

here were comparable,³⁻⁵ with the exception of acebutolol, which was probably underestimated by some 25-50%.⁶

Owing to the design of this trial the effect of dose increments cannot be differentiated from a further period of exposure to the drugs, and this must be borne in mind when comparing the results. There was little to choose between atenolol and propranolol during the low-dose period, although in higher dosage atenolol was significantly better than all other drugs.

Pindolol proved disappointing in both its lack of hypotensive effectiveness and its high side-effect score, which might limit the use of higher doses. In an open study, however, Sedgwick and Crowder⁷ reported a low incidence of side effects with doses of 5-15 mg given three times a day. Wilson *et al.*,⁸ who studied five patients, found that an average of 29 mg given once daily was as effective as the same amount given in divided doses. Two of their patients reported insomnia, which was abolished by taking the drug in the morning rather than at night. Pindolol has considerable intrinsic sympathomimetic activity, which was reflected in the high resting pulse rate recorded in my study.

My findings suggest that the theoretically useful combination of alpha-blockade and beta-blockade possessed by labetalol will not be competitive as a once-daily treatment. This is unfortunate, for we still lack a good peripheral vasodilator that acts for at least 24 hours and could complement a once-daily regimen of a beta-blocker with or without a diuretic. Labetalol also caused as many side effects as pindolol, both having nearly twice the side-effect score of the other drugs.

The reduction of exercise-induced peaks of blood pressure and heart rate is commonly cited as a major advantage of beta-blockers, but we do not know whether such peaks carry important risks. None of the drugs used here totally prevented significant increases in either heart rate or systolic blood pressure with exercise. Although the measurements were made at least

24 hours after the last dose of tablets, they raise the question whether it will ever be possible to inhibit such increments in blood pressure or heart rate for the whole 24-hour period after a single daily dose of a beta-blocker; and if not would it matter?

The hypotensive potential of bendrofluazide as a once-daily treatment compared with some of the beta-blockers was confirmed, and this drug is likely to remain an important contender as a first-line choice for mild and moderate essential hypertension, particularly in countries with limited budgets, since the beta-blockers are all much more expensive. The hypokalaemic and hyperuricaemic effects of bendrofluazide are rarely important.

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Need for beta-blockade in hypertension reduced with long-term minoxidil

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Summary and conclusions

Sequential changes in plasma renin activity and urinary aldosterone and noradrenaline were assessed in eight patients with severe hypertension after minoxidil had been added to their treatment. Doses of 2.5-27.5 (mean 12.5) mg/day reduced the mean blood pressure from 166/113 ± 6/2 mm Hg to 124/88 ± 4/2 mm Hg in one week. Plasma renin activity and urinary aldosterone and noradrenaline increased twofold to threefold initially but returned to baseline values within two to three weeks

and remained unchanged during a mean follow-up of 5.1 months. Beta-blocking drugs were then withdrawn slowly in six patients without adverse effects, though blood pressure and heart rate increased in three patients, who required minimal doses of beta-blockers. Plasma renin activity and urinary aldosterone and noradrenaline did not change significantly after beta-blockade had been stopped. We conclude that the need for beta-blockade is greatly reduced with long-term minoxidil treatment and that it may be unnecessary in some patients.

Introduction

Minoxidil¹ used in combination with beta-blocking agents has proved useful for treating hypertension resistant to other drugs.² It was more powerful than hydralazine in patients already treated with diuretics and propranolol,³ and was particularly useful in patients with hypertension and renal failure.⁴ In most studies minoxidil increased plasma renin activity¹⁻⁵—an effect that occurs with other vasodilator drugs.⁶⁻⁷ These drugs also stimulate the secretion of catecholamines, which may oppose their antihypertensive effect¹⁻⁵ and explain why giving minoxidil without concomitant beta-blockade was unsuccessful.¹

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Clinical characteristics of patients

