Once Daily Propranolol in the Treatment of Mild to Moderate Hypertension:

A Dose Range Finding Study

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Summary. Propranolol was administered in a single dose of 80 mg, 120 mg, 160 mg, 240 mg, or 320 mg, to 23 patients with essential mild to moderate hypertension in a randomised, double-blind cross-over study. All treatments produced a significant fall in lying and standing blood pressures compared with placebo, but there was no statistically significant difference in the effects of the different doses. The percentage of patients showing a satisfactory fall in blood pressure was not different in the five treatment groups. The major anti-hypertensive effect of each dose was present by two weeks. The frequency of side-effects were similar on all the doses.

Key words: Propranolol, hypertension.

Propranolol has been in wide clinical usage for over ten years. Its anti-hypertensive activity was discovered in 1964 by Pritchard and Gillam [1] with starting doses of 10 mg, three or four times a day. It has since been shown to be effective in controlling hypertension when used in a twice daily regime [2] and at a higher starting dose of 40 or 80 mg twice a day [3].

The long term adherence of asymptomatic, hypertensive patients to a dosage regime is likely to be good only if the treatment is simple and free from side-effects. Atenolol, a cardio-selective beta-adrenergic blocking drug has been shown to control the 24 hour blood pressure on a once daily regimen [4]. Wilson et al. [5] have demonstrated that the anti-hypertensive effect of propranolol dosed three times a day may be maintained when the same total daily dose is given together in the morning. Ross and Baber (personal observation [6]) noted the same effect in 11 patients, but found side-effects to be unacceptable in doses of 240 mg and above.

For the present study, it was accepted that propranolol is an effective anti-hypertensive agent, and the design allows for the comparison of the anti-hypertensive effect at five different doses of propranolol. The comparison of effect on blood pressure with these single doses was made at 24 h.

Patients and Methods

Twenty-five patients who were either newly diagnosed essential hypertensives, or had never received a beta-blocker as treatment for hypertension were studied. Patients gave their consent to take part in the trial and the Committee for the Safety of Medicines was informed. All anti-hypertensive treatment was withdrawn prior to the placebo run-in period. Twenty-three patients completed the trial. There were nine men aged 49–66 and fourteen women aged 34–66. The patients were selected at the end of the four week placebo run-in period if their diastolic blood pressures after five minutes rest in the supine position was (a) 100–120 mmHg if 55 years or less or (b) 105–125 mmHg if between 55 and 65 years. Patients with a history of congestive cardiac failure, asthma or electrocardiographic evidence of second or third degree heart block were excluded, as well as those who were pregnant. There were no diabetics in the study and patients had a serum creatine under 1 mg per ml.

The study was of a double-blind, cross-over design. After a four week placebo run-in period, patients began active treatment provided their blood pressure conformed with the required criteria. The treatment comprised five randomly allocated, four week periods of either 80 mg, 120 mg, 160 mg, 240 mg, or 320 mg of propranolol, taken in a single dose with the evening meal. The tablets were all identical.
Patients proceeded through the trial successfully, but in six of them, it was necessary to reduce the number of tablets in one or more of the treatment periods because of side-effects on higher dosage. One patient was withdrawn from the trial because of hospital admission for an operation, unrelated to his treatment and another defaulted from follow-up.

Patients were seen at each fortnight (between 6 and 7 p.m.) and were instructed not to take the dose on the visit day to the clinic. Blood pressure readings were taken, therefore, at least twenty-four hours after the ingestion of tablets. At each visit a resting pulse rate was recorded together with blood pressure and after five minutes lying and two minutes standing. Volunteered symptoms were noted, followed by those elicited by direct questioning.

**Statistical Method**

The data were collected for all patients, but in six subjects, in whom the dose was reduced below 80 mg, they were excluded from the analysis. In patients where the reduced dose exceeded 80 mg, analysis was made at the appropriate dose level.

The blood pressure, pulse rate and weight measured at the end of each four week active treatment period, were analysed by non-orthogonal analysis of variance. The fitted model took account of patient effects, treatment effects and the effect of the length of time in trial (period effects). Overall tests of effects were made by means of Fishers' F-test.

Treatment means were adjusted for imbalance in the design and pairs of means were compared using Student's t-test, the estimate of error being obtained from the residual means square from the analysis of variance. Comparison of treatment means with the run-in placebo means were made using a paired Student's t-test.

**Results**

The blood pressures, heart rates lying and standing and the weights after four weeks on placebo and the effects of the five treatments on these values are shown in Table 1 on the twenty-three patients. All treatments decreased lying and standing blood pressure and pulse rates in comparison with placebo. These changes are significant at least at the one per cent level. There were no significant differences between blood pressure and pulse rates at the first and second placebo visits.

None of the differences between the effects of the active treatments on blood pressure, or heart rate, reached statistical significance. There were period effects for lying and standing systolic blood pressure, and standing pulse rate, which reached statistical significance (p < 0.01) and this corresponded to a general downward drift of blood pressure and pulse rate throughout the trial. For example, for resting systolic blood pressure, when the first period of randomised treatment is compared with the fifth, the level in period one is 146.6 mmHg and in period five 129.6 mmHg and for systolic standing blood pressure, 142.7 mmHg in period one and 129.2 mmHg in period five.

**Patient Response**

Table 2 shows the number of patients with a satisfactory, fair and poor response to the five doses of propranolol. Satisfactory response was defined as a final lying diastolic blood pressure of 90 mmHg or less. Fifteen patients on 120 mg, 160 mg, and 240 mg, achieved this response.

**Side-Effects**

These are shown in Table 3. No patients had to be withdrawn because of side-effects, although the total number experienced in each treatment group was greater than in the placebo period. Tiredness and breathlessness were reported most commonly at all doses, but wheeziness was reported only on two occasions. Treatment was reduced in six patients because of dizziness and/or tiredness, usually on doses over 160 mg/day.

**Discussion**

Although propranolol has now been in use for over ten years, many questions of practical importance in its clinical usage remain to be answered. The study addresses itself to two of these:

1. What is the correct dose for a particular hypertensive patient and
2. What is the optimum dosage frequency?

Prichard and Gillam [1] used 10 mg three or four times a day as a starting dose and in some patients increased this dose to 3 g over a period of months. Zacharias et al. [7] in their experience of over five years' treatment with propranolol in over 300 patients, have a range of treatment from 80 mg to 2 g, averaging 400 mg. More recently, Conway [8] in a group of patients with mild to moderate essential hypertension, noted a full anti-hypertensive effect with 240 mg a day of propranolol, and a similar result was obtained in the study by Galloway et al. [9].