Long-term Treatment of Severe Hypertension with Minoxidil, Propranolol and Furosemide

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SUMMARY

Thirteen patients with severe hypertension were treated with combined minoxidil, propranolol, and furosemide (mean daily doses 33 mg, 475 mg, and 578 mg, respectively) for nine to twenty-five months (mean 13.8). Average mean blood pressure while on aggressive therapy with conventional medication was 144 ± 14 mm Hg; on minoxidil and propranolol it was 108 ± 10 mm Hg (P < 2.5 × 10⁻⁴, paired t-test). Sodium retention was a frequently observed limiting factor to optimum blood pressure control and required large doses of furosemide to control. Propranolol blunted the reflex tachycardia associated with arteriolar dilator therapy but all patients continued with a clinically hyperdynamic circulation. Seven of seven had elevated ejection fractions on echocardiogram, and two of three had elevated cardiac indices. Three of three who had heart catheterization had pulmonary hypertension which was aggravated by exercise. An additional three patients on hydralazine, propranolol, and furosemide also had pulmonary hypertension suggesting this is not unique to minoxidil. Two of thirteen developed pericardial effusions. Renal function improved in three and worsened in three.

MINOXIDIL, a piperidino-pyrimidine derivative (Upjohn U-10,858), is an orally effective vasodilator acting directly on vascular smooth muscle. This effect appears to be most pronounced at the arteriolar level thereby reducing peripheral vascular resistance without significant sympathetic release or increase in venous capacitance. Peak plasma levels occur within 1 hour following an oral dose. The serum half-life is approximately 4½ hours but its duration of action may be up to 24 hours, apparently because of binding of the active drug in vascular wall.1-4 Gilmore et al. initially demonstrated, in short-term studies, the effectiveness of minoxidil in combination with propranolol (Inderal) for the control of hypertension in hospitalized subjects.5 Limas and Fries reported the effective use of minoxidil, in combination with conventional antihypertensive medications, in treating uncontrollable hypertension in uremics on chronic hemodialysis.6 Gottlieb et al. in a non-blinded study claimed superiority of minoxidil over hydralazine (Apresoline), both used in conjunction with propranolol and diuretics.7 Pettinger and Mitchell have suggested minoxidil and propranolol may be an alternative to nephrectomy in the treatment of refractory hypertension.8

We herein report our own successful experience with minoxidil, used in combination with propranolol and a diuretic, for the long-term treatment of a highly selected group of outpatients with severe hypertension uncontrolled by vigorous treatment with conventional antihypertensive medications. The study is non-blinded, and each patient serves as his own control only in a sequential manner. Although all patients were refractory to conventional medications at the time of institution of minoxidil, the protocol does not justify definite conclusions regarding relative effectiveness of conventional medication vs minoxidil-propranolol therapy. The purposes of this study are to confirm previously reported effectiveness of short-term therapy with minoxidil and to extend this to an evaluation of chronic outpatient therapy.

Material and Methods

Patients

The study group is comprised of 13 patients who have remained on minoxidil therapy in combination with propranolol and furosemide (9) or periodic hemodialysis (4) for nine months or longer. Criteria for institution of minoxidil was poorly controlled hypertension defined as supine diastolic blood pressure (BP) greater than 105 mm Hg and systolic BP greater than 160 mm Hg while on large doses of conventional antihypertensive medication (table 1). Four of 13 patients had standing diastolic BP less than 105 mm Hg but had disabling side effects of therapy or rapidly worsening renal function associated with sodium depletion. There were eight males and five females, seven black and six white, seven to fifty-six years of age.

Methods

All patients initially had complete history and physical examination and appropriate laboratory evaluation, in-
including a rapid sequence intravenous pyelogram, to assess complications and etiology of hypertension. All patients gave written informed consent for treatment with minoxidil as well as larger than standard doses of propranolol and furosemide. Nine patients were converted to minoxidil as outpatients. Upon institution of minoxidil, all previous therapy except propranolol and diuretic or dialysis was discontinued. The starting dose of minoxidil varied from 2.5 mg every eight hours to 5.0 mg every six hours.

