THE EFFECTS OF ATENOLOL (TENORMIN) AND METHYLDOPA ON SIMPLE TESTS OF CENTRAL NERVOUS FUNCTION

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- 1 Two identical studies, one comparing the effect of single doses of a new β -adrenoceptor blocker, atenolol (Tenormin) (50 mg and 100 mg) and placebo, and the other comparing the effect of single doses of methyldopa (250 mg and 500 mg) and placebo, in healthy volunteers, were carried out.
- 2 In both studies the effect of the drugs upon reaction time, critical flicker frequency, subjective drowsiness, pulse rate and blood pressure was measured.
- 3 Atenolol produced no effect upon reaction time, critical flicker frequency or subjective feelings, while methyldopa produced a statistically significant prolongation of reaction time and a statistically significant increase in the subjective sensation of drowsiness.
- 4 Atenolol produced statistically significant reductions in systolic and diastolic blood pressure and in pulse rate while methyldopa was without effect.
- 5 It is concluded that atenolol is unlikely to produce the side effects of sedation or drowsiness.

Introduction

The use of the β -adrenoceptor blocking group of drugs for the treatment of hypertension has gradually gained acceptance over the last 11 years since Prichard (1964) first reported the anti-hypertensive effects of pronethalol. Nonetheless, the most frequently described drug for hypertension in the United Kingdom today is methyldopa. In a comparative study of bethanidine, guanethidine and methyldopa, Prichard, Johnston, Hill & Rosenheim (1968) concluded that 'methyldopa, provided it is tolerated, produced the best all round blood pressure control of these three drugs, but 20% of our patients could not tolerate it'. One of the main problems with methyldopa therapy is the high incidence of tiredness, drowsiness and sedation associated with the drug — 47% reported by Oates, Seligmann, Clark, Rousseau & Lee (1965), 75% by Prichard *et al.* (1968), 41% by Johnson, Kitchin, Lowther & Turner (1966), and 'most cases' by Hamilton & Kopelman (1963).

There is now extensive evidence that β -adrenoceptor blockers as a group are effective anti-hypertensive agents. Simpson (1974) has recently

reviewed this evidence for propranolol, practolol, oxprenolol, alprenolol, pindolol, sotalol, acebutolol, and INPEA. He concluded that, with the exception of the last three drugs upon which little has, as yet, been published, there was strong evidence for their antihypertensive effect.

One of the benefits reported with the β -adrenergic receptor blockers is their relative freedom from side effects, and certainly the incidence of drowsiness and sedation is negligible compared with methyldopa (Simpson, 1974). Clinical pharmacological studies have generally supported the view that β -adrenoceptor blocking drugs do not have any marked CNS depressant effect. Thus, Donleavy, Maclean & Oswald (1971), Lader & Tyrer (1972), Orzack, Branconnier & Gardos (1973), Tyrer & Lader (1974) and Ogle & Turner (1974) were unable to show any obvious sedative properties of propranolol or (Lader & Tyrer, 1972) sotalol. However, Bryan, Efiang, Stewart-Jones & Turner (1974) saw a prolongation of reaction time with propranolol although this has not been confirmed. In studies with oxprenolol Turner & Hedges (1973) were unable to demonstrate any CNS effects orally or intravenously in normal subjects.

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Atenolol (Tenormin†) is 4-(2-hydroxy-3 isopropylaminopropoxy)phenylacetamide, a compound that has been shown in animals by Barrett, Carter, Fitzgerald, Hull & Le Count (1973), Harry, Knapp & Linden (1973) Hainsworth, Karim & Stoker (1973) and Harry, Knapp & Linden (1974) to be a cardioselective β -adrenoceptor blocker that is devoid of intrinsic sympathomimetic and membrane stabilising properties. A study by Graham, Littlejohns, Prichard, Scales & Southorn (1973) in normal human subjects has confirmed the β -adrenoceptor blocking properties of the compound. A preliminary study in twenty hypertensive patients by Hansson, Aberg, Jameson, Karlberg & Malmcrona (1973) has shown a beneficial reduction in mean blood pressure in the group from 161.5/105.3 mm Hg recumbent, to 140.5/87.9 mm Hg and from 171.8/112.1 mm Hg standing, to 142.4/92.4 mm Hg.