Case No	Age (years)	Sex	Diagnosis	Duration of hypertension (years)	Fundal grade	Last treatment before study* (mg/day)	Last sitting blood pressure (mm Hg)	Serum creatinine ($\mu\text{mol/l}$)
1	48	F	Essential hypertension	1	I	C 100; S 100; P 320; H 100	150/105	88.4
2	27	M	Essential hypertension	1	I-II	C 100; S 100; P 320; H 100	157/108	168.0
3	48	M	Essential hypertension	9	I	C 100; S 100; P 240; H 100	153/105	123.8
4	47	M	Essential hypertension	4	II	C 100; S 100; O 320; H 100	165/105	238.7
5	45	F	Essential hypertension	7	II	C 100; S 100; O 320; H 100	158/108	97.2
6	42	M	Essential hypertension	21	II	C 100; S 100; P 320; H 100	140/113	115.0
7	47	M	Essential hypertension	9	I-II	C 100; P 240; H 100	170/105	97.2
8	35	M	Chronic glomerulonephritis; renal transplantation	6	I	C 100; S 100; MD 2000; H 100	180/115	203.3

*C = Chlorthalidone. S = Spironolactone. P = Propranolol. O = Oxprenolol. H = Dihydrallazine. MD = Methylodopa.
Conversion: SI to traditional units—Serum creatinine: $1 \mu\text{mol/l} \approx 0.01 \text{ mg/100 ml}$.

We decided to assess the long-term sequential changes in plasma renin activity, aldosterone, and catecholamines in hypertensive patients after substituting minoxidil for dihydrallazine, and to determine the need for continuous beta-blockade.

Patients and methods

Six men and two women aged 27-48 years were studied. All had had severe hypertension for 1-21 (mean 7) years. In seven essential hypertension was diagnosed on the basis of a compatible history and physical findings, routine laboratory evaluation, a rapid-sequence pyelogram, and (in four) renal arteriograms. One man had undergone renal transplantation one year before for chronic glomerulonephritis, and another had associated hypogonadism of unknown aetiology. Fundi were graded I-II according to the Keith-Wagener classification. Initial serum creatinine averaged $141 \pm \text{SE}$ of mean $19.4 \mu\text{mol/l}$ ($1.6 \pm 0.22 \text{ mg/100 ml}$). All patients had received a combination of three or four antihypertensive agents (table), yet sitting blood pressure consistently exceeded 140 mm Hg systolic and 100 mm Hg diastolic (mean $159/108 \pm 4.4/1.4 \text{ mm Hg}$). Each patient gave informed consent for treatment with minoxidil.

Ten days before admission dihydrallazine was discontinued; other antihypertensive drugs were unchanged. During the first three days in hospital blood pressure was stabilised and two full baseline measurements were made. On the fourth morning minoxidil, 2.5 mg by mouth, was begun. Each day thereafter 2.5-5.0 mg was added in divided doses until the diastolic pressure fell below 90 mm Hg or side effects occurred. The dose necessary to accomplish satisfactory reduction ranged from 2.5 to 27.5 (mean 12.5) mg/day. Each patient received a diet containing 100 mmol(mEq) sodium daily.

After 10 days in hospital patients were followed up in the outpatient department, at first weekly and then every four weeks if free of symptoms. They were seen by the same physician and at the same time of day. They were advised to restrict salt intake. At the end of phase 1—that is, after 1-9 (mean 5.1) months—sodium intake was again restricted to about 100 mmol/day to duplicate baseline conditions.

In phase 2 the dose of beta-blocking drugs was halved every month in six patients and when it had reached 40 mg daily they were stopped. Patients were then followed up for another 4-9 (mean 6.2) months, and three were again given small doses of propranolol (less than 40 mg/day).

Certain modifications to treatment were necessary after minoxidil was started. Minor adjustments in the dose of minoxidil were made in two cases after discharge for better control of blood pressure or because of side effects. Weight gain due to sodium retention necessitated intermittent or continuous frusemide in four patients (see Results). The dose of spironolactone had to be halved in two patients because of gynaecomastia, without compensation by another drug.

