THE EFFECTS OF ORAL ACEBUTOLOL AND PROPRANOLOL ON FOREARM BLOOD FLOW IN HYPERTENSIVE PATIENTS

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- 1 Nine hypertensive patients received by mouth daily doses of 400 mg of acebutolol and then, after a 2 week washout period, 80 mg of propranolol for 2 week periods in an open study.
- 2 Both treatments caused equivalent cardiac blockade as assessed by reduction in exercise tachycardia.
- 3 Both treatments lowered blood pressure, although this effect on pressure was better maintained in the case of acebutolol.
- 4 Forearm blood flow, at rest, was significantly reduced at 2 h after dosing with propranolol, but not after acebutolol.
- 5 This difference between the two drugs is probably due to the cardioselectivity of orally administered acebutolol in man.

Introduction

Since Lands *et al.* (1967) distinguished β_1 -adrenoceptors from β_2 -adrenoceptors, β -adrenoceptor blocking agents have been classified according to their effects on these two receptors. Those drugs which antagonise mainly β_1 receptors are said to be cardioselective, whilst those which affect both β_1 and β_2 receptors are said to be non-selective.

There is limited data as to the effect that β -adrenoceptor blocking agents have on blood flow in human skeletal muscle. There is some evidence that non-selective agents may reduce resting blood flow in skeletal muscle (Johnsson, 1967; Warren, McSarley & Naik, 1978). However, Hartling *et al.* (1980) found that the hyperaemia during exercise was unaltered by either propranolol or atenolol. They did, however, find that propranolol reduced the post-exercise hyperaemia, whereas atenolol did not. Theoretically, it is possible that cardioselective agents may interfere less with normal blood flow to skeletal muscle than non-selective agents.

Acebutolol has been shown to be a cardioselective β -adrenoceptor blocking agent (Basil *et al.*, 1973; Harms, 1976). The purpose of this study was to compare the effects of chronic oral doses of acebutolol and propranolol on forearm blood flow in untreated hypertensive patients in amounts which caused equivalent cardiac β -adrenoceptor blockade.

Methods

Nine patients (six male, three female) of mean age 41 ± 10 years with untreated essential hypertension who

had at least three outpatient blood pressure recordings of $> 150/100$ mmHg were studied. Informed consent was obtained from each patient prior to the study, which was approved by the Hospital Ethics Committee. None of the patients had cardiomegaly, ECG abnormality, renal impairment or greater than grade II retinopathy. None of the patients were taking any other drugs at the time of the study. Each study lasted 9 weeks and was designed as follows:

Day 1: 08.00 h: Introduction to forearm plethysmography with demonstration of the technique, followed by an exercise test on a bicycle ergometer, with continuous ECG recording, starting at a workload of 50 watts, increasing that workload by 50 watts each 3 min, until exhaustion. By plotting heart rate against workload it was possible to estimate a workload which would be required to produce a heart rate of 150 beats/min after 8 min of exercise, in the absence of drugs.

Day 8: 08.00 h: Repeat demonstration of forearm plethysmography and then exercise test on the bicycle ergometer at the workload previously estimated to produce a heart rate of 150 beats/min.

Day 15: 08.00 h: Control recordings of forearm blood flow (carried out as described below), then repeating the exercise test as before. Upon completion of the exercise test, acebutolol (400 mg) was administered orally and 2 h later forearm blood flow was again recorded; venous blood was drawn for drug level estimation, and the exercise test was then repeated.

Each patient was given 6×400 mg tablets of acebutolol so that 400 mg could be self-administered daily for 6 days, and then the patient was seen again in 7 days, 24 h after the previous dose.

Day 22: 08.00 h: Forearm blood flow was recorded following which venous blood was drawn for measurement of drug level. The exercise test was then repeated and the patient given acebutolol 400 mg and enough tablets to continue the same dose for a further 6 days, to be seen again in 7 days, once again, 24 h after the previous dose.

Day 29: 08.00 h: Forearm blood flow was recorded, following which blood was drawn for measurement of drug level. The exercise test was repeated. The patient was given oral acebutolol (400 mg) and 2 h later forearm blood flow was again recorded and blood was drawn for measurement of drug level, following which the exercise test was repeated.

Treatment with acebutolol was then ceased and after a 2 week washout period the patient was seen again and the above study from Day 15 to Day 29 was repeated, substituting propranolol (80 mg) for acebutolol (400 mg).

At each visit, upon completion of the plethysmography measurements, blood pressure was recorded, using a standard sphygmomanometer and recording Korotkov sounds I and V.