The patients were seen in clinic frequently during early stages of therapy and every four to six weeks when stable. Blood pressure and pulse rate in supine and standing positions and after walking for five minutes, weight, and examination by physician were recorded for each visit. Extracellular volume (ECV) was assessed clinically by observation of serial body weights, jugular venous distention, presence or absence of edema, postural BP changes and heart and lung auscultation. Edema, with or without signs of central venous congestion, was considered evidence for expanded ECV. CBC with differential, direct platelet count, SMA-12 chemistry battery, serum electrolytes, creatinine and antinuclear antibody were obtained every two months minimum, and chest X-ray and electrocardiogram every four months minimum. Plasma renin activity (PRA) was assayed by radioimmunoassay of generated angiotensin-I using a modification of the method of McDonald and Fisher.* Normal values in this laboratory are 2 to 5 ng/ml/hour after one hour of ambulation while on ad lib normal sodium diet (U_pV = 150 to 200 mEq/24 hr).

Seven patients have had one or more echocardiograms and three patients have had heart catheterization to more fully define cardiovascular dynamics while on treatment. Echocardiograms were recorded on polaroid film using a Smith-Kline Echoline 20 Echoscope equipped with a 2.25 MHz, 5 inch diameter, focused 10 cm transducer having a pulse repetition of 1000/second. The transducer was positioned along the left sternal border and conventional echocardiograms were obtained as the heart was scanned from base to apex as described by Feigenbaum.15 Mitral valve diastolic motion from point of maximum opening (E) to the point prior to atrial systole (F) (E-F slope) was measured. The E-F slope has been claimed to be an indirect assessment of LV compliance.16 Ventricular dimensions and volumes were taken with the transducer directed inferiorly at a point where the ultrasound beam intersected the right ventricular cavity, interventricular septum, left ventricular cavity and left ventricular posterior wall at the tip of the mitral valve. Pericardial effusions were detected by progressive dampening of the beam at this level. The procedure was performed and interpreted without prior knowledge of previous findings. Thus each patient served as his own control for serial studies.

Right heart catheterization was performed in six patients. Hemodynamic measurements were made with fluid-filled catheters connected to Statham P23Db transducers; recordings were made on an Electronics for Medicine (DR-8) photographic recorder. In all patients, baseline right heart pressures and pulmonary capillary wedge pressures were obtained, and cardiac outputs were measured using indocyanine green dye dilution technique. These parameters were repeated during maximum tolerated exercise on a Quinton Unipro Ergometer Model 844 at a work load from 300-600 kg/min.

### Results

Prior to Minoxidil

Eleven patients were thought to have severe essential hypertension while two patients (cases 3 and 15) had hemolytic uremic syndrome (HUS) complicated by acute renal failure and accelerated hypertension. Four patients previously had started on dialysis (cases 3 and 15, acute peritoneal dialysis; and cases 11 and 17, chronic hemodialysis); serum creatinine ranged from 0.6 to 7.5 mg/dl in the remainder. Left ventricular enlargement was present on chest X-ray in nine of thirteen. Evidence for left ventricular hypertrophy (LVH) was present on electrocardiogram in eleven of thirteen. Two patients (cases 7 and 15) had evidence of neither LVH nor cardiomegaly. None of the patients had evidence of previous myocardial infarction and none had angina pectoris. One (case 6) had a history of cerebral
vascular accident but had minimal neurological impairment. Grade IV hypertensive retinopathy was present in one case, grade III in six, grade II in four and grade I in two.

Immediately prior to starting minoxidil, supine blood pressure ranged from 165–230/110–150 mm Hg while on conventional medications (table 1 and fig. 1). Most patients had troublesome to disabling side effects of therapy, and nearly all patients were sufficiently symptomatic from these or hypertensive complications to preclude regular employment.

Minoxidil

The patients have remained on minoxidil, propranolol, and furosemide (eleven) or hemodialysis (two) with duration of therapy from nine to twenty-five months (mean 13.8). Nine of thirteen remain on minoxidil as of October 1974. In two cases (6 and 15) minoxidil was electively discontinued after eighteen and nine months of successful therapy, respectively. Both patients remain adequately controlled on hydralazine, propranolol and furosemide in dosages to which they had previously been refractory. One (case 10) had progressive renal insufficiency and refractory edema and was started on hemodialysis after thirteen months of therapy. With vigorous ultrafiltration he became normotensive and no longer required minoxidil. After ten months of sustained blood pressure control, one (case 16) discontinued minoxidil without the investigator’s knowledge and had a blood pressure of 216/130 mm Hg after one month of propranolol and furosemide only. In three (cases 3, 11 and 17) attempts to substitute hydralazine for minoxidil were unsuccessful although case 11 now takes only 1 mg/day, and it is unlikely it is needed any longer. Individual blood pressures and medication dosages are displayed in table 2. Medication included minoxidil 1 to 60 mg/day, propranolol 40 to 960 mg/day and furosemide 80 to 1200 mg/day.

