β -ADRENERGIC RECEPTOR BLOCKING DRUGS, HYPERTENSION AND PLASMA RENIN

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- 1 Propranolol and pindolol reduced both the blood pressure and plasma renin activity when given chronically to hypertensive patients.
- 2 There was no correlation between the fall in blood pressure and the fall in plasma renin activity.
- 3 Neither the basal nor the random plasma renin activity predicted the patients who would respond to β -adrenergic receptor blocking drugs.
- 4 Oral propranolol reduced plasma renin activity but did not reduce blood pressure within 4 h of administration; oral pindolol reduced blood pressure but did not reduce plasma renin activity within 4 h of administration.
- 5 The reduction of blood pressure by propranolol and pindolol does not seem to be mediated by changes in plasma renin in most patients.

Introduction

Although β -adrenergic receptor blocking drugs are now widely used to treat hypertensive patients (Prichard & Gillam, 1969; Zacharias, 1971; Morgan, Louis, Dawborn & Doyle, 1972), the mechanism of their antihypertensive action is uncertain. It has been suggested that the site of action may be in the central nervous system (Morgan *et al.*, 1972), whilst the fact that they often lower plasma renin (Michelakis & McAllister, 1972) has led to the suggestion that it is this action which is responsible for the lowering of blood pressure (Bühler, Laragh, Baer, Vaughan & Brunner, 1972). Bühler *et al.* (1972) have claimed that patients with high levels of plasma renin almost invariably respond to propranolol, whereas those patients with 'low renin hypertension' do not. If this observation was to be confirmed it would have important implications, both in relationship to the pathogenesis of hypertension and selection of therapy. This paper reports a study designed to examine whether plasma renin levels could be related to the antihypertensive response to β -adrenoceptor blocking drugs both after acute and also chronic administration.

Methods

Acute study

Eleven untreated hypertensive patients were admitted to hospital. Each patient was studied on

three occasions at intervals of two days, being given on different days either propranolol (160 mg), pindolol (20 mg) or four placebo tablets, in a random order on a double-blind basis. After overnight bed rest, the patient remained in bed and duplicate recordings of blood pressure and pulse rate were made four times between 08.00 h and 10.00 hours. At 10.00 h a venous blood sample was drawn and the tablets were taken. Blood pressure and pulse rate were measured at hourly intervals for 4 h and venous blood samples were drawn at 12.00 h and 14.00 hours. Estimations of plasma renin activity (PRA) were made on each blood sample by radioimmunoassay using the method of Johnston, Mendelsohn & Doyle (1972).

On a subsequent day the responses of the patients to frusemide were studied. Blood pressure was measured and a venous blood sample was drawn at 08.00 hours. Frusemide (40 mg) was given by mouth and the patients allowed out of bed. A second blood sample for measurement of PRA was taken at 10.00 hours.

Chronic study

Seventy-six male patients aged 36-68 years (mean 54 years) were studied. Fifty-three had not been previously treated for hypertension. Twenty-three had been previously treated, but treatment was discontinued 2 weeks before the study. All patients had serum creatinine levels below 0.17 mmol/litre. Five patients had renovascular

hypertension, as determined by functional changes in the intravenous pyelogram, renal arteriography and renal vein renin levels. The remainder had essential hypertension. All patients had diastolic blood pressure levels above 95 mmHg on three or more occasions. No patient had retinal haemorrhages or exudates, or papilloedema.

All patients were admitted to hospital and given a diet containing more than 100 mEq of sodium daily for 5 days. Urinary sodium excretion was measured daily. On the fifth day after admission to hospital the patients remained in bed and a venous blood sample was drawn at 10.00 h for measurement of PRA.

The patients then left hospital without antihypertensive treatment and reported as outpatients 3 weeks later. On this occasion blood pressure was recorded, both lying and standing, blood was taken for PRA determination and a 24 h urine sample was collected for measurement of urinary sodium excretion.

Treatment was then commenced with propranolol (40 mg twice daily) in thirty-nine patients, or pindolol (5 mg twice daily) in thirty-seven patients. The patients were reviewed at intervals of 2 weeks and if the diastolic blood pressure exceeded 95 mmHg the dose was doubled until a

dose of propranolol (640 mg), or pindolol (60 mg) had been attained. PRA was again measured when effective control of blood pressure had been attained or when the maximum dose of each drug had been reached.

