Technique for rapid control of hypertension with oral minoxidil

K. O'MALLEY and J. L. McNAY
Clinical Pharmacology Program, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

Summary
1. Twelve patients with essential hypertension were treated aggressively with minoxidil in order to achieve blood pressure control as rapidly as possible.
2. After an initial dose of 5 mg, dose increments were administered 6 hourly until a fall in blood pressure was observed.
3. The size of additional doses was determined by the magnitude of and response to the lowest effective dose and the therapeutic objective.
4. Over a time-interval of 24–42 h blood pressure was reduced to normal or near normal in each case.
5. Analysis of the relationship between blood pressure response and cumulative dose indicates that at sub-optimum blood pressure responses it is safe and efficacious to give half the antecedent cumulative dose as a single dose in arriving at the therapeutic objective.

Key words: dose–response curves, hypertension, minoxidil.

Introduction
Although there are a number of drugs available for parenteral use in the treatment of hypertensive emergencies (Koch-Weser, 1974), the possible application of orally administered anti-hypertensive agents to rapid control of blood pressure has received little attention. The vasodilator anti-hypertensive, minoxidil, has been shown to control blood pressure in patients resistant to conventional drugs (Gottlieb, Katz & Chidsey, 1972; Limas & Freis, 1973; Pettinger & Mitchell, 1973). However, there is a wide interpatient variation in responsiveness to this drug, indicating that use of conventional means of titrating blood pressure would be very time-consuming.

Patients and methods
We studied the effect of rapid minoxidil loading on blood pressure in twelve hypertensive patients who were resistant to or had intolerable side effects with conventional anti-hypertensive drugs.

Sodium intake was restricted to 100 mequiv./day. Supine blood pressure was measured every 3 h. For the purpose of constructing curves relating dose of minoxidil to blood pressure response, blood pressure data were expressed as mean arterial pressure. Duplicate blood pressures were recorded 3 h and 6 h after drug administration. The effect of minoxidil was calculated as the difference between these values and those for the corresponding times of the control day. In the case of patients 9, 10 and 12, who had very high blood pressure readings, drug effect was taken to be the average of the 3 h and 6 h values minus the blood pressure values taken immediately before initiation of minoxidil therapy.

Dosing was started with 2.5 mg in one patient (no. 3) and with 5 mg in the remaining patients. In the absence of a response to the initial dose, the same dose (5 mg) was given 6 h later, and so on every 6 h in 100% increments of cumulated previous dosage up to a maximum of 20 mg in a single dose. In the presence of a reduction in pressure, further dosing increments were adjusted depending on the response observed until a major fall in blood pressure was achieved. Dose–response data were plotted with log (cumulative dose of minoxidil) against change in mean arterial pressure for each dose amount used. Lines of best fit were calculated by the method of least squares.
Results

Base-line blood pressure ranged from 159/109 to 238/161 mmHg, the corresponding mean arterial pressure being 126-190 mmHg. Mean arterial pressure fell by an average 43 mmHg (range 19-80). In no case was an excessive hypotensive response observed; but the number of doses administered varied from four in three patients to seven in three others, the average being 5.6. As dosing was on a 6-hourly basis, this represents a duration of minoxidil loading between 24 and 42 h (mean 33 h). There was a fivefold range of total loading dose, from 20 to 100 mg. The mean loading dose was 53 mg.

Dose–response curves

Dose–response curves for ten patients are shown in Fig. 1. The data for two patients could not be fitted to single straight lines. As these two patients had the lowest base-line mean arterial pressure, spontaneous time-dependent fluctuations in blood pressure were of sufficiently large magnitude that differentiation from drug-related changes in blood pressure was difficult. In two further patients (no. 6 and no. 11) the blood pressure response appeared to be biphasic, comprising an initial fall followed by a return toward base-line. In these two cases there was a subsequent dose-related effect on blood pressure. The linear portions of the curves for these patients are included in Fig. 1. Log linear relationships were demonstrated for the remaining patients, with correlation coefficients of 0.85 or greater. The threshold dose, calculated by extrapolation of the dose–response curve to the log dose axis, varied from 1.2 to 24.5 mg. The dose–response slope, represented as the response expected for a doubling of dose, ranged from 6.5 to 30 mmHg. No correlations were found between base-line mean arterial pressure on the one hand and threshold dose or dose–response slope on the other.

Discussion

A major problem in achieving control of blood pressure is the great range of responsiveness of patients to anti-hypertensive agents. In the present study there was considerable interpatient variability in response to minoxidil. The dose required to produce a 20 mmHg fall in mean arterial pressure varied from 6 mg in patient no. 12 to 45 mg in patient no. 6, a greater than sevenfold range (Fig. 1).

The rationale on which the minoxidil dosing schedule utilized in the present study is based depends on: (a) dose-related responses to the drug, (b) cumulation of dosage at a rate appropriate to the slope of the dose–response relationship, and (c) suitably rapid onset of maximum drug effect. In man, we have shown in single-dose studies that the log dose of minoxidil was related to hypotensive effect (J. L. McNay & K. O’Malley, unpublished work). Further, as the peak effect of minoxidil was apparent in 4–8 h, we considered it safe to use a 6-hourly dosing regimen.

The use of total cumulative dose is obviously an approximation of the actual pharmacodynamic results of the sequential dosing in the present study, since it assumes no decay either of drug from receptor site or of drug-related effect during the loading period. As the duration of action of the drug is long and as the dose–response curves are reasonably log-linear, the approach was valid.

In the present study, it was first necessary to arrive at the lowest effective dose expeditiously. This was done by starting with a dose of 5 mg (in one case, 2.5 mg) and, in the absence of a change of blood pressure.
pressure, a second 5 mg dose was given 6 h later and so on cumulatively at 6-hourly intervals. The number of doses required to pass threshold was one to four.

Additional dosing, designed to produce a major reduction in blood pressure, was also carried out on a 6-hourly basis, again using a logarithmic progression. It was always safe to give one-half the cumulative loading dose once a response was seen (Fig. 1), in arriving at the therapeutic objective.

In contrast to the single-dose studies alluded to above, we were not able to show a correlation between base-line mean arterial pressure, on the one hand, and threshold or slope of the dose–response curve on the other. In the single-dose studies, the rate of decay of minoxidil effect on blood pressure was directly related to base-line mean arterial pressure, so that rate of decay of minoxidil effect in the more severely hypertensive patients would be expected to be greater than in the milder cases. With cumulative dosing, this would have the effect of decreasing the slope of dose–response curves in more severely hypertensive patients and thus would tend to normalize the slopes for the group as a whole. A correlation between base-line mean arterial pressure and slope would therefore cease to be apparent. However, a lack of correlation between base-line mean arterial pressure and threshold dose could not be explained in similar terms. One possible explanation is that, as the patients in the present study were not on propranolol, the threshold values obtained may in part reflect different degrees of compensatory reflex increase in sympathetic activity in response to vasodilatation.

Aggressive loading with an orally active anti-hypertensive agent has previously been described. Shand, Nies, McAllister & Oates (1972) used guanethidine. By the criteria for inclusion in the present study (see Patients and methods section) our patients would not be candidates for treatment with guanethidine. Gupta & McNay (1972) used oral bethanidine and although good control of standing blood pressure was rapidly achieved, no significant effect on supine blood pressure was observed.

In conclusion, we have developed a technique for rapid and safe control of hypertension with oral minoxidil based on 6-hourly cumulative dosing. Such a regimen should be considered as an alternative to using parenterally administered drugs in the management of severe hypertension.

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References