In hospital blood pressure, heart rate, body weight, plasma renin activity, and 24-hour urinary excretion of sodium, potassium, creatinine, noradrenaline, adrenaline, and aldosterone were measured daily. After discharge sitting blood pressure, heart rate, and weight were determined at each visit and plasma and urine measurements repeated. We specifically looked for side effects.

Blood samples for analysis of renin activity were chilled and immediately centrifuged in the cold; plasma was separated and frozen at -30°C . Renin activity was analysed by angiotensin I radioimmunoassay.⁸ Urinary aldosterone was quantified by radioimmunoassay,⁹ and urinary catecholamines were determined by a

fluorometric method.¹⁰ Electrolytes and creatinine concentrations were measured in the central hospital laboratory.

Statistical comparisons between groups were performed with Student's *t* test for paired data.

Results

PHASE 1

No major adverse effects occurred during the introduction of minoxidil. One patient withdrew from the study early because of non-specific side effects, and another, the man with hypogonadism, died suddenly in another country; necropsy was not performed and the cause of death was not ascertained.

After dihydrallazine had been stopped the average blood pressure in the eight patients increased from $150/108 \pm 4.4/1.4$ to $166/113 \pm 5.7/2.4 \text{ mm Hg}$. One week after they started minoxidil it was $124/88 \pm 4.2/1.9 \text{ mm Hg}$. After discharge the mean arterial pressure rose slightly in the six patients completing the trial (fig 1). This was ascribed to sodium retention due to minoxidil and relaxation of the dietary sodium restriction. Body weight increased by an average of 1 kg and frusemide, 40-80 mg/day, was therefore given by mouth to four patients with a resultant fall in pressure. By the end of phase 1 the mean arterial pressure was $99 \pm 2.4 \text{ mm Hg}$ and body weight $79 \pm 5.2 \text{ kg}$. Heart rate changed little, averaging 69 ± 4 and 75 ± 6 beats/min on days 1 and 8 of minoxidil administration respectively.

During the first six days of minoxidil treatment plasma renin activity rose progressively from a mean of 9.7 ± 3.1 to $26 \pm 7.2 \mu\text{g/l/h}$ (fig 1). Urinary sodium excretion fell from 133 ± 26 to $86 \pm 18 \text{ mmol/24 h}$. Individual peak renin values (mean $30.4 \pm 7.6 \mu\text{g/l/h}$) were reached

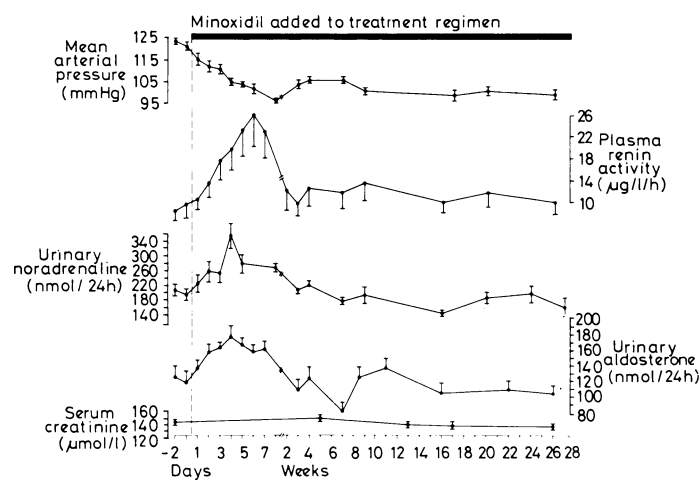


FIG 1—Changes in mean ($\pm \text{SE}$ of mean) arterial pressure, plasma renin activity, urinary noradrenaline and aldosterone excretion, and serum creatinine concentration after minoxidil (phase 1) in six patients completing study.

