ACEBUTOLOL IN HYPERTENSION— A DOUBLE-BLIND TRIAL AGAINST PLACEBO

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- 1 Eleven hypertensive patients were studied in a double-blind comparison of acebutolol, a β -adrenoceptor blocker, and placebo.
- 2 Optimum dosage defined in an open assessment varied from 200–600 mg twice daily.
- 3 Blood pressure and pulse rate fell significantly while patients were lying, standing and after exercise.
- 4 Blood pressure remained as well controlled on each patient's optimum daily dose when taken once daily, and assessed 24 h post dose.
- 5 There was no correlation between blood pressure reduction and changes in heart rate. On once daily therapy while blood pressure remained unchanged at 24 h post dose there was a significant reduction in β -adrenoceptor blockade as measured by percentage reduction in exercise tachycardia.
- 6 There was no significant change in urinary catecholamine excretion or echocardiographically estimated cardiac output.
- 7 A correlation was found between the change in plasma renin activity (log transformed) and blood pressure reduction.

Introduction

The value of β -adrenergic receptor blocking drugs in hypertension is well established (Lorimer, Dunn, Jones & Lawrie, 1976). However, each new hypotensive drug must be evaluated carefully and guidelines have been proposed (Prichard, 1975). If β -adrenoceptor blockers are equipotent in hypertension at optimum dosage as has been suggested (Davidson, Thadani, Singleton & Taylor, 1976), preference for individual agents may depend on dosage schedules, patient compliance, frequency of side effects and particularly long-term safety.

Acebutolol [(+)-1-(2-acetyl-4-butyramidophenoxy)-3 isopropyl-aminopropan-1-1 hydrochloride] (Sectral, May & Baker) is a β -adrenoceptor blocking drug which in animals is relatively cardio-selective and has intrinsic sympathomimetic activity (Basil, Jordan, Loveless & Maxwell, 1973). In man it is effective in the management of cardiac arrhythmias (Biron, Proulx, Lapointe, Nadeau & Tremblay, 1975) and angina (Lewis, Bakst, Kitchiner & Gotsman, 1973), and an open multicentre trial has suggested that it is also effective in hypertension (Ashton, 1976).

We have performed a double-blind crossover trial of acebutolol compared to placebo in moderate hypertension to assess its potency, safety and acceptability.

Within the limitations of an outpatient study we have measured indices of sympathetic activity, cardiac

output and plasma renin activity to examine possible mechanisms of the drug's action in hypertension.

Methods

Males and females aged 25–65 years were eligible if their lying diastolic blood pressure (phase 4) was between 100–120 mm Hg on three occasions and if they gave informed consent. Patients were excluded if there was evidence of accelerated or secondary hypertension, cardiac or renal failure, diabetes, bronchospasm or atrioventricular block, or if there was a history of stroke or myocardial infarction in the previous 3 months. Twenty patients entered the dose ranging assessment and eleven patients (three women) aged 40 ± 10 years (mean ± 1 s.d.) completed the whole study.

Baseline investigation

Initial assessment involved full clinical examination, weight, chest X-ray, ECG and measurement of peak expiratory flow rate. Full blood count, creatinine, urea and electrolytes, calcium and phosphate, serum lipids, liver function tests, autoantibodies (ANF, smooth muscle and mitochondrial) and plasma renin activity (PRA), were measured after overnight fasting and

following 1 h recumbency. An outpatient 24 h urine collection was made at the same time to measure urinary sodium, potassium, creatinine, VMA and free catecholamines. Analysis was by standard laboratory methods except for PRA which was measured by radioimmunoassay using an adaptation of the method of Cohen, Grim, Conn, Blough, Guyer, Kem & Lucas (1971), and free catecholamines which were measured by a modified fluorimetric method (Townshend & Smith, 1973).

Measurements

At each visit blood pressure was measured using the London School of Hygiene sphygmomanometer and defining diastolic pressure as Korotkow phase 4 (muffling). Pulse was measured over 30 s and peak flow using a Wright's peak flow meter and recording the best three attempts.

Measurements were made with patients lying after a minimum of 3 min rest (pulse and blood pressure only), standing after 1 min and immediately after exercise. Moderate exercise was performed on a single 12-inch step and consisted of 30 complete steps in 1 min. Patients were seen at approximately the same time of day at each visit and while taking medication between 2 and 4 h after their last dose. All measurements were made by the same observer (MAM).

Side effects

Side effects were assessed at each visit both by direct questioning and the completion of a 35 symptom questionnaire.

