

Pharmacology and Pharmacokinetics of Minoxidil

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Summary: Minoxidil is a potent oral vasodilator acting on the arteriolar side of the circulation. Reflex tachycardia and sodium retention are consequences of increased sympathetic activity. Its biotransformation is 90% hepatic, with no evidence of accumulation of minoxidil when it is given chronically in patients with either normal or abnormal renal function. The half-life is approximately 3 hr, regardless of whether the dose is given singly or on a multiple-dose basis. It is widely distributed throughout the body, and hence its volume of distribution is greater than 200 liters. There appears to be a dissociation between the peak plasma concentration and the antihypertensive response owing to the fact that minoxidil rapidly leaves the plasma on its way to the principal site of action, that is, the vascular smooth-muscle receptor site. No tolerance or refractoriness appears to develop with long-term minoxidil administration. **Key Words:** Minoxidil—Pharmacology—Pharmacokinetics—Hemodynamics.

Innovations in the clinical pharmacology of antihypertensive agents have provided the clinician with potent and unique drugs. Minoxidil represents the most potent oral vasodilator available, and despite various side effects, it offers a significant resolution of hypertension refractory to conventional antihypertensive agents. The purpose of this paper is to review the pharmacology of vasodilators and the clinical pharmacology and pharmacokinetics of minoxidil.

PHARMACOLOGY OF VASODILATORS

Drugs which act primarily and directly on vascular smooth-muscle cells without depending on an inhibition within the adrenergic nervous system are called vasodilators (Table 1). Vasodilators result in an alteration in cellular calcium metabolism, which may mediate the vasodilating response by interfering with calcium movements within vascular smooth muscle. These fluxes are responsible for initiating or maintaining the contractile state. Diazoxide and minoxidil have been demonstrated to block calcium uptake into the cell membrane, whereas

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TABLE 1. Qualitative comparison of the effects of vasodilators on cardiovascular function

Drug	Route	Dose (mg)	Site of action		
			Arteries	Veins	Heart ^a
Hydralazine	p.o./i.v.	40–200	+	±	+
Minoxidil	p.o.	5–40	+	±	+
Prazosin ^b	p.o.	1–20	+	+	–
Nitroprusside (sodium)	i.v.	0.03–0.150 ^c	+	+	±
Nitrate (sodium)	i.v.	100 ^c	±	+	–

^a Reflex tachycardia.
^b Weak vasodilator; greater activity as alpha-receptor antagonist.
^c Infusion rate (mg/min).

nitroprusside has been demonstrated to inhibit intracellular calcium release or the effects of calcium on the activation of contractile proteins (1–5).

Vasodilators can act on both the arterial and venous sides of the circulatory system. Those vasodilating drugs that act on the arterial side, such as minoxidil, hydralazine, and diazoxide, cause a decrease in arteriolar resistance and a fall in the afterload of the heart with an augmentation of blood flow. Simultaneously, the absence of vasodilator effect on the veins leads to an increase in venous return, producing an elevated preload. This reduction in afterload and increase in preload combine to produce an increase in cardiac output. Besides this mechanical increase in cardiac output, autonomic reflexes lead to an increase in heart rate and cardiac output. Drugs such as nitroprusside and possibly prazosin act not only on the arterial side of the circulation, but on the venous side as well. Nitrates act principally on the venous limb of the circulation. The venodilator reduces venous capacitance system, thus reducing preload on the heart, as well as decreasing the cardiac output. Changes in afterload with venodilators depend on the degree of arteriolar dilatation characteristic of the particular compound (1).