Therefore, we have investigated the effect of single doses of atenolol in normal volunteers upon reaction time, critical flicker fusion, subjective sedation, pulse rate and blood pressure, in comparison with placebo. We have also carried out an identical study using single doses of methyldopa.

Methods

Two studies of identical design were carried out.

Study 1. Atenolol

Six males under the age of 40 years and in the weight range of 60-95 kg gave their informed consent to taking part in the study. They were adjudged fit and healthy by means of a medical examination and standard haematological and clinical biochemical tests.

The subjects attended for study on three separate occasions at least 3 days apart. On each occasion they took one tablet which could be either placebo or atenolol (50 mg or 100 mg). The tablets were given on a randomised latin square design, and by use of identical tablets the study was made double blind.

Immediately before taking the tablet and at 1.5, 3, 4.5 and 7 h thereafter, resting pulse rate (by palpation of the left radial artery) and resting blood pressure (by sphygmomanometry in the left arm) were recorded. At the same times, reaction time (using the method of Bayliss & Duncan, 1974)), critical flicker fusion (using the method of Turner, 1964), as modified by Bayliss & Duncan (1974)) and the subjective sensation of drowsiness

(using the visual analogue method of Aitken (1969)) were recorded.

Study 2. Methyldopa

The design and methods of this study were identical to Study 1 except that methyldopa (250 mg or 500 mg) together with matching placebo were used. All but two of the subjects taking part in Study 1 took part in Study 2 but the studies were about eight weeks apart.

Results

Study 1. Atenolol

The mean age of the six subjects in the study was 30.5 years (range 24-39 years) and their mean body weight 78.6 kg (range 60.4-92.2 kg).

Effect on reaction time (RT) Neither dose level produced any statistically significant effect at any time compared with placebo ($P > 0.05$ Student's *t* test).

Effect on critical flicker fusion (CFF) Neither dose level produced any statistically significant effect on CFF at any time compared with placebo ($P > 0.05$ Student's *t* test).

Effect on subjective feeling Neither dose level produced any statistically significant effect on drowsiness scores at any time, compared with placebo ($P > 0.05$ Student's *t* test).

Effect on blood pressure (BP) Figure 1 shows the mean percentage change in both systolic and diastolic BP on placebo and the two dose levels of drug. The higher dose level produced a statistically significant reduction in systolic blood pressure at all times ($P < 0.05$ at 1.5 h and $P < 0.01$ at 3, 4.5 and 7 h, Student's *t* test). There was a significant reduction in diastolic BP at 3, 4.5 and 7 h ($P < 0.05$ Student's *t* test) also on the higher dose. The lower dose had no significant effect.

Effect on pulse rate (PR) Figure 2 shows the mean percentage change in pulse rate on placebo and the two dose levels of the drug. At 4.5 h there was a significant reduction in pulse rate with both the higher dose ($P < 0.05$) and the lower dose ($P < 0.01$ Student's *t* test).

Study 2. Methyldopa

The mean age of the six subjects in this study was 31.0 years (range 24-39 years) and their mean body weight was 75.7 kg (range 60.4-87.6 kg).

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Figure 1 Percentage mean change ($n = 6$) in systolic and diastolic blood pressure produced by single doses of atenolol (50 mg, ■), atenolol (100 mg ○) and placebo (●) over a 7 h period.

* significantly different from placebo ($P < 0.05$);

** significantly different from placebo ($P < 0.01$).

Figure 2 Percentage mean change ($n = 6$) in pulse rate produced by single doses of atenolol (50 mg, ■), atenolol (100 mg, ○) and placebo (●) over a 7 h period.