Following institution of minoxidil a diastolic BP of less than 95 mm Hg was obtained within twenty-four hours in seven, one week in nine, and one month in eleven of thirteen cases. Two patients (cases 8 and 9) required three and a half and four months of therapy, respectively, to attain diastolic BP less than 95 mm Hg.

Subsequent to the initial reduction of BP, ten of thirteen patients have had at least one transient increase in BP associated with several clinically evident factors. Most frequently observed, particularly in those with azotemia, was apparent sodium retention manifest by increasing weight and edema but without jugular venous distension or evidence of pulmonary venous congestion. Less commonly observed was clinical evidence of a hyperdynamic circulation; tachycardia greater than 85–90 per minute during quiet supine rest and an increase in pulse rate, pulse pressure and mean BP after standing three minutes or walking. The tachycardia was observed within hours and edema appeared within one week of starting minoxidil.

Of these factors, the expanded ECV proved the most difficult to treat requiring as much as 1200 mg/day of furosemide in nondialysis patients and more vigorous ultrafiltration in dialysis patients. The tachycardia and apparent hyperdynamic circulatory state was treated by increasing the dose of propranolol to as much as 960 mg/day to bring resting pulse rate to 60–70/minute and diminish exercise-induced increase in pulse rate or BP. When the increase in BP was associated with neither expansion of ECV nor inadequate beta-adrenergic blockade, the dose of minoxidil was increased. Diastolic BP has thus been decreased and maintained at less than 85 mm Hg in four cases.
less than 90 mm Hg in nine cases, and less than 95 mm Hg in eleven cases (fig. 1 and table 2). In the two cases whose diastolic BP is currently greater than 95 mm Hg on therapy, both have continued to have refractory ECV expansion.

Headache was infrequently noted in the first several days of minoxidil therapy. This always responded within hours to increased propranolol. Hirsutism was always noted and was controlled with diuretics or shaving. With these exceptions, side effects were notably absent, and patient acceptance was excellent. All patients are followed as outpatients and none remain medically disabled from hypertension.

Twenty-four PRA assays, taken at random from ten patients while on therapy, ranged from 1.2 to 57 ng/ml/hr. Only six of twenty-four such determinations were under 5 ng/ml/hr despite the high doses of propranolol. Neither hemato logic nor hepatic toxicities were detected. No positive antinuclear antibodies were encountered. No clinical evidence of cerebrovascular insufficiency was apparent. Two patients (11 and 17) on chronic maintenance hemodialysis at start of therapy remain on dialysis. Two cases (3 and 15) who were on acute dialysis at the start of therapy have recovered sufficient renal function to discontinue dialysis. Case 3 now has a serum creatinine of 1.2 mg/dl, and case 15 had a serum creatinine of 0.7 mg/dl at the time of elective discontinuation of minoxidil. In only three cases has there been any worsening of renal function (cases 10, 12, and 14); one (case 10) progressed to dialysis. All others have had stable or improved renal function (fig. 2).

Despite the marked peripheral edema frequently observed, no patients had clinical or radiographic evidence of pulmonary venous congestion and none had elevation of jugular venous pressure. No significant change in cardiothoracic ratios was observed on serial chest X-rays (CT ratio 54.2 ± 5 pre vs 56.2 ± 8 on minoxidil). Two patients with normal electrocardiograms at the time of institution of minoxidil retained normal electrocardiograms while three of eleven with evidence of left ventricular hypertrophy have shown reversion to a normal electrocardiographic pattern. No clinical or electrocar-

**Table 2**

*BP is average of at least three determinations on separate clinic visits during the most recent two months of therapy.

Abbreviations: M = minoxidil; P = propranolol; F = furosemide; G = guanethidine; S = spiro lactone.