Plethysmography

An air-filled forearm plethysmograph was used to measure forearm blood flow, with subjects supine with their left arm suspended just above the level of the heart to facilitate venous drainage, in a room with the temperature controlled at 28°C. The subjects rested in the room for 20 min before resting blood flow was recorded. One minute before recording blood flow a wrist cuff was inflated to supra-systolic levels (Kerslake, 1949). Air reservoirs of 50:1 were used for rapid inflation of the cuffs and care was taken that the venous occlusion pressure was below the diastolic blood pressure. The plethysmograph was connected to a capacitance differential manometer from Si-Plan (England) and this in turn was con-

nected to an Oxford Strip Recorder with paper speed at 10 cm/min. Blood flow was measured by the method of Hewlett & van Zwaluwenberg (1909) and a mean was taken of 10 consecutive recordings.

Statistical analysis was carried out using analysis of variance (Snedecor & Cochran, 1967).

Measurement of plasma drug levels

Acebutolol and diacetolol The plasma levels of acebutolol and its major human metabolite, diacetolol, were determined, in each sample obtained after administration of acebutolol, by a specific high pressure liquid chromatography method utilising fluorescence detection. Briefly, this involved addition of a suitable amount of an internal standard (M&B 17,764, the propionamido analogue of acebutolol and diacetolol) followed by extraction of the alkalised plasma with a 4:1 v/v mixture of diethyl ether: chloroform. After removal of the organic layer it was blown down to dryness in a stream of oxygen-free nitrogen. The residue was dissolved in a 100:1 of mobile phase (see below) and suitable aliquots were injected onto the column. The analytical column, 15 cm $\times$ 4.6 mm packed with Spherisorb S5 ODS (5 m) was protected by a small guard column, 5 cm $\times$ 4.6 mm containing Whatman Co.: Pell ODS, which was positioned between the injector and the analytical column. The mobile phase consisted of 0.01 M phosphate buffer (pH 4.0), methanol, acetonitrile 7:3:1 v/v, respectively. Acebutolol, diacetolol and M&B 17,764 were detected by their native fluorescence as they were eluted from the analytical column.

Propranolol The plasma level of propranolol was determined, in each sample obtained after administration of propranolol, by a specific high pressure liquid chromatography method utilising fluorescence detection. Briefly, this involved addition of a suitable amount of an internal standard M&B 19,421; DL-1-(4-*n*-butyramido-2-*n*-butyrylphenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride followed by extraction of the alkalised plasma with at 4:1 v/v mixture of diethyl ether:chloroform. After removal of the organic layer it was blown down to dryness in a stream of oxygen-free nitrogen. The residue was dis-

Table 1 Forearm blood flow response (mean $\pm$ s.e. mean) to oral acebutolol (400 mg) and propranolol (80 mg) ((ml/100 ml⁻¹ forearm tissue min⁻¹)

	Control	2 h post-dose	2 h (2 weeks) post-dose	24 h (1 week) post-dose	24 h (2 weeks) post-dose
Acebutolol	2.02 $\pm$ 0.13	1.78 $\pm$ 0.17	1.84 $\pm$ 0.23	1.93 $\pm$ 0.19	1.88 $\pm$ 0.23
Propranolol	1.93 $\pm$ 0.12	1.63 $\pm$ 0.13*	1.60 $\pm$ 0.21*	1.69 $\pm$ 0.19	1.65 $\pm$ 0.23

* Significantly different from control $P < 0.01$

solved in 100:1 of mobile phase (see below) and suitable aliquots were injected onto the analytical column, 15 cm $\times$ 4.6 mm, containing Spherisorb nitrile bonded silica (5 μ m). The mobile phase consisted of 0.01 M phosphate buffer (pH 5.0), methanol, acetonitrile, 6:3:1 v/v, respectively. Propranolol and M&B 19,421 were detected by their native fluorescence as they were eluted from the column.

Figure 1 Forearm blood flow seen before, 2 h after and 24 h after oral acebutolol (400 mg, O) and propranolol (80 mg, ●), respectively. The times refer to the period since the last dose, whether 1 or 2 weeks of treatment (mean $\pm$ s.e. mean). There is a significant ($P < 0.05$) fall in forearm blood flow 2 h after propranolol 80 mg. ** $P < 0.01$.

Results

Effects on forearm blood flow

Forearm blood flow was not significantly reduced either 2 h after or 24 h after oral acebutolol (400 mg). Propranolol (80 mg), however, reduced forearm blood flow significantly 2 h post-dose (Table 1 and Figure 1), but at 24 h post-dose, forearm blood flow was not significantly different from the resting control blood flow.