The significance of changes in blood pressure and PRA were estimated by a paired and unpaired *t* test and correlation coefficients determined by the method of least squares.

Results

Acute study

Eleven patients received placebo, propranolol, pindolol and frusemide. The placebo induced no significant changes in blood pressure, pulse rate or PRA (Table 1). Propranolol induced a fall in diastolic blood pressure of 10 mmHg or more in only one patient. There was no significant fall in the group mean. The mean pulse rate decreased from 74 ± 4 to 62 ± 3 ($P < 0.001$) beats/minute. PRA fell in nine of the eleven patients and was unaltered in the other two patients. The mean plasma renin 2 h after propranolol was significantly less than control (Table 2). There was still

Table 1 Diastolic blood pressure and plasma renin activity (PRA) (mean $\pm$ s.e. mean, $n = 11$) before and 2 h after placebo, pindolol, propranolol or frusemide

	Diastolic BP (mm Hg)		PRA ($\mu\text{mol A}_1 \text{ ml}^{-1} \text{ h}^{-1}$)	
	Control	2 h	Control	2 h
Placebo	112 ± 4.3	111 ± 3.8	0.57 ± 0.11	0.52 ± 0.10
Propranolol	115 ± 4.9	113 ± 5.7	0.60 ± 0.15	$0.33 \pm 0.09^{**}$
Pindolol	112 ± 4.5	$99 \pm 4.7^*$	0.61 ± 0.14	0.52 ± 0.14
Frusemide	111 ± 3.8	113 ± 4.2	0.49 ± 0.11	$0.73 \pm 0.15^*$

* $P < 0.005$; ** $P < 0.001$ compared with control, paired *t* test.

Table 2 Change (mean $\pm$ s.e. mean) in blood pressure and plasma renin activity (PRA) after β -adrenoceptor blocking drugs

	n	Fall in supine BP (mm Hg)		Fall in PRA ($\mu\text{mol A}_1 \text{ ml}^{-1} \text{ h}^{-1}$)
		Systolic	Diastolic	
Propranolol	39	$27.4 \pm 2.8^*$	$17.3 \pm 2.2^*$	$0.20 \pm 0.05^{**}$
Pindolol	37	$22.5 \pm 2.2^*$	$14.4 \pm 1.6^*$	$0.20 \pm 0.05^{**}$
Total	76	$24.9 \pm 2.0^*$	$15.9 \pm 1.4^*$	$0.20 \pm 0.04^{**}$

* $P < 0.001$, ** $P < 0.01$ from values before treatment.

No significant difference between effect of propranolol or pindolol on blood pressure or PRA, $P > 0.05$.

Changes in blood pressure and PRA are compared with blood pressure and PRA at first outpatients visit immediately before treatment was started.

Figure 1 The fall in diastolic blood pressure with propranolol (○) or pindolol (●) is plotted against the basal plasma renin activity (PRA) measured on a high sodium intake diet while in hospital. There was no significant relationship between these variables.

no fall in blood pressure and the PRA was below control values 4 h after propranolol. By contrast, pindolol induced a fall of diastolic blood pressure of 10 mm or more in five patients, and there was a significant decrease in the group mean blood pressure. The mean pulse rate decreased from 75 ± 4 to 65 ± 2 ($P < 0.001$) beats/minute. There were minor falls in PRA, but the mean PRA after pindolol was not significantly below the control or placebo value. In individual patients there were marked changes in PRA with no fall in blood pressure when propranolol was given and conversely there were marked falls in blood pressure with no change in PRA when pindolol was administered.

Three of the eleven patients had small or absent rises in PRA after frusemide, but in the whole group there was a significant rise in mean plasma renin level but no mean change in blood pressure.