<table>
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<th>Case no.</th>
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<th>Renal function</th>
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<td>Drugs &amp; dose (mg/day)</td>
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<td>Standing</td>
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<td></td>
<td></td>
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<td>P</td>
<td>F</td>
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<td>17</td>
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**Figure 2**

Serum creatinine at time of institution of minoxidil is shown at t = 0, and most recent creatinine at t = total duration of minoxidil therapy for each patient. The two patients who started and remained on dialysis were chronic dialysis patients while the two who started on dialysis but recovered were acute renal failure and both had hemolytic uremic syndrome.
diographic evidence of myocardial infarction was observed and no patient developed angina pectoris.

Seven patients had one or more echocardiograms with results as shown in table 3. Of note is the persistent increase in ejection fraction, increased left ventricular posterior and septal wall thickness with hyperkinetic ventricular motion, left atrial dilatation, but absence of left ventricular dilatation. Mitral E-F slope was normal in all studies. Two of these seven patients (8 and 16) also had large, though hemodynamically insignificant, pericardial effusions confirmed on echocardiogram.

Three patients (14, 16 and 17) had heart catheterization with data shown in table 4. Associated with stress of the procedure, mean brachial artery pressure was elevated in all at rest and increased still further with exercise in two of three. Mean pulmonary artery pressure was also elevated in all at rest and increased still further with exercise in two of three. Mean pulmonary artery wedge pressure was elevated in two of three both at rest and with exercise. Cardiac index was elevated in two of three at rest and increased still further with exercise. Pulmonary vascular resistance was increased in two of three at rest and in both showed further increase with exercise.

In order to determine if the pulmonary hypertension was unique to minoxidil treated patients, an additional three patients with severe hypertension, not otherwise included in the study group, underwent heart catheterization while on high dose hydralazine, propranolol and furosemide therapy (table 5). These patients demonstrated hemodynamic measurements similar to the minoxidil treated group. Two of three had elevated mean pulmonary artery blood pressure at rest and the remaining patient had elevated mean pulmonary artery pressure to 21 mm Hg with supine exercise. Mean pulmonary artery wedge pressure was normal in all at rest although it increased in two of three with exercise. Active pulmonary vascular resistance was elevated in two of three at rest and

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**Table 3**

<table>
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<tr>
<th>Case no.</th>
<th>Date of study</th>
<th>LVDD (NI = 5.5 cm)</th>
<th>LVIDS</th>
<th>EF (NI = 55% - 65%)</th>
<th>LVIDD thickness (NI &lt; 1.2 cm)</th>
<th>Septal thickness</th>
<th>RVID (NI &lt; 2.3 cm)</th>
<th>LA internal diameter (NI &lt; 3.5 cm)</th>
<th>MV E-F slope</th>
<th>Effusion</th>
<th>Medication at time of study (mg/day)</th>
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*Mean values are calculated using most recent data for each patient.

Abbreviations: LVDD = left ventricular internal diameter in diastole; LVIDS = LV internal diameter in systole; EF = ejection fraction; RVID = right ventricular internal diameter; LA = left atrial; MV = mitral value; M = minoxidil; P = propranolol; F = furosemide.

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**Table 4**

<table>
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<tr>
<th>Case no.</th>
<th>Date of study</th>
<th>Conditions of study (r = rest; e = exercise)</th>
<th>Mean brachial artery BP (NI = 10-15 mm Hg)</th>
<th>Mean pulmonary artery pressure (NI ≥ 12 mm Hg)</th>
<th>Mean pulmonary wedge pressure (NI = 2.8-3.8 L/min/m²)</th>
<th>Cardiac index (NI &lt; 1.5 L/min/m²)</th>
<th>Pulmonary vascular resistance (NI &lt; 1.5)</th>
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*Cardiac output by thermodilution technique — all others by indocyanine green dye.

Abbreviations: M = minoxidil; P = propranolol; F = furosemide.
remained normal both at rest and with exercise in the third patient.

Discussion

Hydralazine and minoxidil, while chemically dissimilar, both dilate systemic arterioles, evoke reflex sympathetic activity and tend to be associated with sodium retention. Eight of our patients were taking hydralazine 100 mg every six hours in combination with propranolol in sufficient dose to keep resting pulse rate less than 75 per minute, and diuretics sufficient to maintain clinically normal ECV. None had sustained diastolic BP less than 110 mm Hg. The substitution of minoxidil for hydralazine, along with continued propranolol and furosemide was effective in lowering BP. While this study was not designed to compare hydralazine and minoxidil, it would appear that in severe hypertension minoxidil may be more effective. Controlled, double-blind studies to test this are presently underway.