Conversion: SI to traditional units—Urinary noradrenaline: $1 \text{ nmol/24 h} \approx 0.16 \mu\text{g/24 h}$. Serum creatinine: $1 \mu\text{mol/l} \approx 0.01 \text{ mg/100 ml}$. Urinary aldosterone: $1 \text{ nmol/24 h} \approx 0.36 \mu\text{g/24 h}$.

between days 4 and 8, which corresponded with the maximum increase in dosage to a mean of 10 ± 2.4 mg/day. During the second and third weeks plasma renin declined to a mean of 10 ± 2.2 $\mu\text{g/l/h}$. This occurred despite slightly larger doses of minoxidil. Renin activity tended to rise again slightly during weeks 3-12, mainly because of concurrent treatment with frusemide. At the end of phase 1, when frusemide was stopped, renin remained at the pre-minoxidil concentration of 11.5 ± 3.6 $\mu\text{g/l/h}$ and urinary sodium excretion was 137 ± 21 mmol/24 h.

No changes in adrenaline excretion occurred during the study, but noradrenaline excretion increased from 207 ± 29.6 to 355 ± 33.1 nmol/24 h (35 ± 5 to 60 ± 5.6 $\mu\text{g/24 h}$) in the first four days (fig 1). It fell to 207 ± 11.8 nmol/24 h (35 ± 2 $\mu\text{g/24 h}$) at the end of the second week, and to 148 ± 17.7 nmol/24 h (25 ± 3 $\mu\text{g/24 h}$) at the end of phase 1.

Urinary aldosterone excretion increased from 119 ± 22.2 nmol/24 h (43 ± 8 $\mu\text{g/24 h}$) to a peak of 180 ± 16.6 nmol/24 h (65 ± 6 $\mu\text{g/24 h}$) by day 4 (fig 1). It then fell to below the starting value in parallel with plasma renin and urinary noradrenaline. At the end of phase 1 the mean excretion of urinary aldosterone was 105 ± 19.4 nmol/24 h (38 ± 7 $\mu\text{g/24 h}$).

Serum creatinine did not change appreciably during the study (fig 1). Mean serum value was 146 ± 24.8 $\mu\text{mol/l}$ (1.65 ± 0.28 mg/100 ml) at the beginning and 139 ± 20.3 $\mu\text{mol/l}$ (1.57 ± 0.23 mg/100 ml) at the end of phase 1. Creatinine clearances tended to increase slightly during the study, from 72 ± 13.6 to 81 ± 17.5 ml/min. The difference, however, was not significant ($P > 0.05$).

PHASE 2

No major adverse effects occurred during withdrawal of beta-blocking drugs.

Mean arterial pressure increased gradually from 102 ± 2.5 to 107 ± 2.8 mm Hg with stepped reduction of the dose of beta-blockers (fig 2). Two months after complete withdrawal it averaged 117 ± 3.0 mm Hg. Heart rate increased (together with blood pressure) from 65 ± 2.5 to 82 ± 4 beats/min ($P < 0.05$), and at two months it was 84 ± 4 beats/min. Only one patient developed tachycardia (112 beats/min). Body weight increased to 82 ± 6 kg.

Mean plasma renin activity did not change appreciably during phase 2. It rose from 11.0 ± 2.3 to 13.6 ± 2.5 $\mu\text{g/l/h}$ during withdrawal, and at two months was 14.0 ± 3.0 $\mu\text{g/l/h}$. Urinary noradrenaline excretion behaved similarly, being initially 148 ± 24.8 nmol/24 h (25 ± 4.2 $\mu\text{g/24 h}$) and at the end 154 ± 23.0 nmol/24 h (26 ± 3.9 $\mu\text{g/24 h}$). Urinary aldosterone also remained much the same, initial and final values being 114 ± 18.0 and 117 ± 20.0 nmol/24 h (41 ± 6.5 and 42 ± 7.2 $\mu\text{g/24 h}$). Serum creatinine and creatinine clearance remained constant during phase 2.