Chronic study

Either propranolol or pindolol reduced the blood pressure by a similar amount (Table 1). Sixty-six

of the seventy-six patients had a fall in diastolic blood pressure of 5 mmHg or greater. The basal PRA of the hospitalized patients were scattered as shown in Figure 1. A similar scatter was seen with the PRA measured at their outpatient visit. The fall in blood pressure, either systolic or diastolic (Figure 1), did not correlate with the initial basal plasma renin level. If the fall in blood pressure was plotted against PRA at their initial outpatient visit, there was likewise no correspondence. It should be noted that certain patients with extremely low PRA ($< 0.10 \text{ pmol ml}^{-1} \text{ h}^{-1}$) had falls in diastolic blood pressure of 20 mmHg or more (Figure 1).

The long-term administration of pindolol or propranolol both caused a significant fall in PRA (Table 2). There was no correlation between changes in blood pressure and changes in PRA (Figure 2).

The relationship between PRA and daily urinary sodium excretion is shown in Figure 3. Using data published by Brunner, Laragh, Baer, Newton, Goodwin, Krakoff, Bard & Bühler (1972), and also our own mean values on a high, medium and low sodium diet, it was possible

Figure 2 The changes in blood pressure and plasma renin activity (PRA) in ambulant patients treated with propranolol (○) or pindolol (●) are plotted against each other. There was no significant correlation between these variables.

Table 3 Response (mean $\pm$ s.e. mean) of blood pressure related to plasma renin group

Renin subgroup	No. of patients	Mean fall in diastolic BP (mm Hg)	No. of patients with > 10 mm Hg fall
Low	17	20.0 $\pm$ 3.3*	13
Normal	39	15.8 $\pm$ 2.1*	24
High	20	15.0 $\pm$ 4.6*	14

* $P < 0.001$ from values before treatment.

arbitrarily to divide patients into 'high', 'normal' and 'low renin' categories. The responses to either chronic administration of pindolol or propranolol related to these groups is shown in Table 3. It is evident that there was no significant difference in the fall in blood pressure between the three groups.

Discussion

This study demonstrates that although β -adrenergic receptor blocking drugs often cause a

fall in blood pressure, and often cause a fall in plasma renin activity, the two are not closely related. The acute administration of propranolol leads to a fall in PRA in almost all patients, without significant change in blood pressure, whereas the acute administration of pindolol often causes a fall in blood pressure, with no change in PRA. These observations make it clear that β -adrenergic receptor blocking drugs are capable of reducing blood pressure by a mechanism independent of plasma renin.

Similarly, although chronic administration of both propranolol and pindolol cause a fall in both

Figure 3 Basal plasma renin activity (PRA) of patients treated with propranolol (○) or pindolol (●) plotted against 24 h urinary sodium excretion. The dotted lines indicate the mode in which this group was divided into high, low and normal renin hypertension. These dotted lines are based on the data published by Brunner *et al.* (1972) and our own mean values for normal males on a high (200 mEq/day, PRA = 0.36 pmol A₁ ml⁻¹ h⁻¹), medium (100 mEq/day, PRA = 0.48 pmol A₁ ml⁻¹ h⁻¹) and a low (10 mEq/day, PRA = 0.92 pmol A₁ ml⁻¹ h⁻¹) sodium intake.

PRA and blood pressure in most patients, the changes in the two measurements do not have any significant relationship. Moreover, in this group of patients, initial levels of plasma renin gave no guide as to the likely antihypertensive response of individual patients to either propranolol or pindolol.

The findings reported here lend no support to the claim advanced by Bühler *et al.* (1972) that plasma renin levels offer a specific method of selecting patients likely to respond to β -adrenergic

receptor blocking drugs. It remains possible that there is a small group of patients in whom the elevated blood pressure is directly due to increased secretion of renin and angiotensin, and, if this is so, such patients might be expected to benefit from the renin lowering effect of these drugs as well as from their other actions. Patients with malignant hypertension were specifically excluded from this study, whereas Bühler *et al.* (1972) included a number of these in their study, which might provide an explanation for the difference in

results. However, in the present study patients with initially low levels of plasma renin often responded dramatically to these drugs.

The mechanism of the antihypertensive action of these drugs remains obscure. The suggestion that they act by resetting control mechanisms (Prichard & Gillam, 1969), possibly by an action related to β -adrenoceptor blockade in the central nervous system (Morgan *et al.*, 1972), seems the

most plausible hypothesis. It seems clear that a simple action in lowering plasma renin levels can be discounted in most patients, as the main antihypertensive mechanism.

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