CLINICAL AND PHARMACOKINETIC STUDIES OF MINOXIDIL, A NEW ANTIHYPERTENSIVE AGENT

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SUMMARY

1. Minoxidil is a direct-acting vasodilator which has been used in combination with propranolol and hydrochlorothiazide to lower blood pressure in hypertensive patients.

2. The therapeutic efficacy of minoxidil was compared with that of hydralazine used in the same combination in eleven patients refractory to standard antihypertensive therapy.

3. The recumbent blood pressure of these patients on propranolol and hydrochlorothiazide alone averaged 191/128 mmHg and decreased to 142/92 mmHg during addition of minoxidil and only to 168/108 mmHg during hydralazine treatment.

4. In addition to its greater efficacy, minoxidil exhibited a prolonged duration of action and there was no evidence of diminished response during treatment for as long as 2 years.

5. The paucity of side effects and the powerful activity of minoxidil in combination with the other drugs suggests that this agent may be of great value in the chronic therapy of hypertension.

Key words: antihypertensive drugs, minoxidil, propranolol.

In the management of hypertension, patient compliance, or acceptance of therapy, represents the major problem faced by the physician today. Since patient compliance will depend on the side effects of the antihypertensive drugs that are used, it is important to consider the type of drug combination which may lower the blood pressure to an acceptable level with a minimum of side effects. We have provided evidence that direct-acting arterial vasodilators in combination with \( \beta \)-adrenergic antagonists may represent such therapy (Gilmore, Weil & Chidsey, 1970). More recently others have confirmed this concept of combined therapy with vasodilators and \( \beta \)-antagonists (Sannerstedt, Stenberg, Johnsson & Werkö, 1971; Zacest, Gilmore & Koch-Weser, 1972). Because of the potential value of this therapeutic approach and because of the pharmacodynamic activity of the vasodilator, minoxidil, which we have used, a summary

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of our more recent observations with this drug is presented including a comparison of minoxidil
with hydralazine (Gottlieb, Katz & Chidsey, 1972).

MATERIALS AND METHODS

All patients were studied during hospitalization in the Clinical Research Center of the University
of Colorado Medical Center. Fully informed consent for these studies was obtained in all
cases including the administration of the investigational drug, minoxidil, and of radioactively
labelled drug. The eight patients who received 50 μCi of [14C]minoxidil were exposed to a total
of 5 mREM of radiation. Blood pressures and pulses were taken four times a day in the recumbent
and standing positions. Radiochemical preparation of [14C]minoxidil and its metabolites
were done by methods described by Gottlieb, Thomas & Chidsey (1972) and other chemical
analyses by standard methods of clinical chemistry.

RESULTS AND DISCUSSION

The supine blood pressure averaged 191/128 mmHg in eleven hypertensive patients who were
observed during a control period of 2–7 days while receiving propranolol (40–160 mg/day) and
hydrochlorothiazide (50–100 mg/day). After a control period, addition of hydralazine (200–
800 mg/day) lowered the supine blood pressure to 168/108 mmHg with no evidence of postural
hypertension. When hydralazine was discontinued and minoxidil (2.5–30 mg/day) was substi-
tuted, there was a significantly greater reduction in blood pressure to a level averaging 142/92
mmHg (P < 0.1). In each instance the vasodilator was given incrementally to the maximum
dose over a period of 5–7 days.

The disposition of minoxidil was determined by administering [14C]minoxidil orally to
eight patients after controlling their hypertension with minoxidil, in the manner described
above. The drug was cleared from plasma with a half-life which averaged 4.2 h. The metabolic
clearance rate was 588 ml/min, approximating the hepatic plasma flow. Although essentially
all of the 14C-label was found in the urine, less than 10% of the administered dose appeared
there unchanged. The rapid and extensive metabolism of minoxidil was found to involve
conjugation with glucuronic acid, primarily occurring in the first 12 h after the drug’s ad-
ministration, and later the formation of two more water-soluble metabolites whose chemical
structures remain to be determined.

Two unique properties of minoxidil remain to be emphasized: its duration of action which is
probably longer than 24 h and its lack of tachyphylaxis on chronic administration. Although it
is difficult to determine exact time–response curves for a hypotensive drug in patients, we have
made a few observations which lead us to believe that the duration of blood pressure lowering
with minoxidil exceeds that of other current vasodilators. We compared the hypotensive
responses of diazoxide (300 mg intravenously) and minoxidil (10 mg orally) and the duration
of activity of the minoxidil is longer than 24 h whereas diazoxide is considerably shorter (Fig.
1). In regard to lack of development of tolerance, we have given minoxidil in combination with
propranolol and a diuretic to eight patients for periods of 6–24 months and have observed no
evidence of diminishing hypotensive effect or necessity to increase the dose of drug.

Finally, side effects have been minimal and these have been hirsutism and sodium retention.
The sodium retention has been easy to control with thiazide diuretics unless renal insufficiency
Studies of minoxidil

FIG. 1. The recumbent blood pressure in a 54-year-old black female who was hospitalized for a period of 2 weeks for study. After receiving propranolol and hydrochlorothiazide alone for 1 week, the blood pressure had become stabilized at approx. 210/110 mmHg. Diazoxide (300 mg intravenously) and minoxidil (10 mg orally) were given sequentially. It may be seen that the hypotensive response to diazoxide persists for less than 24 h whereas that to minoxidil is more than 48 h.

is present when frusemide has been required. Caution is required regarding the potential of vasodilators to produce coronary insufficiency in patients with coronary artery disease, but this has not been a problem with the combination of propranolol in the patients which have been treated in our clinic. However, the propranolol is necessary not only to control the acute baroreceptor-mediated reflex changes after vasodilatation with minoxidil, but appears to be important in attenuating the cardiac hyperactivity for periods greater than one year. Thus, β-adrenergic receptor blockade remains as important a complement to vasodilator therapy for chronic administration as for initial therapy.

REFERENCES