The vasodilators lack organ specificity in altering the resistance vessels (6,7). There is little or no increase in flow in patients given vasodilators in whom the initial renal blood flow or PAH (para-aminohippuric acid) clearance is diminished. It is true that hydralazine can cause an increase in glomerular filtration and in renal blood flow initially, but with chronic administration these revert to base-line values. While minoxidil does not effect a redistribution of visceral organ blood flow to the kidney (8), renal blood flow is maintained and renal vascular resistance is markedly diminished (9). Normal autonomic reflexes that are stimulated by decreases in arterial pressure and in distention of the aortic tree are mediated by a decline in inhibitory impulses from baroreceptors impinging on the vasomotor centers in the brain (10). This results in an increase in cardiac rate, contractility, and vasoconstrictive impulses. The more potent the vasodilator action on the arterial side of the circulation, the less the degree of vasoconstriction. This latter circumstance applies to minoxidil. One effect of vasodilators on the kidney is that of sodium retention, which may be due to an alteration in the distribution of intrarenal blood flow. This leads to an increase in the reabsorption of sodium

within the proximal tubule, resulting in the expansion of plasma and extracellular fluid volume (6). Second, there is stimulation of renin activity, presumably due to reflex stimulation of the sympathetic nervous system (11–13). This increase in renin activity leads to the production of angiotensin II, stimulating aldosterone production, and finally resulting in sodium reabsorption. Minoxidil plays a definite role in sodium retention and in renin stimulation; these two reflex effects occur less with prazosin administration.

In contrast to vasodilators that reduce peripheral resistance by direct mechanisms which are independent of autonomic control, drugs which produce a fall in peripheral vascular resistance by interfering with sympathetic vasomotor tone are classified as indirectly acting vasodilators. Such drugs include reserpine, methyldopa, and clonidine, which have their major site of action within the central nervous system; guanethidine, which acts on the peripheral adrenergic neuron terminals; and the classic alpha-blocking drugs, phenoxybenzamine and phentolamine, which act at the prejunctional and postjunctional alpha-adrenergic receptor sites. Prazosin interferes with sympathetic transmission by acting at the postjunctional alpha-adrenergic receptor site of vascular smooth muscle (14). The antihypertensive agents which have central nervous system sites of action can produce, along with their depressor effect, mental depression, varying degrees of orthostatic hypotension, and impotence, as well as gastrointestinal abnormalities such as peptic ulcer and hepatitis. Guanethidine can lead to severe orthostatic hypotension as well as impotence. The classic peripherally acting alpha-blocking drugs will produce reflex tachycardia, despite a minimal drop in arterial blood pressure; irreversibility of alpha-blockade due to phenoxybenzamine and erratic absorption and gastrointestinal side effects due to phentolamine have caused these alpha-blocking drugs to be poorly tolerated in man. On the other hand, prazosin acts at a site within the alpha-receptor which allows norepinephrine, when released into the synaptic cleft, to exert its negative feedback control of neurotransmitter release and thus inhibits its own adrenergic stimulating capability. Classical alpha-blockers, phentolamine and phenoxybenzamine, do not permit norepinephrine to exert a negative feedback control of neurotransmitter release and thus inhibit their own adrenergic stimulating capability. As a result, the adrenergic stimulation from norepinephrine release leads to tachycardia and an increase in renin activity (14). The latter features have not been reported to occur with prazosin consistently. In addition, since prazosin does not have central nervous system activity, there is little or no mental depression, somnolence, or dryness of mouth nor any significant degree of impotence.

CLINICAL PHARMACOLOGY OF MINOXIDIL

It is evident from clinical studies that with the inception of minoxidil therapy, there is satisfactory reduction in blood pressure within 72 hr in patients previously refractory to conventional high-dose antihypertensive medication. The maximum reduction in systolic and diastolic blood pressure is noted after 3 months of continuous minoxidil therapy (15–17). Following this period of time, little further improvement of blood pressure has been noted in patients who have been fol-

lowed for as long as five years (18). Tachyphylaxis to the dosage has not occurred in most cases (15,17,18). It has been demonstrated that in patients with end-stage renal disease associated with refractory hypertension, nephrectomy could be avoided when minoxidil was used to reduce the blood pressure (16).

