HYPOTENSIVE EFFECT OF OXPRENOLOL IN MILD HYPERTENSION: A CO-OPERATIVE CONTROLLED STUDY

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SUMMARY

1. In a multicentre double-blind study, oxprenolol (OX) hypotensive effect was investigated in 329 patients with mild to moderate hypertension.

2. A factorial experimental design with three factors was chosen: OX mg/day 0, 20, 40, 60, 80; dihydrazinophthalazine (DHZ) mg/day 0, 30; and hydrochlorothiazide (HCH) mg/day 0, 30. Each treatment was carried out for a period of 4 weeks after an adequate placebo period.

3. Independently of the association with DHZ and/or HCH, OX yielded a hypotensive effect linearly related to dose \( P<0.05 \) for systolic and diastolic pressure in the standing position, but only for diastolic pressure in the supine position.

4. The addition of DHZ and/or HCH to OX at 80 mg/day caused a significant increase in the final hypotensive effect.

Key words: oxprenolol, \( \beta \)-blockers, hypertension, multicentre study.

Treatment of arterial hypertension with \( \beta \)-blocking agents has been the subject of many conflicting reports. Considerable differences in patient selection and number, in dosage and duration of treatment and in procedures adopted for evaluation of results account for these discrepancies.

As high, or even very high doses of different \( \beta \)-blocking agents have been generally used in most studies (Lydtin, Kusus, Daniel, Schierl, Ackenheil, Kempter, Lohmoller, Niklas & Walter, 1972; Prichard, 1969; Zacharias, Cowen, Prestt, Vickers & Wall, 1972), the effects of lower doses have not been sufficiently evaluated. Further, the possible synergism of \( \beta \)-blocking agents and hypotensive drugs with different modes of action seems worthy of careful investigation (Aenishanslin, Pestalozzi-Kerbel, Durach, Imhof & Turri, 1972; Sannerstedt, Stenberg, Vedin, Wilhelmsson & Werko, 1972; Zacest, Gilmore & Koch-Weser, 1972).

The aim of this study was (i) to evaluate the hypotensive effect of low doses of oxprenolol

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alone and in combination with dihydralazine and/or hydrochlorothiazide in a large number of patients with mild to moderate uncomplicated arterial hypertension and (ii) to assess the suitability of this hypotensive therapy for routine use.

To ensure reliable results and objective conclusions, the use of an appropriate experimental design and of a statistical evaluation of the results were considered essential.

MATERIALS AND METHODS

In a large multicentre study (twenty-three centres) 329 patients, 146 men and 183 women, with ages ranging from 32 to 65 years (average 51.3) were investigated. Of the patients 92% were affected by essential hypertension, the remaining 8% by renal hypertension. The mean duration of diagnosed hypertension was 6.3 years.

Only patients with systolic blood pressure not greater than 250 mmHg and diastolic blood pressure not greater than 130 mmHg were selected. After the placebo period, systolic blood pressure averaged 182.7 mmHg (SEM 1.3, \( n = 329 \)) and diastolic blood pressure 110.8 mmHg (SEM 0.9, \( n = 329 \)). Patients with heart failure, bronchial asthma, heart block, marked bradycardia, grade I to IV retinopathy, blood urea greater than 50 mg/100 ml, serum creatinine greater than 1.5 mg/100 ml and body weight greater than 20% of the predicted values were excluded.

All patients were informed about the purpose and nature of the study and consent was obtained.

For practical reasons, 129 subjects were treated as in-patients, ninety-six as out-patients and 104 as in-patients for an initial period of approximately 3 weeks and as out-patients after discharge from hospital.

A factorial experimental design with three factors was chosen: first factor, oxprenolol absent or 20, 40, 60, 80 mg/day; second and third factor, dihydralazine and hydrochlorothiazide respectively, absent or 30 mg/day. Each treatment was carried out, under double-blind conditions, for 4 weeks after a 1-week single-blind placebo period, preceded by an adequate period of withdrawal of drugs which might possibly interfere. Each patient was randomly assigned to one of the twenty possible treatments.

In each patient, before admission to the study, after the placebo period and at the end of each of the 4 consecutive weeks of effective treatment, blood pressure was measured by using the cuff method three times in succession after the patient had been lying down for 5 min and once after standing for 1 min. Blood pressure recordings were made by the same investigator at the same time of the day for each patient. The following parameters were measured before and after treatment: blood urea, blood sugar, serum uric acid, serum creatinine, ECG and eyegrounds.