The physiology of antihypertensive therapy with vasodilators has been recently reviewed. The primary abnormality of most chronic essential hypertensive patients is an abnormal elevation of peripheral vascular resistance. Arteriolar dilators act directly to reverse this abnormality, but used alone their effectiveness in lowering blood pressure is limited by at least three factors. There is a reflex elevation of sympathetic activity due to stimulation of baroreceptors by the reduced arterial pressure as well as perhaps direct central nervous system stimulation by high levels of angiotensin. Secondly, there is increased peripheral renin activity. This increase in renin activity may be suppressed by beta-adrenergic blockers and appears to be caused in part by heightened adrenergic state rather than by renal artery hypotension per se. Thirdly, there is sodium retention and expansion of ECV. The net result of heightened sympathetic activity and sodium retention is an increase in cardiac output, thereby limiting the hypotensive effect of arteriolar dilators.

Beta-adrenergic blockade with propranolol may decrease the reflex increase in sympathetic activity as well as the rise in renin activity. Diuretics may offset the sodium retention. The combined use of minoxidil, propranolol and diuretic has been reported to be highly effective in controlling severe hypertension for relatively short periods of time. Our experience allows us to examine the long-term use of this form of therapy not only with regard to BP control but of equal importance to assess potential long-term toxicity, cardiovascular and renal consequences. As in other studies, we found minoxidil to be highly effective in controlling BP and have extended this observation to as long as twenty-five months. In many cases the conversion from conventional antihypertensive therapy to minoxidil could be accomplished without hospitalization. In seven of thirteen cases, initial BP control was established within twenty-four hours and was therefore useful in acute hypertensive emergencies.

Because of the increasingly large doses of propranolol required to suppress the apparent hyperdynamic circulatory state, careful assessment of cardiopulmonary consequences was performed using echocardiograms and right heart catheterization. Serial noninvasive evaluation of left ventricular function was performed by echocardiography. The number of patients is small and the results must be considered as preliminary only. Furthermore, indirect echocardiographic assessment of left ventricular function must be confirmed by direct measurement. However, despite the large doses of propranolol, the seven patients so studied had hypertrophied, non-dilated left ventricles with marked hyperkinesis. Furthermore, two of three who had right heart catheterization had elevated cardiac index at rest and ability to further increase cardiac index with exercise. It appears that the large doses of propranolol, while suppressing heart rate, were not effective in suppressing hyperkinetic ventricular function. The possible consequences of such marked hyperkinesis in ad-
dition to its established role in sustaining systemic hypertension remain unknown.

The finding of pulmonary hypertension in all three patients studied by catheterization is of special concern. Its significance, etiology, possible relationship to medication and prognosis if minoxidil-propranolol therapy is continued are urgent questions. Propranolol is known to greatly accentuate the pulmonary vasoconstrictor response to hypoxia, but none of these patients were identifiably hypoxic. Beta-adrenergic blockade has also been shown to enhance pulmonary vasoconstrictor response to hypercapnia, angiotensin II and epinephrine. Minoxidil has produced right atrial lesions in dogs given 20 mg/kg/day for one month, and pulmonary microemboli could contribute to the pulmonary hypertension. No such atrial lesions have been reported in any other animal model including man, however. It seems most likely that the pulmonary hypertension was the net result of the elevated cardiac output and pulmonary blood flow, elevated sympathetic tone and elevated levels of angiotensin II, the effects of which upon the pulmonary vasculature were relatively unopposed because of beta-adrenergic blockade. Such a unique situation was attained in our severely hypertensive patients treated with a potent vasodilator and propranolol. Heart catheterization of two of three hydralazine-treated patients (table 5) demonstrating similar hemodynamic findings further suggests that the pulmonary hypertension is neither unique to minoxidil nor likely to be a direct toxic effect of minoxidil.