Hemodynamically, the response to the administration of minoxidil is a *reduction in the systemic blood pressure* associated with a *decrease in total peripheral vascular resistance*, including forearm vascular resistance. As a result of this fall in peripheral vascular resistance, baroreceptor reflex stimulation produces an *increase of heart rate*, which leads to an *increase in cardiac output*. This response is characteristic of a drug which is a generalized arteriolar dilator. *Venous compliance is not altered* (6). As a consequence of this increase in sympathetic activity through baroreceptor mechanisms, not only do heart rate and stroke volume (19,20) increase, but there is also an increase of sympathetic input to the juxtaglomerular cells in the kidney, leading to renin and aldosterone stimulation (20–24). These changes can be inhibited by propranolol and nephrectomy (15,21). Saralasin, an angiotensin II antagonist, suppresses this aldosterone response (20,25), while augmenting the minoxidil-induced increase in plasma renin activity and lowering the blood pressure substantially (26,27). Early alterations in intrarenal blood flow, secondary to minoxidil-induced adrenergic stimulation [increased urinary norepinephrine (22)], may therefore account for the sodium retention and formation of edema. Unpublished observations have suggested the eventual reversal of this positive salt balance after 6–12 months of chronic therapy.

The overall effect of minoxidil on the pulmonary circulation is a reciprocal decrease in pulmonary vascular resistance with a concomitant rise in cardiac output, i.e., pulmonary blood flow. Thus, pulmonary hypertension does not appear with long-term minoxidil treatment (28–30).

In the periphery, forearm vascular resistance remains depressed, but forearm blood flow reverts towards normal because of the reduced perfusion pressure.

Clinical experience with minoxidil is extensive (16–18,31) and will be summarized in subsequent papers. Three series are depicted in Table 2. The patients received a diuretic or dialysis to reverse the salt retention resulting from minoxidil, as well as a drug to control heart rate, that is, propranolol or clonidine to block the reflex tachycardia that minoxidil can induce. The renin-stimulating properties of minoxidil may overcome propranolol blockade, but the control of

TABLE 2. Comparison among three series^a of long-term minoxidil responses

Reference	Number of patients	Average daily dose (mg)	Pretreatment blood pressure (mm Hg)	Posttreatment blood pressure (mm Hg)	Blood pressure decrease (mm Hg)
17	26	30	190/119	150/90	40/29
31	26	23.2	202/127	154/87	48/40
16	11	32	186/121	147/91	39/30

^a Patients receiving furosemide or dialysis and propranolol or clonidine.

heart rate was adequate with propranolol and was not increased substantially by minoxidil. Plasma concentrations of propranolol between 50 and 100 ng/dl were adequate for control of the heart rate (17) (Tables 3, 4). Of interest is the fact that with sustained reduction of blood pressure, in association with continuation of minoxidil therapy, the increased adrenergic activity subsides, resulting in a fall in plasma renin concentration (20,22,24). In fact, when propranolol is *gradually* discontinued and minoxidil alone is continued, there is an absence of renin stimulation. If propranolol is abruptly discontinued, however, renin elevation may persist. It is clear that the increase in renin lasts a few weeks at most with continuation of the beta-blocker and may not recur following months of therapy if the beta-blocker is discontinued gradually (22).

CLINICAL PHARMACOKINETICS OF MINOXIDIL (TABLE 5)

Absorption

At least 95% of orally administered minoxidil, in tablet form or as solution, is absorbed from the gastrointestinal tract and appears in the plasma within 15–30 min. The peak plasma concentrations occur within 30–60 min (17,32).

Distribution

The volume of distribution of labeled minoxidil is approximately 200 liters (32), whereas that with compressed tablet or solution when given acutely in a single dose is 232 ± 64 liters (tablet) and 258 ± 68 liters (solution) and when given chronically, as tablet, 246 ± 52 liters (17). The mean volumes of distribution for both radiolabeled and cold drug are determined by zero-time extrapolation or postdistribution phase plasma levels. The explanation for this large volume of distribution can be inferred from radioautographic studies in rats. Measurements of total drug-related and organic solvent-extractable (presumably unchanged minoxidil) radioactivity were made in dissected tissue samples from [¹⁴C]minoxidil-treated rats. There was a preferential retention of drug-related materials by the arterial vasculature, i.e., aorta and femoral artery. This selectivity of distribution or binding has also been demonstrated to occur with hydralazine (32–34).

