MINOXIDIL IN THE RAPID CONTROL OF SEVERE HYPERTENSION

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SYNOPSIS

We studied 21 patients with a resting supine diastolic blood pressure equal to or greater than 120 mm Hg. 10 mg minoxidil in combination with 40 mg propranolol and 40 mg frusemide was administered orally. If the diastolic blood pressure was 100 mm Hg or greater 4 hours later, a booster minoxidil dose of 5-10 mg was given. A rapid and significant fall in systolic, diastolic and mean blood pressure was first observed 2 hours after the initial minoxidil dose. The maximum reduction in blood pressure occurred at 7-8 hours, falling from a pretreatment level of 186/124 mm Hg to 142/95 mm Hg. The antihypertensive effect lasted throughout the 24-hour study period although the blood pressure tended to move upwards gradually at the end of the study. No side-effects were recorded. This study indicates that minoxidil may control severe hypertension rapidly, smoothly and safely.

INTRODUCTION

Minoxidil is a very potent orally effective peripheral vasodilator (1). It is generally not recommended for hypertensive emergencies when the use of intravenous sodium nitroprusside, labetolol or diazoxide may be more appropriate. Its main use in hypertension appears to be restricted to patients who are resistant to or unable to tolerate other antihypertensive agents. However some publications have suggested that minoxidil in rapid titration may rapidly control severe hypertension (2-5).

The present study was undertaken to evaluate the efficacy and safety of orally administered minoxidil with propranolol and frusemide in the rapid control of severe hypertension of Singaporean patients.

PATIENTS AND METHODS

Patients

21 patients (20 men, 1 woman) admitted to the Departments of Medicine I and IV with a resting supine diastolic blood pressure (DBP) (Korotkoff phase 5) of 120 mm Hg or greater were studied. None of them had hypertensive heart failure, hypertensive encephalopathy, dissecting aortic aneurysm, acute cerebrovascular accident or acute myocardial infarction. There were 15 Chinese, 4 Indian and 2 Malay patients. Their ages ranged from 26 to 64 years (mean 45) and their weights from 44.5 to 97 kg (mean 63.6). 6 patients had no past history of hypertension and the remaining 15 patients had a mean known duration of hypertension of 6 years.

14 patients had essential hypertension, 4 patients had essential hypertension with nephrosclerosis (serum creatinine 1.4 — 3 mg/dl) and 3 patients had chronic renal failure (serum creatinine 5.4, 6.8 and 25.4 mg/dl respectively). Associated cardiovascular complications included left ventricular hypertrophy on ECG or chest X-ray in 10 patients and ischaemic heart disease in 4 patients. 4 patients had diabetes mellitus and 1 patient had an old right cerebral infarct. At the time of the study, 13 patients were being treated with other antihypertensive agents: propranolol — 10, diuretic — 8, methyldopa — 7 and hydralazine — 3.

Study Design

The patients were admitted to hospital and were put to complete bed rest for the duration of the study. All previous antihypertensive treatment was stopped. Supine blood pressure was measured using a standard mercury sphygmomanometer and mean blood pressure was derived by adding one third of the pulse pressure to the DBP. Initially control blood pressures and pulse rates were taken 2 hourly for 6 hours. The patients were then administered orally 10 mg minoxidil (Loniten® , Upjohn), 40 mg propranolol and 40 mg frusemide. Thereafter blood pressures and pulse rates were taken at 1-hourly intervals for 8 hours, 2-hourly intervals for the next 10 hours and 24 hours after initial minoxidil dose. Patients with a raised DBP 4 hours after the initial minoxidil dose was administered a booster minoxidil dose according to the DBP then: 10 mg minoxidil for DBP > 120 mm Hg, 5 mg minoxidil for DBP 100-120 mm Hg and no minoxidil for DBP < 100 mm Hg. All minoxidil doses were halved for patients weighing less than 50 kg. During the study, if the patient's blood pressure worsened or if he developed heart failure or chest pain, the study was immediately terminated and appropriate treatment was instituted. All complications and side-effects were recorded.

Analysis of Data

Statistical analysis was carried out using Student's paired t-test of significance. The mean of the 4 resting supine blood pressures taken before the study served as the control blood pressure for comparison.

RESULTS

Blood pressure response to minoxidil in 21 patients is tabulated in Table 1. Following the initial minoxidil dose, there was a smooth and substantial fall in systolic, diastolic and mean blood pressure in all patients. The first statistically significant fall in blood pressure was noted at 2 hours. The maximum reduction in blood pressure occurred at 7-8 hours, falling from a pretreatment level of 186/124 mm Hg (mean blood pressure 145) to 142/95 mm Hg (mean blood pressure 110). Thereafter the blood pressure gradually moved upwards. When the study was concluded at 24 hours, the blood pressure averaged 171/112 mm Hg. This was still significantly below the pretreatment level. In 3 patients, the blood pressure returned to pretreatment level at 24 hours. 11 patients needed a booster minoxidil dose at 4 hours because the DBP then was 100 mm Hg or greater.

