The use of minoxidil in the treatment of severe essential hypertension: a report on 100 patients

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Summary

1. One hundred patients with severe essential hypertension have been treated with minoxidil for a mean period of 8.4 months in a study involving eleven European centres. Seventy-two males and twenty-eight females were included in the group; the mean age was 55 years and the initial supine systolic and diastolic pressures averaged 212 (range 150-270) and 125 (range 90-150) mmHg respectively.

2. Reduction of supine diastolic pressure to less than 100 mmHg occurred in 94% of patients within 4 weeks. After the average follow-up period of 8.4 months the mean pressures were 151/91 mmHg. Concomitant therapy with β-receptor-blocking agents and diuretics resulted in satisfactory control of heart rate and weight gain.

3. Side effects included increased hair growth, nausea, fatigue, rash and darkening of the skin. ECG showed mainly T-wave changes and echocardiographic examination indicated improved ventricular emptying.

Key words: diuretics, hypertension, minoxidil, propranolol.

Introduction

Minoxidil (2,4-diamino-6-piperidino-pyrimidine-3-oxide) has a chemical structure unlike other antihypertensive agents. It is a peripheral vasodilator and has been shown to control blood pressure in patients whose hypertension is refractory to existing therapy (Gottlieb, Katz & Chidsey, 1972; Pettinger & Mitchell, 1973). Its use is associated with sodium retention (Zins, 1974), and increased cardiac rate and output (DuCharme, Freyburger, Graham & Carlson, 1973).

Thus therapeutic use of minoxidil almost invariably requires the concomitant administration of a diuretic and a β-receptor-blocking agent is also frequently used.

Most of the reported clinical experience with minoxidil has emanated from the U.S.A., where use of the drug is limited to patients whose lives are threatened by the severity of their hypertension which must in turn be resistant to full or maximally tolerated doses of conventional drugs. This report summarizes the results of minoxidil therapy in a group of European patients whose hypertension, although severe, did not have to conform to these rigid criteria.

Methods

Eleven centres situated in three countries were involved in the study and all data were recorded on copies of a single case-report form. The criteria for admission of patients to the study and subsequent assessment of their progress were common to the two protocols that were used, each of which required the patients to be over 21 years of age, pregnancy to be excluded and a minimum supine diastolic pressure on entry to the study of 120 mmHg (100 in Denmark and Germany). An unsatisfactory response to conventional therapy was also present in all cases.

After initial physical examination and measurement of base-line haematological and biochemical data minoxidil was given orally in the form of 0.024 mmol (5 mg) scored tablets at a suggested starting dose of 0.012 mmol (2.5 mg) daily. The maximum permitted daily dose was 0.18 mmol (40 mg), with
initial dose adjustments being made in one of two ways, either slowly over a 14–21 day period, during which time the dose response was reviewed at least twice weekly (protocol relating to fifty-three patients), or more rapidly over a 4 days period with daily review (protocol relating to forty-seven patients). Most of the patients on the former regimen and all of those on the latter were in hospital during this dose adjustment period. Minoxidil was occasionally added to existing therapy although an attempt was as a rule made to phase out previous anti-hypertensive medication, with the exception of a diuretic. β-Adrenoreceptor-blocking agents were used to control heart rate and were given in relatively high daily doses, 0.81 mmol (240 mg) of propranolol, before minoxidil was started, or at a generally lower dose, 0.13–0.54 mmol (40–160 mg), during minoxidil therapy, as dictated by a rising pulse rate.

Patients were seen weekly or more frequently for at least 1 month and then fortnightly and finally at more extended intervals when a stable state had been reached. At each visit the supine, standing and post-exercise (where possible) blood pressure and pulse rate were recorded together with body weight, side effects and details of any change in dose of minoxidil, diuretic or other component of the therapeutic regimen. Detailed side effect questionnaires, ECG reports, laboratory data and severity evaluation forms were completed at intervals of 2–4 months.

The total number of patients entered into the study during the first 14 months was 160, and among these a sub-group of seventy-two males and twenty-eight females were classified as having essential hypertension. They have been treated with minoxidil for a mean period of 8·4 months; their mean age was 55 years and they consisted of twenty-two patients from Denmark, forty-seven from the U.K. and thirty-one from West Germany. The results obtained in this sub-group of 100 patients are briefly described.

Results

The pre-minoxidil supine blood pressures averaged 212/125 mmHg. At follow up after 1, 4, 8 and 12 months (ninety-four, eighty-four, fifty-one and twenty-two patients respectively) the mean pressures had fallen to 161/94, 155/91, 150/90 and 141/91 mmHg respectively. Measurements taken in the standing position and after exercise showed reductions of the same magnitude: for example, the initial average pressures (standing) of 199/124 mmHg fell to 153/95 mmHg after 1 month and the corresponding initial post-exercise figure of 213/122 mmHg fell to 165/98 mmHg.

The average daily maintenance dose of minoxidil after the mean treatment period of 8·4 months was 0·105 mmol (22 mg) with a range 0·012–0·191 mmol (2·5–40 mg). 26% of the patients required less than 0·071 mmol (15 mg) per day. Although patients in whom the minoxidil dose was rapidly increased showed a greater initial fall of blood pressure than did the group receiving a more gradual increase, the difference in the mean pressures of the two groups was small and did not exceed 16 mmHg systolic and 4 mmHg diastolic after 4 weeks of therapy.

Control of tachycardia was not a significant problem and there was no indication that patients receiving β-receptor blockade before minoxidil, at an initial mean dose of 0·81 mmol (240 mg) of propranolol daily, were any better controlled than the lower-dose group receiving propranolol only as indicated by a rising pulse rate. In this latter group the mean daily maintenance dose after 8·4 months was 0·33 mmol (100 mg) and in the former group 1·62 mmol (480 mg).

In fifty-eight patients the optic fundi were graded initially and after at least 3 months of therapy. Before treatment fourteen were grade 3 and two grade 4, whereas after minoxidil therapy nine were grade 3 and one was grade 4.

Diuretic therapy was necessary in all but one patient and a thiazide alone was used in fifty-five patients. The average weight gain in the series was 0·86 kg after a mean period of 8·4 months on minoxidil therapy.

The most common side effect was hypertrichosis, which was commented on in 24% of the cases, although the actual incidence may possibly have been higher. Two patients left the study because of this side effect. Occurring at a much lower incidence were nausea (five), fatigue (five), dyspnoea (four), rash (two) and darkening of the skin (one). Five patients died, the causes being cerebrovascular accident (two), aortic aneurysm (one), congestive cardiac failure (one) and a progressive renal failure (one). Four patients were lost to follow up and twelve left the study for the following reasons: oedema (three), hypertrichosis (two), gastrointestinal upset (two), rash (one), fatigue (one), hypertensive
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crises (one), ECG changes (one) and myocardial infarction (one).

Analyses of the ECG and echocardiographic findings in a sub-group of thirty patients showed that ECG changes occurred in the majority of patients and were most clearly visible in the precordial leads, V4, V5 and V6. They consisted mainly of inversion of the T wave and, occasionally, some slight depression of the S–T segment was reported. A tendency towards normalization was observed in most patients and about 30% were reported as reverting to their pre-treatment picture. Echocardiographic examination demonstrated a reduction in end-systolic diameter and an increased wall-motion amplitude, indicating improved ventricular emptying.

Discussion

Patients with severe essential hypertension including those refractory to previous medication are likely to respond to a regimen of minoxidil, \( \beta \)-receptor blockade and a diuretic. Reduction of supine diastolic pressure to below 95 mmHg can be expected in most cases. Hypertrichosis is a fairly common side effect.

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References


