Clinical use of minoxidil (Loniten)[1]

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Summary: The powerful peripheral vasodilator minoxidil, in a dose of 5–40 mg daily, controlled the previously refractory blood pressure in 45 out of 47 patients for periods up to fifty-seven months. The majority of the previous polypharmacy was withdrawn, leaving most of the patients taking a beta-blocking drug, minoxidil and a diuretic. Severe sodium retention leading to congestive cardiac failure necessitated the withdrawal of the drug in 3 patients. In one patient the drug was discontinued because of postural hypotension, and it was withdrawn in 2 female patients because of hirsutism. Five patients were removed from the trial as they were started on chronic maintenance haemodialysis or received a renal transplant. Significant glucose intolerance developed in one patient, requiring the addition of an oral hypoglycaemic agent. The 4 deaths that occurred were not directly related to treatment. Following the oral administration of 5 mg minoxidil, an obvious reduction in both the systolic and diastolic pressure was seen in two hours.

Introduction

The introduction of beta-adrenergic blocking agents proved to be a turning point in the management of hypertension. Beta-blockers alone proved extremely effective in controlling 'nervous' hypertension, and in many mild forms of hypertension not brought under control by beta-blockade alone, this was achieved by the addition of a diuretic.

With more severe hypertension with life-threatening complications, the addition of other hypotensive agents to beta-blockade with or without diuretics was essential to gain control. From haemodynamic observations in patients following intravenous administration of beta-blockade followed by hydralazine, it was found (Prichard *et al.* 1975) that the combination of a beta-blocker with a peripheral vasodilator was in many cases a very satisfactory combination for the control of severe, and at the time malignant, hypertension. Nevertheless, there remained a minority of patients in whom beta-blockade, vasodilators, diuretics and not infrequently several other hypotensive agents failed to control or even significantly alter the blood pressure.

At the beginning of 1975 minoxidil (Loniten) was made available to us on trial. Minoxidil (6-amino-1,2-dihydro-1,1-hydroxy-2-imino-4-piperidinopyrimidine) is a powerful peripheral vasodilator acting directly on the smooth muscle of the arteriolar cell wall and does not interfere with adrenergic activity (DuCharme *et al.*1973). The plasma half-life of the parent compound is 4.2 hours, but its biological effect is known to be much longer as its duration of action can be up to 24 hours (Gottlieb *et al.* 1972). This vasodilator hypotensive agent was in the first place used in patients in whom hypertension remained uncontrolled despite the administration of several hypotensive agents, often given simultaneously.

Methods and results

Patient material

Analysis of minoxidil treatment was up to September 1979. Forty-seven patients were included in the study with one patient having two separate treatments. There were 35 men and 12 women with ages ranging from 17 to 75 years. The length of treatment ranged from fifty-

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Table 1. Hypotensive agents taken before and with minoxidil

Hypotensive agent	Number of patients	
	Before minoxidil	With minoxidil
Beta-blockers	41	39
Labetalol	11	6
Diuretic	34	34
Hydralazine	31	7
Diazoxide	9	0
Prazosin	4	0
Methyldopa	19	2
Reserpine	7	0
Bethanidine	6	0
Clonidine	4	0
Guanethidine	3	0
Debrisoquine	4	0
Phenoxybenzamine	2	0
Pempidine	1	0

seven months to two weeks up to this time. Among the 47 patients, 2 are included both of whom had relatively mild hypertension and were given a single oral dose of minoxidil to study the speed of onset of action and the effect on the blood pressure observed for 24 hours. Similar observations of a single oral dose of minoxidil were made in severely hypertensive patients, previously receiving multiple therapy, in whom the effect of a single oral dose was observed over the following 24 hours.

In the 45 patients in whom the change of treatment was successful, there had been a very great variety of treatment, in many cases with polytherapy, with failure to control the hypertension before administration of minoxidil. It is not possible to individualize the treatment in each patient, but an indication can be given by setting out the numbers of patients treated with various hypotensive agents before minoxidil was introduced and after adequate control, in all but two patients, had been achieved with minoxidil (Table 1).