*significantly different from placebo ($P < 0.05$);

** significantly different from placebo ($P < 0.01$).

Effect on reaction time (RT) Figure 3 shows the mean percentage change in RT on placebo and on the two dose levels of methyldopa. At 500 mg the reaction time is significantly longer than on placebo at 3, 4.5 and 7 h ($P < 0.05$ Student's t test).

test). On the 250 mg dose at 7 h reaction time is significantly longer than on placebo ($P < 0.05$ Student's t test).

Effect on critical flicker fusion (CFF) At no time in the study did either dose of methyldopa produce frequencies that were significantly different from those on placebo ($P > 0.05$ Student's t test).

Effect on subjective feeding Figure 4 shows the mean percentage change in the subjective score of drowsiness on placebo and the two dose levels in methyldopa. Over the period of the study the high dose level produced higher drowsiness scores than placebo while there was no difference between the lower dose and placebo. However, only at 7 h was the difference between the mean score on methyldopa (500 mg) and placebo significant statistically ($P < 0.05$ Student's t test).

Effect on blood pressure (BP) There were no statistically significant effects of either dose level on systolic or diastolic blood pressure at any time ($P > 0.05$ Student's t test).

Effect on pulse rate (PR) There were no statistically significant effects of either dose level on pulse rate at any time ($P > 0.05$ Student's t test).

Figure 3 Percentage mean change ($n = 6$) in reaction time produced by single doses of methylodopa (500 mg ▲), methylodopa (250 mg, □) and placebo (●) over a 7 h period.

* significantly different from placebo ($P < 0.05$).

Figure 4 Percentage mean change ($n = 6$) in drowsiness score produced by single doses of methylodopa (500 mg, ▲), methylodopa (250 mg, □) and placebo (●) over a 7 h period.

* significantly different from placebo ($P < 0.05$).

Discussion

The results of the β -adrenoceptor blocker study are in marked contrast to those of the methylodopa study. Atenolol was without effect on reaction time while methylodopa produced a significant prolongation. Neither drug had any significant effect upon critical flicker fusion, although this test is generally considered to be a more sensitive test for a stimulant than a depressant effect. Methylodopa produced a significant increase in the subjective sensation of drowsiness while the β -adrenoceptor blocker was without effect. On the other hand, atenolol produced significant falls in blood pressure and pulse rate while methylodopa was without effect.

Certain tentative conclusions may be drawn from this study. Firstly, the techniques of measuring reaction time and scoring drowsiness after single doses of methylodopa are capable of demonstrating the known sedative properties of that drug. The fact that, using the same technique, atenolol showed no effect suggests that it will not produce sedation or drowsiness as a side effect. Secondly, the fact that atenolol produces an immediate fall in blood pressure may suggest that it is different from other β -adrenoceptor blockers. However, it is possible that the fall in blood pressure in these normal subjects was due to the known anxiolytic effect of β -adrenoceptor blockers (Granville-Grossman & Turner, 1966)

relieving the cardiovascular effects resulting from the stress inherent in a study of this kind. The associated fall in pulse rate was less than might be expected with a β -adrenoceptor blocker and this could have been due to a reflex increase in pulse rate in response to the fall in blood pressure.

Finally, the limitations of these studies must be noted, and they are twofold. Firstly, the fact that only single doses of the drugs were used does not allow an appraisal of the effect of repeated dosing. Thus, it is not possible to determine whether any sedative effect of methylodopa is cumulative over a period of time, becomes less or is bi-phasic. Secondly, that there was no direct comparison between the two drugs in one and the same study does not permit one to make a categorical statement that methylodopa is more sedative than atenolol. However, the evidence on this point is very strong.

In spite of these limitations, the conclusion may be drawn that, while single doses of methylodopa may be shown to be sedative, single doses of atenolol are not and that, while single doses of this new β -adrenoceptor blocker produced a significant fall in blood pressure, methylodopa did not.

We are grateful to Miss E.A. Laws for statistical assistance in the analysis of these studies. Reprint requests should be addressed to P.F.C.B.

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(Received April 17, 1975)