The overall increase in arterial blood pressure and heart rate was due primarily to three patients. Propranolol, 40 mg/day, decreased their mean arterial pressure from 122 ± 3 to 100 ± 3 mm Hg and heart rate from 89 ± 12 to 83 ± 5 beats/min (fig 2). The six patients were maintained on minoxidil treatment for an average of 15 (range 12-18) months. At the end of this period the average blood pressure was $132/89 \pm 4/3$ mm Hg.

Discussion

A potent, non-toxic oral drug is needed for severe hypertension, which cannot be adequately controlled by currently available agents. Minoxidil, a powerful vasodilator effective by mouth, is useful,^{2,4} but it reflexly increases heart rate and salt and water retention, which counteract its pressure-lowering effect.¹ Thus high doses of adrenergic blocking agents have been added to prevent tachycardia and diuretics to enhance sodium excretion.²

We substituted minoxidil for dihydrallazine in eight patients whose diastolic pressure remained high despite large doses of chlorthalidone, spironolactone, and a beta-blocking drug (table). This induced a prompt, dose-related lowering of blood pressure, which became normal in all patients. When it was first given plasma renin and urinary noradrenaline and aldosterone greatly increased despite beta-blockade but reached baseline values after a further two weeks.

Subsequent stepped reduction and withdrawal of beta-

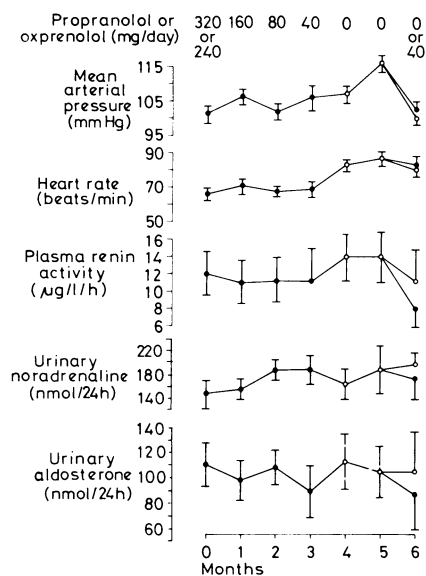


FIG 2—Changes in mean (\pm SE of mean) arterial pressure, heart rate, plasma renin activity, and urinary noradrenaline and aldosterone excretion during withdrawal of beta-blocking drugs in six patients given minoxidil (phase 2). Closed circles: with beta-blockade. Open circles: without beta-blockade.

Conversion: SI to traditional units—Urinary noradrenaline: 1 nmol/24 h ≈ 0.16 $\mu\text{g/24 h}$. Urinary aldosterone: 1 nmol/24 h ≈ 0.36 $\mu\text{g/24 h}$.

blockers caused no change in mean arterial pressure and heart rate in three patients and only slight increases in the other three, who responded to small doses of beta-blockers. Surprisingly, no significant changes in plasma renin activity or urinary noradrenaline and aldosterone occurred during withdrawal.

Changes in renin activity did not appear to be causally related to the blood-pressure reduction induced by minoxidil. The early pronounced rise in plasma renin activity may have been secondary to the increase in catecholamines mediated through baroreceptor reflexes. But renin stimulation by catecholamines seems unlikely with doses of beta-blocking agents high enough to produce changes in heart rate. Furthermore, much larger doses of catecholamines are necessary to overcome beta-blockade and stimulate renin release.¹¹ Increased renin secretion could also result from a direct effect of minoxidil on renal blood flow: if intrarenal vasodilatation does not parallel the reduction in systemic peripheral resistance, blood-pressure reduction results in decreased renal blood flow, which is a stimulus to renin release.¹² The subsequent fall in renin activity could then reflect a secondary readjustment of renal perfusion, due perhaps to decreased subendothelial oedema of the renal arterioles made possible by the return of perfusion pressure to normal. The return to baseline of noradrenaline values could be related to resetting of baroreceptor mechanisms or reduction of vascular reactivity.