It will be obvious from Table 1 that most patients had been on a considerable number of hypotensive agents before starting minoxidil. One of the most striking instances, a girl aged 17 who had two separate courses of minoxidil, had received the following before treatment: propranolol, labetalol, diazoxide, phenoxybenzamine, bethanidine, reserpine, chlorthalidone, frusemide and hydralazine. At the beginning of her first course of minoxidil her lying blood pressure was 190/124 mmHg and at the beginning of second course it was 200/140 mmHg. After nine months on 2.5 mg minoxidil twice daily, the blood pressure was 130/80 mmHg lying with the only other drug being labetalol 300 mg four times daily. Minoxidil had been withdrawn because of hirsutes and the blood pressure rose to 200/140 mmHg lying; one month after restarting treatment at the same dose in association with propranolol 40 mg twice daily the blood pressure was 140/80 mmHg.

Treatment with minoxidil

Dosage ranged from 2.5 mg to 20 mg twice daily. In 39 patients the dosage was given twice daily, in 6 patients three times daily and in only 2 four times a day. All but 3 of the patients had a total daily dose of 20 mg or less with the remaining three receiving 12.5, 15 and 20 mg twice daily.

As can be seen from Table 1, in 39 of the 46 treatments minoxidil was associated with beta-blockers and in 6 with the combined alpha- and beta-blocker labetalol.

There was a striking absence of postural or exercise hypotension. In the first day or two of treatment an occasional patient was aware of a pulsating headache but this tended to pass off subsequently.

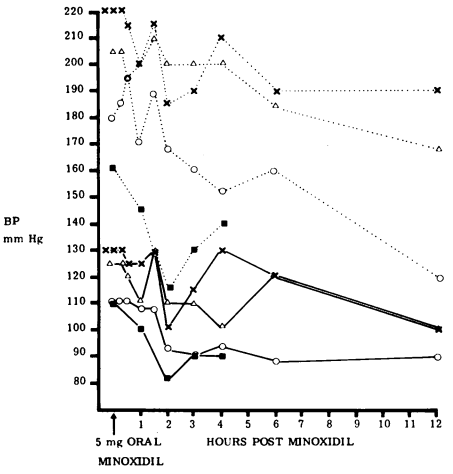

Figure 1. Onset of action of 5 mg oral minoxidil in 4 patients

Sodium retention was a significant problem and in 34 cases minoxidil required the addition of a diuretic agent. It was difficult to decide whether the long-term treatment with a diuretic was always necessary, but where good control was obtained with absence of oedema or significant weight gain and no postural hypotension it has generally been the policy to 'leave well alone'. Apart from beta-blockade, labetalol or a diuretic, hydralazine was continued from the previous medication in 7 patients, and in 2 other patients methyldopa was continued. The ultimate aim is to attempt to control all patients with a beta-blocker, minoxidil and, where required, a diuretic.

Hirsutism was a problem, more particularly in younger women, two of whom asked to have the drug withdrawn; the other patients managed to control unsightly hair growth with depilator creams.

Hyperglycaemia occurred in a single patient and the use of an oral hypoglycaemic agent became necessary. One other patient (with established diabetes controlled with glibenclamide) had developed severe oedema at a time that the drug was stopped, but blood glucose levels had never been significantly raised.