Trial design

There was an initial open dose ranging period. Acebutolol 100 mg twice daily was given and patients were seen fortnightly. The dose was increased by 100 mg twice daily each time unless limited by side effects or unless the lying diastolic blood pressure was 95 mm Hg or less, when no change was made. The dose at which no change was made on two consecutive visits was defined as optimum for each patient up to a maximum of 600 mg twice daily. Following a 2-week 'wash-out' period on placebo, each patient was given their optimum dose and identical placebo twice daily in a double-blind random manner for 6 weeks each with fortnightly assessment. Following this phase each patient was given his total optimum daily dose once daily for 6 weeks open assessment, and was seen fortnightly, each time not less than 24 h after the last dose. Compliance was measured by tablet counts and non-compliance arbitrarily defined as persistent variation from the expected count of 5–10% or variation greater than 10% on any single occasion.

All baseline investigations except CXR, ECG and VMA were repeated at the end of each phase. At the end of both double-blind periods echocardiographic assessment of left ventricular function was made using a standard technique (Popp, Filly, Brown & Harrison, 1975). An internal diameter of the left ventricle was measured at end diastole and end systole and these measurements were used as the basis for estimates of standard haemodynamic parameters.

The echo diameters at end diastole and end systole were cubed to give an estimate of left ventricular volumes. The difference between these measurements gave an estimate of stroke volume which was multiplied by the heart rate to derive cardiac output. Stroke volume using this echo method has been shown to correlate well with angiographic estimates (Popp & Harrison, 1970).

For individuals the mean results for each phase were calculated and group results were expressed as mean $\pm$ 1 s.d. Differences were evaluated by Student's paired *t*-test (two-tailed) or the Wilcoxon pair test where appropriate, and correlations were assessed by linear regression.

Results

Blood pressure

During the open dose ranging all eleven patients showed a fall in blood pressure on doses of acebutolol above 100 mg twice daily. The optimum dose varied and was unrelated to body weight. It was 200 mg twice daily in three, 300 mg twice daily in four, 400 mg twice daily in two, and 500 mg twice daily and 600 mg twice daily in one each. As might be expected with such small groups, the blood pressure falls did not achieve statistical significance for every dose increment. However, mean results for the four whose optimum dose was 300 mg twice daily (Figure 1) suggest a dose response relationship and this was the impression throughout the group.

In the double-blind phase, mean systolic blood pressure dropped approximately 10 mm Hg on placebo compared to pretreatment values ($t > 2.51$, $P < 0.05$). When active treatment was compared to placebo all patients showed a fall in blood pressure. This fall occurred in lying, standing and post exercise measurements, both systolic and diastolic (Figure 2). All group changes were highly significant ($t > 4.18$, $P < 0.01$), with an overall average drop of 21/16 mm Hg. The major changes were seen by 2 weeks in the active phase although there was a suggestion of a small further drop by 6 weeks.

When the optimum daily dose was taken once daily, the blood pressure measured 24 h after the last dose was not significantly different from that measured 2–4 h after the last dose when the optimum daily dose was divided into two. This was true whether the once

Figure 1 Dose-response relationship in open assessment. Group pulse and blood pressure (mean $\pm$ 1 s.d.) for optimum dose 300 mg twice daily ($n=4$).

All statistical comparisons are with pretreatment values ($\Delta P < 0.02$, $\square P < 0.05$).

daily treatment was preceded by placebo or active treatment.

Two patients had only modest drops in pressure on active therapy (5/5 and 5/1 mm Hg lying respectively) and they could be considered poor responders. Only one patient did not attain a lying diastolic of 95 mm Hg although he had an average absolute drop in pressure on 600 mg twice daily.

Pulse rate

The pulse rate did not change significantly on placebo but there was evidence of β -adrenoceptor blockade expressed as percentage reduction in exercise tachycardia (Carruthers, Shanks & McDevitt, 1976) at all doses of active therapy. In the double-blind assessment pulse rate was lower in all positions on active treatment (Figure 2) ($t > 5.9$, $P < 0.001$) but was never lower than 56 beats/min. While on once daily treatment the pulse rate at 24 h after the dose was significantly higher than at the time of peak effect on the twice daily regime ($t > 2.5$, $P < 0.05$) but was still significantly lower than on placebo ($t > 5.2$, $P < 0.001$). The degree of β -adrenoceptor blockade did not correlate with dosage or change in blood pressure and was significantly less on once daily than twice daily dosage (11% reduction in exercise tachycardia compared to 19% ($t = 9.3$, $P > 0.001$)).

Investigations

There was no significant change in peak flow rate at any stage either at rest or after exercise.