Table 2 Mean ($\pm$ s.e. mean) blood pressure response to oral acebutolol (400 mg) and propranolol (80 mg) (mmHg)

	Control	2 h post-dose	2 h (2 weeks) post-dose	24 h (1 week) post-dose	24 h (2 weeks) post-dose
Acebutolol	123 $\pm$ 5	112 $\pm$ 5*	107 $\pm$ 4*	113 $\pm$ 5*	108 $\pm$ 5*
Propranolol	118 $\pm$ 4	115 $\pm$ 4*	109 $\pm$ 5*	110 $\pm$ 5*	117 $\pm$ 5

* Significantly different from control $P < 0.05$

Effects on blood pressure

Significant blood pressure reduction was observed with both acebutolol and propranolol, 2 h after and at 2 h after the first dose at one week only.

After 2 weeks' treatment, blood pressure was significantly reduced by both drugs, when observed 2 h after the dose. However, when observed 24 h after the dose, only acebutolol was shown to have maintained reduction in blood pressure (see Table 2 and Figure 2).

Figure 2 Systolic and diastolic blood pressures following treatment with oral acebutolol (▨) and propranolol (■), respectively (mean $\pm$ s.e. mean). * $P < 0.05$.

There was no correlation between the percentage change in blood pressure and percentage change in blood flow.

Effects on vascular resistance

Vascular resistance, calculated from the mean blood

$$\left(\text{diastolic} + \frac{\text{systolic} - \text{diastolic}}{3} \right)$$

pressure and forearm blood flow, was significantly increased after propranolol 80 mg, but there was no significant change after acebutolol 400 mg (see Table 3).

Table 3 Forearm vascular resistance ($\pm$ s.e. mean) response to oral acebutolol (400 mg) and propranolol (80 mg) (arbitrary units)

	Control	2 h post dose	2 h (2 weeks) post-dose	24 h (1 week) post-dose	24 h (2 weeks) post-dose
Acebutolol	61 $\pm$ 5	63 $\pm$ 6	58 $\pm$ 7	59 $\pm$ 6	57 $\pm$ 7
Propranolol	61 $\pm$ 5	71 $\pm$ 5*	68 $\pm$ 7*	65 $\pm$ 6	71 $\pm$ 7*

* Significantly different from control $P < 0.01$

Effect on exercise tachycardia

Responses to exercise on the bicycle ergometer at a workload estimated to produce a tachycardia of 150 beats/min are shown in Figure 3. Control resting and exercise heart rates in the two studies were similar, as were the rest and exercise heart rates at 3 h post-dose, both of which were significantly less than control. At 24 h post-dose resting heart rates were still similar in the two groups and significantly less than the control heart rates. The exercise induced tachycardia was however, significantly reduced 24 h after the oral administration of 400 mg of acebutolol when compared with that 24 h after the oral administration of 80

mg of propranolol (127 ± 13 v 138 ± 8 respectively, $t = 3.95$, $P < 0.01$, mean $\pm$ s.d.).

Plasma levels

Analysis of plasma samples showed levels of acebutolol, its active metabolite, diacetolol, and propranolol at 2.5 h post-dose and at 24 h post-dose (Table 4). These results show that acebutolol is present in significant amounts at 2.5 h post-dose, that diacetolol is present in appreciable and significant amounts at both 2.5 h and 24 h post-dose, but that propranolol is only present at 2.5 h post-dose, being only detected in one patient at 24 h after dosing.

Figure 3 Heart rate response to 8 min exercise before, 2 h after and 24 h after oral acebutolol (400 mg, A) and propranolol (80 mg, P). The shaded areas represent the heart rate at rest and the clear areas the heart rate after 8 min exercise (mean $\pm$ s.d.). * $P < 0.05$, ** $P < 0.01$.

Discussion

There have been numerous studies reporting the effects of parenteral β -adrenoceptor blocking agents, but few reporting the effects of orally administered substances. Brick *et al.* (1966) could show no change in resting forearm blood flow with parenteral propranolol, but they were using very small doses. Johnson (1967) using a larger dose, showed a significant reduction in resting forearm blood flow with propranolol. He suggested that this was due to blockade of the vasodilatation present at rest due to small amounts of circulating adrenaline. Other workers have compared the effects of propranolol and selective β -adrenoceptor blocking agents, and report that propranolol has greater effect on the isoprenaline induced hyperaemia than the more selective agents (Clement, 1978). Once again these studies were

Table 4 Mean ($\pm$ s.e. mean) plasma levels of acebutolol, diacetolol and propranolol

	2 h post-dose	2 h (2 weeks) post-dose	24 h (1 week) post-dose	24 h (2 weeks) post-dose
Acebutolol (μ g/ml)	0.57 $\pm$ 0.09	0.68 $\pm$ 0.12	0.03 $\pm$ 0.04	0.09 $\pm$ 0.07
Diacetolol (μ g/ml)	0.75 $\pm$ 0.12	1.10 $\pm$ 0.15	0.32 $\pm$ 0.03	0.33 $\pm$ 0.08
Acebutolol + diacetolol (μ g/ml)	1.32 $\pm$ 0.19	1.78 $\pm$ 0.25	0.35 $\pm$ 0.03	0.43 $\pm$ 0.15
Propranolol (ng/ml)	54.2 $\pm$ 13	74.6 $\pm$ 13	ND	ND

ND = not detected, i.e. < 1 ng/ml

undertaken using parenteral infusions of the β -adrenoceptor blocking agents. Warren *et al.* (1978) reported that following a single oral dose, cardio-selective β -adrenoceptor blocking agents, such as metoprolol and atenolol, affect forearm blood flow less than non-selective agents, in normotensive volunteers.