Table 2. Minoxidil withdrawal

Reason for withdrawal	Sex	Age	Lying blood pressure (mmHg)		Length of treatment (months)
			Before minoxidil	At time of withdrawal	
Patients started on regular haemodialysis	M	31	170/130	80/50	11
	M	35	230/150	134/86	1
	M	43	205/115	160/100	2
Patients who had had kidney transplants	M	26	240/150	130/80	1
	F	26	210/120	120/70	2
Hirsutism	F	17	190/124	130/80	9
	F	29	170/102	107/102	3
Severe sodium retention	M	61	260/135	130/80	2
	M	74	180/110	180/120	0.5
	F	44	190/120	140/100	3
Postural hypotension	M	26	180/130	130/70	3

Speed of onset

In order to measure the speed of onset of action, the blood pressure was measured frequently following the administration of 5 mg oral minoxidil. The results in four patients are illustrated in Figure 1. This rapid response is in keeping with the known pharmacology, and means that minoxidil can be used in the clinical management of patients when a rapid reduction in blood pressure is desired. The cardiodynamic changes associated with oral minoxidil and the effects seen with changes in posture and exercise will be published separately.

Failures in treatment

In only two patients was there a failure to control the blood pressure with lying diastolics not exeeding 100 mmHg. In a man aged 47 the lying blood pressure was 220/120 mmHg after fourteen months on minoxidil 20 mg with atenolol 150 mg twice daily, and frusemide 80 mg daily; at this time he developed a left brachial artery embolus and minoxidil was withdrawn. The other patient was a man aged 74 in whom, after two weeks on minoxidil 5 mg four times daily, amiloride 100 mg twice daily and chlorthalidone 100 mg daily, the lying blood pressure was 180/120 mmHg; at this time he developed sodium retention and cardiac failure and minoxidil was withdrawn. In this patient beta-blockade was not associated with the minoxidil and it was not felt advisable to introduce this when he developed cardiac failure.

Minoxidil withdrawal

Minoxidil was withdrawn in 11 patients (Table 2). In the 3 patients with severe sodium retention cardiac failure occurred. The man aged 74 was one of the two patients mentioned above in whom blood pressure control was not achieved. He was the only patient in whom neither a pure beta-blocker nor a combined alpha and beta-blocking drug was used in association with the minoxidil.

The man aged 26 in whom minoxidil was withdrawn because of unacceptable postural hypotension had received a kidney transplant approximately one year beforehand but function was gradually deteriorating. Before starting treatment with minoxidil, blood pressure was 180/130 mmHg lying, 150/110 mmHg standing, on labetalol 600 mg four times daily and frusemide 120 mg twice daily. Three months after being on minoxidil 2.5 mg twice daily with labetalol 200 mg four times daily and frusemide 120 mg twice daily, the blood pressure was 130/70 mmHg lying and 90/50 mmHg standing.

Deaths during treatment

Four patients died while on minoxidil (Table 3). The two men, aged 75 and 69, died of presumed coronary infarcts. The woman of 59 had severe aortic stenosis and died in left ventricular failure. The girl of 17 died in cardiac failure while on regular dialysis, having had an unsuccessful kidney transplant two years previously.

Discussion

In our experience minoxidil has proved to be an extremely valuable addition to the management of hypertension, irrespective of the aetiological background, and where the clinical severity of the blood pressure ranged merely from high diastolic blood pressures

Table 3. Deaths while taking minoxidil (4 patients)

Sex	Age	Lying blood pressure (mmHg)		Lengh of treatment (months)
		Before minoxidil	Last taken	
M	75	220/120	160/100	33
M	69	210/110	170/95	22
F	59	210/120	180/90	0.5
F	17	200/140	140/80	10

without obvious cardiac or small vessel involvement to patients who had severe left ventricular problems and others in whom small vessel damage of 'malignant' hypertension was present.

In almost all instances in the present group of patients the previous hypotensive therapy was reduced to a combination of minoxidil with beta-blockade and a diuretic, although in 7 patients hydralazine and in 2 other patients methyldopa were continued after the introduction of minoxidil.

Despite a surprisingly small dosage of minoxidil, a rapid hypotensive effect occurred and was maintained in 15 patients on a total daily dose of 5 mg and in another 15 on a total daily dose of 10 mg.

The only two significant side effects are sodium retention which, in the presence of normal renal function, was relatively easily controlled with a diuretic; and hirsutism, which led to two young women asking to have the minoxidil withdrawn, although others have continued and managed with depilator agents to control unsightly hair growth.

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