Treatment of hypertension with acebutolol*

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Summary

OF 28 patients included in a trial of oral Acebutolol for the treatment of hypertension, 23 were eligible for assessment. Acebutolol alone was successful in controlling the blood pressure in 17 patients (74%), mild and moderate cases showing the best response, Combination therapy with chlorothiazide did not improve the response rate appreciably. The five treatment failures had had severe hypertension with mean arterial pressure exceeding 140 and had all been previously unresponsive to other antihypertensive agents.

Tolerance throughout the trial was good. The commonest side effect noted was weight gain which was unrelated to fluid retention. Giddiness, lethargy, drowsiness and increased sweating occurred occasionally and transiently. Two patients with chronic obstructive airway disease tolerated the drug without developing bronchospasm, thus confirming the cardioselective property of the drug. Cardiac decompensation occurred in two patients with cardiomegaly necessitating digoxin and diuretic therapy. Despite its intrinsic sympathomimetic activity, the drug should be used with caution in patients with impaired myocardial contractibility.

Introduction

Since Prichard (1964) first described the antihypertensive effect of beta blockers, there has been tremendous progress in this field of therapeutics. Today there are well over 30 beta blocking compounds available, all of which display more or less marked anti-hypertensive properties. Experience in the use of beta blockers as treatment for hypertension in countries all over the world suggests that preference for any preparation is often decided not by its anti-hypertensive activity, but by its safety, tolerability and liability to produce untoward side effects.

The purpose of this study is two fold: firstly, to study the efficacy of Acebutolol as an anti-hypertensive agent in the local patients, and secondly, to evaluate its acceptability from the standpoint of safety and tolerability.

Patients and methods

This trial was carried out in the District Hospital, Segamat, commencing in March 1976 and ending on December 1st 1976, when the last patient in the trial had completed 6 months of continuous therapy with Acebotolol.

Two groups of hypertensive patients were selected for the trial:

(a) New cases: Any patient with three separate blood pressure recordings greater than 150 mm Hg (systolic) and 90 mm Hg (diastolic) taken after 10 minutes rest and at the same visit.

Exclusions:
1. Pregnant women.
2. Patients with drug induced hypertension.
3. Patients with a pulse rate of below 60/min.

(b) Established cases where the blood pressure remained uncontrolled with existing therapy or where there was intolerance to antihypertensive drugs used.

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All previous antihypertensive drugs were terminated for at least one week prior to entering the study. Blood pressure and pulse rate were recorded in the supine position after 10 minutes lying down and in the erect position after 1 minute standing. Three sets of readings were noted for each position. The level of diastolic blood pressure was indicated by the disappearance of the sounds on auscultation.

Besides a thorough clinical examination to assess the extent of target organ damage, the following investigations were carried out initially and after 3 months of therapy with Acebutolol:

1. Body weight
2. Haemoglobin estimation and white cell count
3. Urine examination
4. Blood urea
5. Liver function tests
6. Electrocardiographs (ECG)
7. Chest X-ray

Other investigations were done when necessary. These included blood sugar, serum electrolytes, serum uric acid, serum cholesterol, serum creatinine, intravenous pyelogram, etc.

Following the one week run-in period, Acebutolol was administered according to a twice daily dosage schedule, the initial dose being 400 mg daily. The dosage was adjusted in either direction weekly until control of blood pressure was achieved. In those instances where control remained unsatisfactory, chlorothiazide (and later other adjuvant drugs) was added to the regime.

All cases were followed up at the physician clinic. Side effects were not specifically asked for but would be recorded if volunteered by the patient or in response to the question: Has the treatment upset you in any way?" The only exception to this rule was made when male patients were specifically asked about impotence, as the author felt that the local patients would be too shy to disclose this information volunteerily.

The severity of hypertension and the response to treatment were classified, based on the mean arterial pressure, which was expressed as:

$$\text{M.A.P.} = \frac{\text{Systolic Pressure} + (\text{Diastolic Pressure} \times 2)}{3}$$

The upper limit of normal mean arterial pressure was taken to be 110 which is equivalent to systolic and diastolic readings of 150/90 or 130/100. Table I shows the criteria used for the grading of severity of hypertension and response to treatment.

Results

Twenty-eight patients were admitted to the trial. Of these 23 were eligible for assessment, 16 being male while 7 were female, and were made up of 6 Malays, 15 Chinese and 2 Indians. Their mean age was 50.5 years and ranged from 35 to 67 years. Twelve had associated conditions (6 with diabetes mellitus, 3 with angina pectoris, 2 with chronic obstructive lung disease and 1 with stroke), and 12 had previous antihypertensive therapy.

Of the 5 patients who did not complete the trial, one had the drug withdrawn upon her request when she became pregnant. The other four defaulted despite repeated attempts to trace them.