No side-effects were recorded; in particular no palpitation, oedema or drowsiness was recorded. The pulse rate did not vary more than 10/minute from the pretreatment rate during the study period.

TABLE 1
BLOOD PRESSURE RESPONSE TO MINOXIDIL

Hours following initial dose of minoxidil	Blood pressure mm Hg		
	Systolic	Diastolic	Mean
0	186 ± 4	124 ± 1	145 ± 2
1	182 ± 4	118 ± 3	139 ± 3
2	167 ± 5*	110 ± 3*	129 ± 3*
3	158 ± 6*	104 ± 3*	122 ± 4*
4	149 ± 5*	101 ± 3*	117 ± 3*
5	147 ± 6*	100 ± 3*	116 ± 4*
6	143 ± 4*	96 ± 2*	112 ± 3*
7	143 ± 4*	95 ± 2*	110 ± 3*
8	142 ± 4*	95 ± 3*	111 ± 3*
10	144 ± 4*	96 ± 2*	112 ± 3*
12	146 ± 4*	96 ± 2*	113 ± 2*
14	153 ± 4*	101 ± 2*	118 ± 3*
16	158 ± 5*	105 ± 2*	122 ± 3*
18	165 ± 6*	109 ± 2*	127 ± 3*
24	171 ± 5*	112 ± 3*	132 ± 3*

*P < 0.05 compared with 0 hours

mean values ± SEM

N = 21

DISCUSSION

In this study, the antihypertensive effect of orally administered minoxidil with propranolol and frusemide occurred within 2 hours, was maximal at 7-8 hours and lasted for 24 hours. The possibility of a placebo response is not excluded but the severity of

hypertension in our cases precluded a concomitant placebo response study. Nonetheless a pronounced placebo response is unlikely for the following reasons: i) blood pressure remained raised after 6 hours of complete bed rest prior to minoxidil administration ii) blood pressure decreased in all patients following initial and/or booster doses of minoxidil iii) blood pressure tended to return towards pretreatment level at the end of the study. Likewise propranolol and frusemide may have contributed to the blood pressure reduction. Since approximately half of the study population was already on these 2 drugs at the start of the study, they could not be wholly responsible for the blood pressure reduction. It is thus logical to conclude that minoxidil is the predominant cause of the observed blood pressure reduction. The rapid and smooth reduction of blood pressure as shown in Table 1 has an attractive therapeutic implication; it avoids the undesirable consequence of a precipitous fall in blood pressure on compromised vascular circulation in vital organs.

Following ingestion, minoxidil is almost completely absorbed. The plasma concentration of minoxidil peaks within an hour. The plasma half-life is 4.2 hours but the antihypertensive effect may last for 3-4 days (4). This prolonged activity may be related to the high affinity of minoxidil for vascular smooth muscles and other sites (1, 4). Minoxidil is metabolised in the liver and only about 10 per cent of the unchanged drug appears in the urine. Thus Pettinger recommended little or no dosage adjustment in patients with renal disease (4). In 3 of our patients with chronic renal failure, unadjusted minoxidil doses achieved blood pressure control without any side-effects.

Previous studies have reported rapid blood pressure reduction using an accelerated minoxidil dose schedule (2, 3, 5). O'Malley and McNay achieved normalization of blood pressure within 24-42 hours in 12 hypertensive patients by using half the previous cumulative doses at 4-hourly intervals (2). Grim et al studied 12 hypertensive patients by initiating minoxidil therapy at a dosage of 1 mg, with 1 mg increments at 6-hourly intervals and achieved blood pressure normalization after 7 days (3). Alpert and Bauer studied 9 symptomatic hypertensive patients by initiating therapy with 20 mg minoxidil with a booster minoxidil dose at 4 hours if the DBP remained raised and achieved blood pressure normalization after 6 hours (5). Our study is similar to that of Alpert and Bauer and it showed that a similar clinical response is seen with a smaller initiating dose of 10 mg. Since blood pressure was controlled within hours, duration of hospital stay may be shortened considerably.

Short-terim use of minoxidil is not associated with any serious side-effects. Minoxidil-induced tachycardia and sodium retention are counteracted by the concurrent use of propranolol and frusemide. Hypertrichosis is seen consistently only in long-term use of minoxidil over 4 weeks. Although hypertrichosis may be most distressing and objectionable in woman, this side-effect is responsible for topical minoxidil being evaluated currently in the treatment of alopecia areata.

In summary, this study suggests that an accelerated minoxidil dose schedule is an acceptable alternative for rapid blood pressure reduction. Hospitalised patients with severe hypertension may be given 10 mg minoxidil with 40 mg propranolol and 40 mg frusemide, followed by 5-10 minoxidil if the diastolic blood pressure remained raised at 4 hours.

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