Statistical evaluation was performed according to an analysis of variance for a factorial design. The effects of three main factors, namely the three drugs pertaining to this study, and their interactions, were examined.

RESULTS

Blood pressure mean values and error variance did not differ significantly among the three groups of patients (in-patients or out-patients exclusively and mixed group); consequently results were pooled for the analysis.
Oxprenolol in hypertension

According to the factorial design, results were analysed as main factors (drugs) and as interactions.

Oxprenolol was followed by a significant decrease in lying diastolic ($P<0.05$) and standing systolic ($P<0.05$) and diastolic ($P<0.01$) blood pressure. This effect was linearly related to dosage. A trend to decrease related to dosage, though not statistically significant, was observed in lying systolic blood pressure.

After 4 weeks of treatment, in the 80 mg of oxprenolol group blood pressure decreases, obtained by linear interpolation, were 9.5 mmHg for lying diastolic, 22.5 mmHg for standing systolic and 14.0 mmHg for standing diastolic.

Dihydrallazine reduced significantly only lying systolic blood pressure ($P<0.05$). Hydrochlorothiazide elicited a significant decrease in lying and standing systolic and diastolic blood pressure ($P<0.001$).

In the analysis of the interactions between drugs there was a significant interaction between oxprenolol and dihydrallazine in lying ($P<0.001$) and standing ($P<0.05$) systolic blood pressure: dihydrallazine enhanced the time-course of the hypotensive effect of oxprenolol, particularly at the 80 mg level (Fig. 1).

A significant interaction was not observed between oxprenolol and hydrochlorothiazide nor between dihydrallazine and hydrochlorothiazide.

Generally the combination of oxprenolol + dihydrallazine + hydrochlorothiazide gave greater reductions in blood pressure, although the interaction was not statistically significant. The greatest reduction was obtained with oxprenolol (80 mg) + dihydrallazine + hydrochlorothiazide. In this group, final actual blood pressure decreases were 30.5 mmHg (12.5%) and 14.4 (16.0%) for lying systolic and diastolic respectively; 32.1 (17.7%) and 20.0 (17.2%) for standing systolic and diastolic. All these decreases were significantly different ($P<0.01$) from those obtained in the group of patients who received only a placebo for 5 weeks. In this group, blood pressure decreases were 1.5 mmHg (0.8%) and 4.2 (3.9%) for lying systolic and diastolic,
and 6.9 (3.9%) and 5.0 (4.6%) for standing systolic and diastolic. Maximal placebo effect occurred after 2 weeks.

No systematic orthostatic effect was observed. Heart rate decrease averaged 5%. None of the clinical and laboratory variables under study showed significant changes.

Eleven patients were withdrawn from the trial because of lack of co-operation. Treatment had to be interrupted in thirty-nine patients: in twelve of these for early normalization of blood pressure, in twenty-four for inadequate hypotensive control, and major side-effects (heart failure and bronchospasm) occurred in three. In all the other patients tolerance was good.

**DISCUSSION**

The results of the present study are consistent with the reports demonstrating a hypotensive effect during β-blocking treatment of patients with arterial hypertension. The decrease in blood pressure obtained in this study after a relatively short period of treatment (4 weeks) is comparable with the results reported in long-term studies (Prichard, 1972; Zacharias et al., 1972). Although the full hypotensive effect of β-blockers is claimed to take place after several weeks or months of treatment (Prichard, 1972), in this study a clinically appreciable reduction in blood pressure was observed at the end of the first week of effective treatment and continued in the following weeks. In analysing the data relative to patients who completed the study, responders were not separated from non-responders; it is likely that, in responders only, the hypotensive effect could have been greater.

The main feature of our study is that a large number of patients and an appropriate experimental design allowed the demonstration of a clear hypotensive effect of oxprenolol at a much smaller dose, 80 mg/day, than the ones usually reported in literature.

The possibility of obtaining a satisfactory reduction in blood pressure with a low dose of a β-blocking drug makes this treatment more interesting for a wider clinical use. Side effects were, in fact, extremely rare. The combination of oxprenolol with a small fixed dose of dihydralazine and hydrochlorothiazide enhanced significantly the hypotensive effect elicited by the β-blocking drug alone. The mechanism of action of this therapeutic combination is not yet fully elucidated, though its practical usefulness in the treatment of patients with mild to moderate arterial hypertension is clearly shown by the present study.

**REFERENCES**