The observation of peripheral edema formation in the absence of jugular venous distension, hepato-jugular reflex, clinical or radiographic evidence of pulmonary venous congestion is of interest. Renal sodium retention is known to occur as a consequence of arteriolar dilator therapy. This may be a consequence of increased aldosterone and perhaps in part due to a primary action of minoxidil on renal sodium excretion. There is evidence to suggest minoxidil, hydralazine, diazoxide and guanycydine all increase proximal sodium reabsorption, perhaps in part because of redistribution of renal blood flow. Furthermore, the absence of rigid dietary sodium restriction along with large doses of propranolol in patients with histories of congestive heart failure might be suspected to have led to low output heart failure and subsequent sodium retention. No evidence of depressed myocardial function was observed, however, and in some cases who had previously been given digitalis for control of congestive heart failure, the cardiac glycosides were discontinued in an effort to suppress the observed myocardial hyperkinesis. The formation of peripheral edema without evidence of central or pulmonary venous congestion may be explained by an imbalance of Starling forces in the peripheral capillary bed favoring transudation of fluid. It may be that marked reduction of peripheral vascular resistance at the arteriolar level exposes the capillary to increased hydrostatic pressure which, uncompensated for by increase in oncotic pressure, leads to edema formation.

Pericardial effusions observed in two of thirteen patients are unexplained. They may represent a manifestation of fluid retention but the reason for the localization to the pericardium is unknown. Myocardial blood flow is known to increase after minoxidil therapy, and an imbalance of Starling forces in the pericardial and superficial myocardial capillaries may occur, leading to enhanced pericardial fluid formation.

Treatment with arteriolar dilators may result in myocardial ischemia, especially in patients with occlusive coronary artery disease. A few patients with severe left ventricular hypertrophy may develop clinical angina pectoris with angiographically patent coronary arteries apparently because of a relative coronary insufficiency to the greatly hypertrophied myocardium. There is a potential for ischemic myocardial damage in these patients as well. Beta-adrenergic blockade will suppress the reflex tachycardia and may reduce the risk of myocardial ischemia. It has been claimed that the incidence and severity of myocardial necrosis associated with acute reduction of BP by minoxidil, diazoxide, or hydralazine may be reduced by concurrent treatment with propranolol. Of interest is reported evidence that minoxidil, both with and without propranolol, increases myocardial blood flow at all depths of the myocardium in dogs.

None of the patients in this series had angina pectoris prior to treatment nor developed angina on minoxidil. We have subsequently treated several patients with angina pectoris, left ventricular hypertrophy and angiographically patent coronary arteries with minoxidil while keeping pulse rate below 70 per minute with propranolol. None of these patients have had worsening of their angina pectoris, and in fact, subjectively have increased their pain-free exercise tolerance as BP decreased. However, the safety of treating patients with angina pectoris and severe hypertension with minoxidil and propranolol remains unproven. Further carefully controlled clinical trials must be carried out before it can be recommended.

**Summary and Conclusions**

The combination of minoxidil, propranolol and furosemide appears to be highly effective in controlling severe hypertension for up to twenty-five months. The oral route of administration and long
duration of action make minoxidil well suited to outpatient use. Side effects, with the exception of hirsuitism, were notably absent, and patient acceptance was excellent. The patient's sense of well-being was good and rehabilitation potential excellent. No long-term toxic effects of therapy were detected. Severe sodium retention requiring large doses of furosemide to avoid increasing body weight and edema was a frequently observed factor associated with tolerance to the hypertensive effect of arteriolar dilatation. Despite the frequent occurrence of edema, no cases of clinical or radiographic pulmonary venous congestion occurred. With sustained control of BP and avoidance of excessive ECV depletion, renal function improved in three, worsened in three, and remained stable in seven. Propranolol was effective in blunting the sympathetic response to arteriolar dilators although all patients maintained a clinically hyperdynamic circulation with high pulse pressure. Seven of seven had elevated ejection fraction as determined by echocardiography, and two of three had elevated cardiac index determined with heart catheterization. Pulmonary hypertension was found in all three patients who had heart catheterization, and two of thirteen developed pericardioc effusions. The causal relationship of the pulmonary hypertension or pericardial effusions to therapy remains unproven.

Acknowledgment

Cases 9, 10, 11 and 12 are followed by Drs. M. Blumenkrantz and J. Coburn at Wadsworth Veterans Administration Hospital, Los Angeles. Our special appreciation also to the assistance of hypertension research nurses Vicki Durrant, Vivian Wright, JoAnne Gray, Andrea Geving, and Sue Clapp, and to Sue Sestich for her assistance in preparing the manuscript.

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Circulation. 1975;52:706-713
doi: 10.1161/01.CIR.52.4.706

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