We felt it important to examine the effects of orally administered β -adrenoceptor blocking agents on skeletal muscle blood flow in hypertensive patients. We chose acebutolol in a dose of 400 mg once per day, as we have previously shown this dose to be effective in lowering blood pressure (Watson, Stallard & Littler, 1980). Propranolol (80 mg orally) was chosen as a starting oral dose, and would have been increased in any subject had it been shown that there was no equivalent cardiac β -adrenoceptor blockade, on exercise testing. In fact, in all subjects there was very similar reduction in exercise-induced tachycardia with these doses, at 3 h post-dose. We found that forearm blood flow was significantly reduced at 2 h after administration of propranolol. With acebutolol, however, no significant reductions in forearm blood flow were obtained.

By 24 h after propranolol forearm blood flow had risen towards the control level, and no propranolol was detected in plasma at this time (Table 4). There are two possible reasons for orally administered acebutolol having significantly lesser effects than propranolol on forearm blood flow. Firstly, it is possible that acebutolol, being cardioselective, has lesser effects on β_2 -adrenoceptors in vascular smooth muscle than does a non-selective agent, and/or secondly, that acebutolol, having some intrinsic sympathomimetic activity (Basil *et al.* 1973) may be itself augmenting the effect of any circulating adrenaline. The changes seen in forearm vascular resistance, namely a rise after propranolol but no change after acebutolol, support the postulate that non-selective agents may allow unopposed α -activity, and thus to exert a more marked influence on blood flow.

The equivalence of the oral doses of acebutolol and propranolol was assessed by determining the reduction in exercise-induced tachycardia seen with both drugs. At 3 h post-dose there was no difference between the two, showing equal cardiac β -adrenoceptor blockade. At 24 h, however, the exercise-induced tachycardia was significantly greater in the propranolol group, compared with the acebutolol group, confirming greater cardiac β -adrenoceptor blockade at 24 h after oral acebutolol. This is perhaps due to there being appreciable and significant levels of diacetolol, the active metabolite of acebutolol, present at 24 h in all patients. Propranolol, on the other hand,

could only be detected in one patient at 24 h and even then at a very low concentration.

Blood pressure was reduced by acebutolol (400 mg) at 2 h and 24 h. The mean reduction in mean pressure being 13 ± 3 mm ($10 \pm 2\%$) and 12 ± 3 mm ($10 \pm 2\%$), respectively. These changes are similar to those previously reported (Watson *et al.*, 1980). Propranolol (80 mg), however, brought about a lesser fall at 2 h, 6 ± 2 mmHg ($6 \pm 2\%$) and at 24 h, 4 ± 2 mmHg ($4 \pm 2\%$). This could in part be explained by slightly lower control pressures in the propranolol study and from other work propranolol at a dose of 80 mg once daily is unlikely to maintain blood pressure reduction over 24 h (Leakey *et al.*, 1980).

There has been some interest in the effects of β -adrenoceptor blocking agents have in patients with peripheral vascular disease. Marshall, Barritt & Roberts (1976) found that cold extremities and absent pulses were far more common in patients treated with these agents, than those treated with methyl dopa. Steiner *et al.* (1979) however could find no difference in frequency of symptoms in hypertensive patients with Raynaud's phenomenon, when comparing propranolol, labetalol and placebo. The finding in our study that propranolol decreases forearm blood flow whilst acebutolol does not, provides a possible explanation for reduced peripheral vascular symptoms occasionally seen following a change from a non-selective to a selective agent (Marshall *et al.*, 1976). However, our study was looking at forearm blood flow and not flow through the extremities; it would seem important to compare the effects selective and non-selective agents may have on blood flow through the extremities.

In conclusion, then we have confirmed that acebutolol 400 mg once per day is effective in maintaining reduced blood pressure. Furthermore, the present study has demonstrated that in oral doses causing equivalent cardiac β -adrenoceptor blockade, acebutolol has no significant effect on forearm blood flow, whilst propranolol causes a significant reduction in forearm blood flow, when this is measured two hours after dosing.

This study suggests that a cardioselective drug such as acebutolol, having less effect on skeletal muscle blood flow, may be preferable to a non-selective drug such as propranolol, in patients with peripheral vascular disease.

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