Effect of long-term, once-daily administration of atenolol, metoprolol, pindolol and slow-release propranolol on ambulatory blood pressure and its variability

J. S. FLORAS, J. V. JONES, M. O. HASSAN AND P. SLEIGHT
Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, U.K.

Summary

1. Twenty-four-hour intra-arterial blood pressure recordings were made before and after chronic β-receptor blockade in 34 patients with essential hypertension.

2. Subjects were randomized in double blind fashion to either atenolol, metoprolol, pindolol or slow-release propranolol.

3. Drugs were administered in a once-daily variable dose regimen for a period of 3–8 months (mean 5.0 ± SD 1.4).

4. All four drugs reduced blood pressure significantly 24 h after the last dose but there were considerable differences in control when each intervening hour was assessed separately.

5. Not all β-receptor blockers in conventional formulations are equally effective as antihypertensive agents over 24 h when taken once daily.

Key words: atenolol, metoprolol, pindolol, propranolol, β-receptor blockade.

Introduction

There has been a general movement towards reducing the number of tablets that hypertensive patients have to take in order to improve drug compliance, often to once per day.

β-Receptor-blocking agents have been given in this way [1] and the efficacy assessed by clinic, rest and exercise blood pressure measurements. Such measurements have usually taken place the following day and give no assessment of blood pressure control over the intervening period. Ambulatory monitoring of blood pressure by means of indwelling intra-arterial cannulae has been used to study β-blockers in this way. The findings have been variable. We report here the results of a randomized double blind trial of atenolol, metoprolol (in its conventional formulation), pindolol and a slow-release formulation of propranolol (in its slow release form), all administered once daily, on blood pressure and its variability.

Methods

Thirty-four subjects with previously untreated hypertension were studied. Ten were women and 24 were men. Secondary causes of hypertension were excluded.

Twenty-four-hour recordings of blood pressure and electrocardiogram were made off treatment in all subjects. The technique has been described in detail elsewhere [2]. All 34 subjects were then randomized in a double blind fashion to atenolol, metoprolol, pindolol or slow-release propranolol taken once daily. The initial doses of these drugs were: atenolol 100 mg, metoprolol 200 mg, pindolol 15 mg and propranolol 160 mg. There were nine patients in each group, except for the propranolol group, where there were seven. The hospital pharmacists administered the drugs and their randomization and neither the patients nor doctors knew which patient was on which drug. Dosages were increased (occasionally reduced) at intervals by asking the pharmacy to move to the next dose on a pre-arranged schedule.

After 3–8 months (mean 5.0 ± SD 1.4) of once-daily administration we obtained a second 24 h record of ambulatory blood pressure. Tablets were taken in the morning at around 08:00 hours. As on the first occasion the arterial cannula was inserted around 10:00 hours and the 24 h recording started between 12:00 and 13:00 hours. Thus the 24 h records were obtained from the period 5–28 h after taking the last oral dose.
The cannulae were removed at the end of the 24 h recording period. Subjects were asked to keep to a similar routine to their first study. The nature of the procedure was explained to each participant, and informed, written consent was obtained on both occasions. The protocol was approved by the hospital ethics committee.

Results

Doses of drugs by the time of the second study were: atenolol 128 ± 56 mg; metoprolol 311 ± 105 mg; pindolol 33 ± 10 mg; propranolol 457 ± 194 mg.

Although 24 h after the last single, daily dose, blood pressure was significantly reduced with all four drugs, their efficacy during the 24 h period of ambulatory monitoring differed. This period covered in fact hours 5–28 after the last dose, which was taken at 08.00 hours on the day of the study, but the recording started only at 12.00 noon to allow a variety of exercise tests and noradrenaline measurements (not reported here) to be made beforehand. Atenolol significantly lowered mean arterial pressure for 24/24 h, metoprolol for 12/24 h, pindolol for 15/24 h and slow-release propranolol for 22/24 h.

Atenolol significantly reduced the variability of blood pressure (defined as the standard deviation about the mean of the frequency histogram) over the period when the subjects were awake. This was not seen with the other three drugs. The waking periods before and after sleep were also compared. Both atenolol and long-acting propranolol were found to reduce the variability of systolic blood pressure in the awake period before sleep but only atenolol continued to exert this effect on the second morning after sleep. The variability of mean arterial pressure and diastolic blood pressure were unaffected by any of the four drugs.

Significant increases in pulse interval were seen with atenolol (20/24 h), metoprolol (20/24 h), pindolol (10/24 h) and propranolol (24/24 h). Pindolol caused the heart rate to be faster during sleep on treatment than off treatment. This trend was present for all sleeping hours but reached statistical significance in two of them.

Discussion

This study has shown that all β-blocking agents are not equally effective in controlling blood pressure when given once daily. At 28 h after the last single daily dose mean blood pressure was significantly lower with all four drugs. Had the efficacy of these agents been assessed solely at this time then all would have been deemed successful antihypertensive agents when administered in this once-daily way. In contrast to atenolol or slow-release propranolol, both of which tended to maintain their blood pressure reduction for the whole 24 h, metoprolol and pindolol did not have a persisting antihypertensive effect throughout the evening of the first day or during sleep. It has been shown by others [3] that twice-daily metoprolol appears to be effective in lowering blood pressure over the full 24 h. One could speculate, therefore, that slow-release metoprolol could probably be as effective as slow-release propranolol in controlling blood pressure when used once daily.

On the other hand, pindolol, which has a great deal of intrinsic sympathomimetic activity [4] when compared with other β-blockers, failed during sleep to lower the heart rate, which was even faster than in the untreated state. Blood pressure control at this time was poor and it may be that at times of low natural sympathetic tone (such as during sleep) intrinsic sympathomimetic activity can become manifest.

In conclusion we suggest that not all β-adrenoceptor-blocking drugs are equally effective antihypertensive agents over 24 h when taken once daily. Some may need to be taken more often or in slow-release formulations, and it is possible that intrinsic sympathomimetic activity, unmasked by sleep, renders such agents relatively less effective as either antihypertensive or anti-anginal agents at this time.

References