Although withdrawal did not cause major increases in blood pressure and heart rate, beta-blockers are probably required (possibly in small doses) in the early phase of minoxidil treatment. In some patients they may become unnecessary after prolonged treatment with minoxidil, when renin and noradrenaline have returned to pretreatment values, though this is difficult to predict in individual cases.

Withdrawal of beta-blockers did not result in increased plasma renin activity. Do they perhaps cease to exert a renin-suppressing effect in long-term treatment? Similar observations have been reported with diuretics that stimulate renin secretion.¹³ These findings suggest that the influence of various drugs on renin secretion and the effect of renin secretion on blood pressure need to be reassessed by long-term studies.

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Severity of coronary atherosclerosis related to lipoprotein concentration

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Summary and conclusions

The influence of individual lipoproteins on the severity of coronary atherosclerosis was studied in 41 patients undergoing coronary angiography. The extent of atherosclerosis was quantified by a coronary atherosclerosis score (CAS) based on the number and severity of lesions in eight proximal segments of the coronary circulation. The concentration of high-density lipoprotein (HDL) showed a strong inverse association with CAS, which was independent of the effects of age and other lipoproteins. On multivariate analysis concentrations of other lipids—namely, total plasma cholesterol, low-density lipoprotein (LDL) cholesterol, and the combined effect of LDL cholesterol plus very-low-density lipoprotein triglyceride—showed direct, significant correlations with CAS, but these were weaker than that of HDL.

This study shows that concentrations of several circulating lipoproteins are related to the severity of coronary atherosclerosis, HDL having an apparent retarding effect. These findings may partly explain the influence of lipoproteins on the development of clinical coronary heart disease.

Introduction

Recent epidemiological studies have elucidated the importance of individual lipoproteins in predicting future clinical coronary

heart disease. High-density lipoproteins (HDLs) appear to exert the greatest influence independently of other lipoproteins,¹⁻³ with low-density lipoproteins (LDLs) having a weaker, though still significant, independent relation with coronary heart disease.^{1,2} This correlates negatively with HDL and positively with LDL, so probably HDL retards while LDL accelerates the development of clinical events. While this does not necessarily indicate a similar influence on the progression of underlying atherosclerotic disease, the influx and efflux of cholesterol in tissues are closely linked to the metabolism of LDL and HDL respectively,⁴⁻⁶ and therefore the severity of atherosclerosis could be related to these two variables. We attempted to verify this by relating the concentrations of circulating plasma lipids and lipoproteins to the extent and severity of coronary atherosclerosis as quantified by angiography.

Patients and methods

We studied 151 consecutive patients referred to the cardiovascular diagnostic unit at Alfred Hospital for coronary angiographic evaluation of chest pain suggestive of coronary heart disease. One of us (PJJ) selected a subgroup of 41 patients (28 men, 13 women), without knowledge of the clinical history or coronary anatomy, on the basis of plasma lipid concentrations, ensuring that the ranges of ages and lipid profiles resembled those of the whole group. This subgroup therefore included patients with both normal and raised plasma cholesterol and triglyceride concentrations. There was no significant difference in mean whole-plasma cholesterol and triglyceride concentrations between the entire patient population and the selected subgroup. None of the patients had valvular disease. Table I shows their clinical characteristics.

TABLE I—Clinical data on patients

	Men (n=28)	Women (n=13)
Mean age in years (range)	48.8 (34-61)	55.6 (41-65)
No (%) with proved myocardial infarction	16 (57)	5 (38)
No (%) with risk factors for coronary disease:		
High blood pressure (>160/100)	5 (18)	3 (23)
Smoked more than 10 cigarettes daily within past 5 years	16 (57)	6 (46)
Fasting glucose (concentration above 6.7 mmol/l (120 mg/100 ml))	2 (7)	1 (8)
Mean (±SD) body surface area (m ²)	1.88 ± 0.14	1.60 ± 0.30

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