By the criteria of grading described earlier, 7 cases were classified as mild hypertension, 7 moderate and 9 severe (Table II). Successful control of blood

Table I

Criteria used for grading severity of hypertension and response to treatment

	Grade	M.A.P.	Equivalent B.P. Readings
Severity of hypertension	Mild	<123.3	up to 170/100
	Moderate	<133.3	up to 180/110
	Severe	133.3 & above	
Response to treatment	Excellent	<106.6	up to 140/90
	Good	<116.6	up to 150/100
	Fair	116.6 & above with fall >20 mm	
	Poor	116.6 & above with fall <20 mm	

pressure (graded as excellent and good) was achieved in 18 patients or 78.3%. The mild and moderate cases had the best results without any failure.

Figure 1 shows the M.A.P. before and after 3 months of Acebutolol for each of these 23 cases.

Table II

Classification and response in the 23 cases of hypertension studied

Severity of Hypertension	No. of Patients	Grade of Response			
		Excellent	Good	Fair	Poor
Mild	7	6	1	0	0
Moderate	7 (2)*	3	4	0	0
Severe	9 (4)	0	4	5	0
Total	23 (6)	9	9	5	0

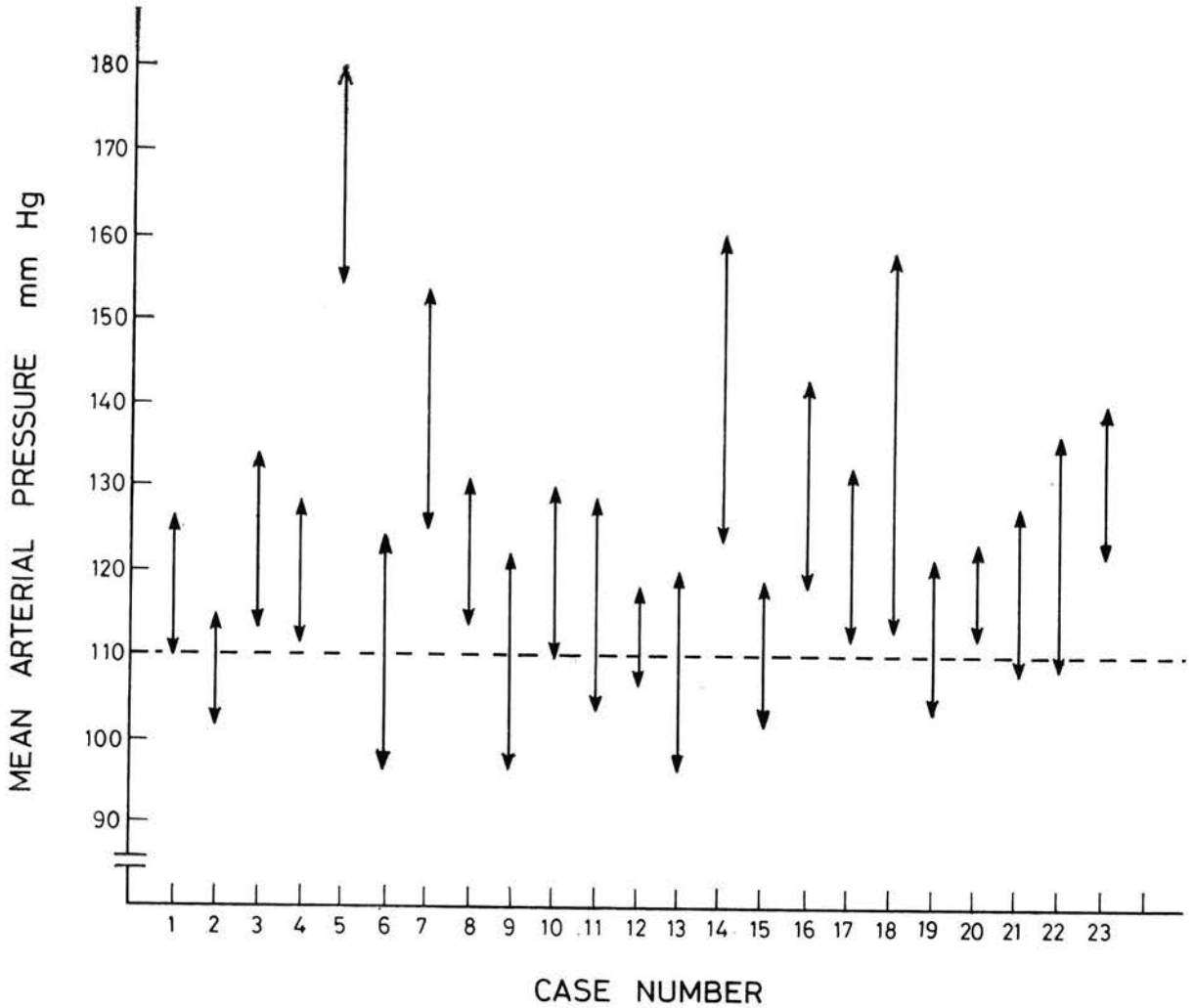

Figure 1: Mean arterial pressure before and after treatment with Acebutolol (23 cases). Dotted line indicates the upper limit of normal mean arterial pressure.