Figure 2 Group pulse and blood pressure in double-blind trial (mean $\pm$ 1 s.d.) ($n=11$). Adjacent values are compared statistically ($\Delta P < 0.01$, $\square P < 0.05$). Pretreatment $\square$, Placebo $\square$, Active $\times$ 2 daily $\blacksquare$, Active $\times$ 1 daily $\square$.

The urinary excretion of noradrenaline and adrenaline showed no consistent pattern of change. The group mean noradrenaline excretion ($n=10$) on placebo was 228 nmol/24 h and 192 nmol/24 h on active therapy. The results for adrenaline were 67 nmol/24 h on placebo and 76 nmol/24 h on active treatment (Table 1). These differences were not significant using the Wilcoxon pair test which was preferred because the results were not normally distributed.

None of the other clinical or biochemical parameters changed significantly during the double-blind period except plasma renin activity. This dropped on active treatment in nine out of eleven patients. The group change was from 0.92 ± 0.58 pmol $\text{cm}^{-3} \text{h}^{-1}$, (1.32 ± 0.83 ng $\text{ml}^{-1} \text{h}^{-1}$) on placebo to 0.46 ± 0.47 pmol $\text{cm}^{-3} \text{h}^{-1}$ (0.66 ± 0.67 ng $\text{ml}^{-1} \text{h}^{-1}$) on active therapy ($t = 2.28$, $P < 0.05$). It has been suggested that PRA is lognormally distributed (Padfield, Beevers, Brown, Davies, Lever, Robertson, Schalekamp & Tree, 1975) and when the change in log transformed PRA was measured it was also significant ($t = 2.38$, $P < 0.05$).

The initial level and change in level of PRA both before and after log transformation were compared with the lying blood pressure, both systolic and diastolic. The initial PRA was significantly correlated only with the fall in lying systolic blood pressure

Figure 3 Correlation of the reduction in PRA (log transformed) and the drop in systolic blood pressure comparing the active and placebo phases of the double-blind trial. $r = 0.71$, $P < 0.05$.

($r = 0.62$, $P < 0.05$) but this was not true after log transformation.

The change in PRA was significantly correlated with the fall in both systolic and diastolic blood pressure, and this relationship remained after log transformation ($r > 0.62$, $P < 0.05$) (Figure 3).

Echocardiography

Six patients had acceptable tracings on both active and placebo treatment. The echo internal ventricular diameter, a measured parameter, enlarged in all but

one patient. However, the magnitude of the change was at the border-line of that expected in this department when measurements are repeated serially in untreated subjects. It was only significant with respect to end diastolic diameter which increased from 4.26 ± 0.25 cm to 4.42 ± 0.30 cm ($t = -2.73$, $P < 0.05$). The derived parameters of left ventricular function showed small and variable individual changes but no overall significant change (Table 1). In particular, estimated cardiac output at rest changed from 4.01 ± 1.27 l/min to 3.75 ± 1.10 l/min which was not significant and there was no correlation between output changes and drop in blood pressure.

Side effects and withdrawals

One patient withdrew from open dose ranging because of malaise and dizziness which developed after 10 days on acebutolol 200 mg twice daily. Three patients defaulted and two were withdrawn for non-compliance. One woman became pregnant and was withdrawn. In the double-blind assessment, one patient was withdrawn for non-compliance and one further woman became pregnant and was withdrawn.

Four patients complained of tiredness or leg aching for a few days following the start of active treatment. However, these symptoms did not recur in the active double-blind phase, and overall there were no more symptoms on active treatment than on placebo when compared by a simple ranking procedure.

Discussion

Within the dose range 400–1200 mg a day, acebutolol appears to be an effective agent in moderate

Table 1 Individual patient data for catecholamines and echocardiography

	NA (nmol/24 h)		Ad (nmol/24 h)		EDd (cm)		ESd (cm)		Stroke volume (ml)		Cardiac output (l)	
	P	A	P	A	P	A	P	A	P	A	P	A
Patient 1	328	136	86	60								
2	121	122	75	72								
3	96	134	65	51	3.80	4.02	2.55	2.62	37	47	2.15	2.35
4	243	136	57	48	4.42	4.55	2.21	2.39	76	80	5.70	5.04
5	215	181	87	297	4.22	4.41	2.79	2.75	53	65	3.76	3.97
6	115	300	17	24								
7	436	195	159	85	4.23	4.13	2.99	2.98	49	43	3.50	2.45
8	121	216	42	62								
10	292	83	49	17	4.35	4.67	2.80	3.35	60	63	5.20	4.40
11	309	420	29	45	4.53	4.71	2.91	3.00	68	78	3.74	4.26
Mean	228	192	67	76	4.26	4.42	2.71	2.85	57	63	4.01	3.75
1 s.d.					0.25	0.30	0.29	0.34	14	15	1.27	1.10

