10 and 14 hours after a single daily dose of S-R with that 12, 10 and 3 hours after the last dose when taking C-O twice daily. The two methods of administration produced very similar levels of blood pressure, with no systematic differences in efficacy at different times of day. Millar-Craig and Raftery (1978) reported results in one patient with essential hypertension; intra-arterial blood pressure was monitored continuously for 24 hours while on no treatment and again after 7 weeks of oxprenolol S-R 160 mg at 8 a.m.; treatment produced a fall in blood pressure throughout the 24 hours which was greater than the mean fall in ten essential hypertensives who had received 240 mg C-O daily in divided doses for 8 weeks.

In the conduct of clinical trials involving measurement of blood pressure, a compromise must be reached between the accuracy and total information achieved by invasive, ambulatory, intra-arterial monitoring and the practicality of reproducible recordings, preferably observer-blind, in what is often a busy clinic situation. Home blood pressure measurement adds another parameter which is complementary. Because of repeated measurement, the influence of the occasional, atypical reading is diluted, permitting confident interpretation of small, consistent changes.

The excellent response to both formulations of oxprenolol in this study is explained by selection of patients previously shown to respond well to beta-blockers. Inclusion of 'non-responders' to beta-blockers would have made any differences between the two formulations difficult to uncover. The fact that all patients had previously been treated successfully with a beta-blocker, together with strict exclusion conditions, probably explains the very low incidence of side-effects. If side-effects increase proportionally with peak plasma levels achieved, then S-R oxprenolol could have an advantage over C-O, but this question would have to be examined in a large number of patients, not already selected for their acceptance of beta-blocking drugs. Oxprenolol S-R has a place on the list of beta-blockers shown to be effective in single daily dosage which already includes pindolol (Gordon 1975, Gordon 1976, Frithz 1976), metoprolol (Gordon 1976, Reybrouck *et al* 1978), propranolol (Gordon 1976) and atenolol (Douglas-Jones & Cruikshank 1976).

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