In 17 patients or 74% Acebutolol alone was adequate to control blood pressure, the daily dosage used ranged from 400 to 800 mg. (Table III) Adjuvant drugs were required in 6 patients, with thiazide being the drug of initial choice. The time taken for initial control of blood pressure in the 18 successful cases was variable, the majority taking less than 8 weeks.. (Table IV)

All the 5 failures were from the severe group and had been given combination therapy before. They were given 800 mg Acebutolol per day with one or more of these adjuvant drugs: Chlorothiazide, methyldopa, debrisoquin or guanethidine. The fall in their M.A.P. ranged from 21.7 to 40.0 but the final M.A.P. remained above 116.6 in all cases.

The fall in blood pressure was accompanied by slowing of pulse rate in every case, the majority of patients had pulse rate reduced by 10 to 25 beats per min.

Only one patient showed some biochemical change at the end of 3 month course of Acebutolol. He had a rise in SGOT from 40 i.u./L to 75 i.u./L.

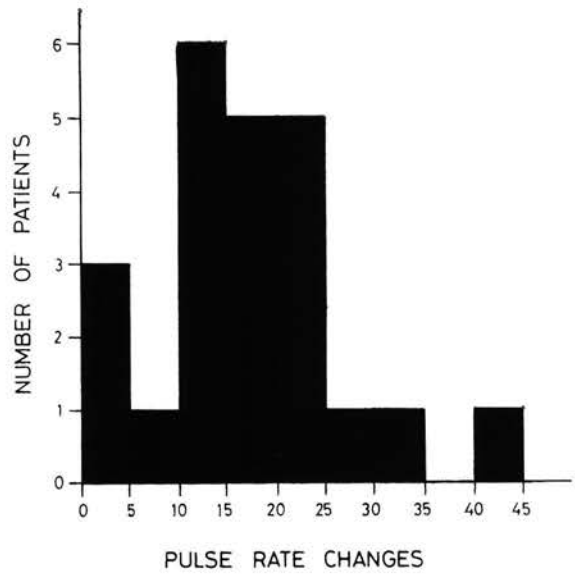

Figure 2: Pulse rate changes following Acebutolol therapy.

Table III

Dosage of Acebutolol used in the 23 cases studied

Dosage of Acebutolol mg/day	Adjuvant Drugs	No. of Patients
400	–	15*
600	–	1
800	–	1
800	Chlorothiazide	1
800	Chlorothiazide + Methyldopa	3
800	Chlorothiazide + Debrisoquine	1
800	Chlorothiazide + Methyldopa + Guanethidine	1

* including two patients given thiazide for heart failure after blood pressure had been controlled.

Table IV

The time taken for initial control of blood pressure in the 18 successful cases

	1 wk	2 wk	4 wk	6 wk	8 wk	10 wk	12 wk	16 wk
mild	3	0	1	2	1	0	0	0
moderate	1	2	1	0	0	0	2	1
severe	0	0	1	1	1	1	0	0
Total	4	2	3	3	2	1	2	1

However, this proved to be a transient phenomenon when SGOT estimation was repeated at 6 months.

Eight patients had significant ECG abnormalities before commencement of the trial. In four the abnormalities remained unchanged after 3 months of treatment. Table V summarises these ECG abnormalities.

Discussion

The antihypertensive effect of beta blockers has been confirmed by so many investigators and in such a large number of patients that it is now universally accepted as proven.

Table V

Summary of significant ECG abnormalities seen in 8 cases prior to commencement of trial

Case No.	Before Treatment	After Treatment
4	LBBB and LVH	No Change
6	LVH with strain	No change
8	Flattened T wave in V5, V6	T wave upright
14	Flattened T wave in II, III, avF, V5 and V6	T wave upright
18	LVH with inverted T wave in I, II, avL, V4 to V7	Reduced amplitude of S in V1 and R in V6
19	QS in V2 and V3	No change
23	LVH with ST segment depression in I, avL, V4 to V6	Reduced amplitude of S in V1 and R in V6 with inverted T wave in II, III, avF, V5 and V6
28	RBBB	No change

LBBB = left bundle branch block
LVH = left ventricular hypertrophy
RBBB = right bundle branch block

Cardiomegaly was seen in the chest X ray films of 11 patients but only two patients showed reduction of cardiothoracic ratio after 3 months of treatment.