P, placebo; A, acebutolol

NA, noradrenaline; Ad, adrenaline

EDd, end diastolic diameter; ESd, end systolic diameter

hypertension with a potency similar to other β -adrenoceptor blockers. It has a low incidence of side effects and is well tolerated. When it was given on a once daily basis the blood pressure remained as well controlled at the time of assessment as on twice daily treatment. The ability to control blood pressure on once daily treatment has been suggested with a number of β -adrenoceptor blockers; propranolol and pindolol (Wilson, Morgan & Morgan, 1976), atenolol (Wilcox & Mitchell, 1977) and sotalol (Gabriel, 1977). Although as in the majority of the above trials the blood pressure was measured only once in the day in each phase, it seems reasonable to expect that the pressures at 24 h post dose on once daily treatment would reflect minimum control. Confirmation that once daily therapy provides similar control throughout the 24 h would require further evaluation involving inpatient or home measurement studies with blood pressure recorded throughout the dose interval.

A number of mechanisms has been suggested to explain the action of β -adrenoceptor blockers in hypertension and these have been reviewed recently (Fitzgerald, 1975). We measured indices which we hoped would reflect changes in these mechanisms and correlated them with the effect on blood pressure.

β -adrenoceptor blockade appears necessary for the hypotensive effect (Waal-Manning, 1970) but hypotensive action occurs later and in doses higher than those required to show β -adrenoceptor blockade with respect to heart rate (Ablad, Ljung & Sannerstedt, 1976). In our study the degree of β -adrenoceptor blockade as judged by the percentage reduction in exercise tachycardia did not correlate with blood pressure changes. In addition, the degree of β -adrenoceptor blockade with respect to heart rate changed substantially at 24 h post dose on once daily therapy without a change in blood pressure, showing a separation of these effects, although previous data on a differential effect on heart rate has been conflicting (Wilson *et al.*, 1976; Gabriel, 1977).

It has been suggested that β -adrenoceptor blockers act through a fall in cardiac output (Frolich, Tarazi, Dunstan & Page, 1968). In the six patients who had a full echocardiographic assessment there was no consistent effect on estimated cardiac output and the changes which occurred did not show any relationship to the fall in blood pressure. Although such indirect data from a small group should be interpreted cautiously, previous workers using standard haemodynamic measurements have suggested that with some β -adrenoceptor blockers there may be no change in cardiac output when in oral steady state (Franciosa, Freis & Conway, 1973; Wilson, Watson, Peel, Langley & Turner, 1968). The urinary excretion of catecholamines used as a measure of overall sympathetic activity (DeQuattro & Sjoerdsma, 1968)

showed no consistent pattern of change and no correlation with the effect on pressure. There were large variations in individual results when measured in the pretrial and placebo phases, and on active treatment approximately equal numbers showed increases and decreases.

Some workers believe that the hypotensive response to these drugs can be correlated with the initial level and subsequent change in plasma renin activity (Bühler, Laragh, Baer, Vaughan & Brunner, 1972) although this has not been a consistent finding (Stokes, Weber & Thorwell, 1974). Our data suggested a relationship between the change in log transformed PRA and drop in lying blood pressure. However, these results should be interpreted with caution. There was substantial variation in PRA results in some individuals on different occasions when not on active treatment. This variation was not explained by changes in urinary sodium excretion (Woods, Pittman, Pulliam, Werk, Waider & Allen, 1976). PRA is affected by a large number of factors relating to the patient, collection techniques and assay method (Williams, 1976), and *significant* variation has been shown even under carefully controlled conditions (Weinburger, Rosner, Kem, Joyner & Foust, 1972). Under these circumstances comparison of single measurements, especially in small groups, may hide true correlations or suggest spurious ones.

A similar correlation has been suggested with acebutolol before (Menard, Beylgagna, N'Guyen, Degoulet & Corvol, 1976), but this is not true in all studies (Fournier, Hardin, Alexandre, Lombaert, Ronco, Bezoc, Desmet & Quinchar, 1976).

A number of problems arise when attempting to define the drug's mode of action in an outpatient study. Urinary catecholamine excretion showed marked variation off active treatment and may not be an adequate measure of sympathetic activity. It is possible that measurement of plasma catecholamines, where available, might be a more accurate reflection of sympathetic activity. Similarly problems remain in interpreting data on plasma renin activity. We therefore do not consider that we have been able to definitely define this drug's specific mode of action in hypertension, although this may be due in part to small numbers and the limits imposed by the methods available in an outpatient study.

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