Table VI summarises the side effects of therapy as reported by the patients. It is worth noting that of 9 patients who gained weight, 6 had concurrent diuretic therapy. Transient dizziness in all the 3 patients occurred without a demonstrable postural drop in blood pressure. There was no complaint of impotence although one patient admitted loss of libido.

Table VI

Summary of the side effects of therapy reported in 18 patients

Side Effects	No. of Patients
Weight gain (>3 lb. in 3 months)	9 (6 on thiazide)
Transient giddiness	3
Excessive sweating	2
Precipitation of heart failure	2
Poor appetite with weight loss	1
Loss of libido	1

What is the therapeutic efficacy of the beta blockers as a group? Lewis (1974) stated that the response rate of hypertensives to beta blockers alone lies within the range of 50–90% and possibly depends among other things on the initial height of the blood pressure. With propranolol, alone and in combination with diuretics, the effectiveness ranged from 66- to 88% (Prichard & Gillam, 1969). This was confirmed by Zacharias *et al.* (1972). Other beta blockers, including alprenolol, oxprenolol, pindolol, sotalol and timolol, have been shown to be effective in reducing blood pressure to approximately the same degree (Lorimer *et al.*, 1976).

The response rate of hypertensives to Acebutolol as found in this trial was 78.3% comparing favourably with other beta blockers in general and with propranolol in particular.

In clinical practice, beta blockers and diuretics are probably the most common combination used. The enhanced antihypertensive effect of such a combination is very variable as reported by different workers. Brunner (1974) found that the antihypertensive effect of beta blockers could best be compared with that of thiazide diuretics, and that like diuretics, beta blockers exerted a clinically satisfactory reduction of blood pressure in only 20–40%

of cases when prescribed alone. However when employed in combination with diuretics the response rate rose to 70–80%. He therefore concluded that beta blockers were seldom suitable as monotherapy.

However, other workers reported different findings. For example, Dorph & Binder (1969) found that the combined use of oxprenolol and hydrochlorothiazide was not significantly more effective than oxprenolol alone, and Safar *et al.* (1974) obtained similar findings with pindolol and clopamide.

A report from the General Practitioner Research Group in U.K. (Practitioner 1976) found that Acebutolol alone, produced a modest hypotensive effect which was not quite so great as that produced by bendrofluozide alone, although the difference was not statistically significant. The combination of the two drugs produced a more rapid and more effective hypotensive action, which was more than might be expected by a simple summation of the effects of the two drugs together.

In the present trial, the combination of Acebutolol and chlorothiazide did not appreciably increase the hypotensive action of Acebutolol, which alone was effective in 74% of cases. Thus Acebutolol may be regarded as suitable for monotherapy of hypertension. Recently, plasma renin level has been found to be useful in the rapid identification of patients with essential hypertension sensitive to Acebutolol. Lowering of blood pressure after Acebutolol treatment correlated with initial plasma renin activity and reduction in plasma renin activity (Menard *et al.*, 1976).

Beta blockers as a group possess several advantages over the other antihypertensive drugs. Tolerability is good. An enhanced sensation of well being is often experienced by patients taking them. They are effective in controlling blood pressure in both lying and standing position. Coronary complications of hypertension may be reduced by beta blockade therapy. And lastly, abrupt withdrawal of the drug does not result in an immediate rise in blood pressure. In fact, antihypertensive effect of continued treatment can be detected for up to 4 weeks of cessation of therapy. Hence, a missed dose has little therapeutic disadvantage (Taylor, 1976).

Beta blockers vary in their propensity to producing side effects. Propranolol being non-cardioselective and lacking intrinsic sympathomimetic activity may cause bronchospasm and cardiac decompensation. The same may be said for sotalol and timolol. Pindolol has more marked effect on central nervous system. Practolol, which is cardioselective and possesses intrinsic sympathomimetic activity may cause gastro-intestinal upset and oculocutaneous lesion.

Acebutolol has similar pharmacological properties as practolol. It was found to be well tolerated by patients in this trial. Oculocutaneous lesions did not occur. Weight gain was common and was not associated with fluid retention. It could be a result of the metabolic effect of beta blockers on fat and carbohydrate metabolism. Sexual potency was unaffected in all the patients. Although a case of loss of libido was reported, this could not be definitely attributed to Acebutolol therapy. Giddiness, lethargy, drowsiness and sweating disturbances occurred occasionally and could be due to transient central nervous system disturbances. Bronchospasm did not occur in this group of patients although two of them had chronic obstructive airway disease. This is supportive evidence of the cardioselectivity of Acebutolol. However, two patients developed cardiac decompensation necessitating digoxin and diuretic therapy. Thus, although Acebutolol claims to possess intrinsic sympathomimetic activity, it should nevertheless be used with caution in patients with cardiomegaly.

Acknowledgement

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