Metabolism

Nearly 90% of minoxidil is metabolized in man mostly by conjugation with glucuronic acid at the *N*-oxide position in the pyrimidine ring but also by conver-

TABLE 3. Renin response in 3 representative patients to propranolol alone and in combination with minoxidil

Patient	Plasma renin activity (ng/ml hr)		
	Control	Propranolol	Propranolol + minoxidil
LH	11.4	1.2	3.4
RN	5.0	1.9	4.7
OS	0.26	0.30	0.74

TABLE 4. Relationship between heart rate, minoxidil, and propranolol doses and plasma propranolol concentration^a

Base line upright plasma renin (ng/ml hr)	Pretreatment heart rate after exercise ^b (beats/min)	Minoxidil dose (mg/day)	Heart rate on minoxidil after exercise (beats/min)	Propranolol dose (mg/day)	Heart rate after exercise on minoxidil and propranolol (beats/min)	Plasma propranolol concentration (ng/ml)
11.7	110	20	130	480	76	110
32.2	86	15	112	160	78	110
0.71	68	15	96	240	74	80
5.3	96	30	124	480	82	104
—	96	15	128	80	74	32
0.42	94	35	118	240	74	152
Mean	92 ± 5.7				76 ± 1.3	98

p < 0.05

^a Note that the minoxidil-induced increase in heart rate is controlled by plasma propranolol concentrations between 50–100 ng/ml.^b Fifty yard run.

TABLE 5. Pharmacokinetics of minoxidil

Parameter	Acute dosing		Chronic dosing (tablet)
	Solution	Tablet	
$T_{1/2}$ (hr)	3.09 ± 0.64	2.77 ± 0.51	2.84 ± 0.43
K_e (hr^{-1})	0.21 ± 0.05	0.29 ± 0.05	0.27 ± 0.04
AUC (ng/ml hr)	472 ± 140	526 ± 179	542 ± 186
V_d (liters)	246 ± 52	258 ± 68	232 ± 64

Means $\pm$ SEM are shown.

sion to more polar metabolites (32,35). According to recent observations, the major metabolite, minoxidil-*O*-glucuronide has cardiovascular and antihypertensive activity, but less than that of the parent compound.

There is virtually no evidence at the present time to indicate that an adaptive increase in the rate of minoxidil metabolism is produced by repetitive dosing. Thus, in man, the whole-body clearance rate for minoxidil is unaltered 7–10 days after chronic drug administration. This is supported by the fact that the elimination half-life following a single dose of minoxidil is 2.77 ± 0.51 hr, and the K_e is 0.29 ± 0.05 hr^{-1} ; when given chronically, the half-life is 2.84 ± 0.43 hr, with a K_e 0.27 ± 0.04 hrs^{-1} (17). The area under the curve after a single dose is similar whether given in the absence of or during chronic administration of minoxidil (542 ± 186 ng/ml hr, single dose, and 472 ± 140 ng/ml hr, chronic) (Fig. 1) (17).

Excretion

The kidney is the principal excretory organ for minoxidil and metabolites in all species studied, e.g., rat, dog, monkey, and man (32,33). Ninety percent or more of the administered radiolabeled drug ultimately appears in the urine regardless of the route of administration. The percentage of total drug-related material in human urine over a 24 hr period (Table 6) demonstrates that minoxidil-*O*-glucuronide is the major byproduct of minoxidil metabolism. Minoxidil and/or reduced minoxidil may account for 12% of the total drug-related material in the urine. Experimental data suggest that the drug is excreted exclusively by filtration and that there is no secretion nor reabsorption as it traverses the renal tubule. On the basis of equilibrium dialysis, minoxidil does not appear to be protein bound. In the absence of functional renal tissue, minoxidil and its metabolites can be removed by hemodialysis (see papers by W. M. Bennett et al. and J. O. Wells, this volume).

RELATIONSHIP BETWEEN THE PHARMACOKINETICS OF MINOXIDIL AND SENSITIVITY OF RESPONSE

Based on the above pharmacokinetic data, the extent and time course of blood pressure reduction by minoxidil in hypertensive patients does not correspond closely to its concentration in blood (Fig. 2). This may be explained by (a) an unusually flat dose–response relationship to the drug and (b) slowly reversible binding of the drug to the vascular smooth-muscle receptors.

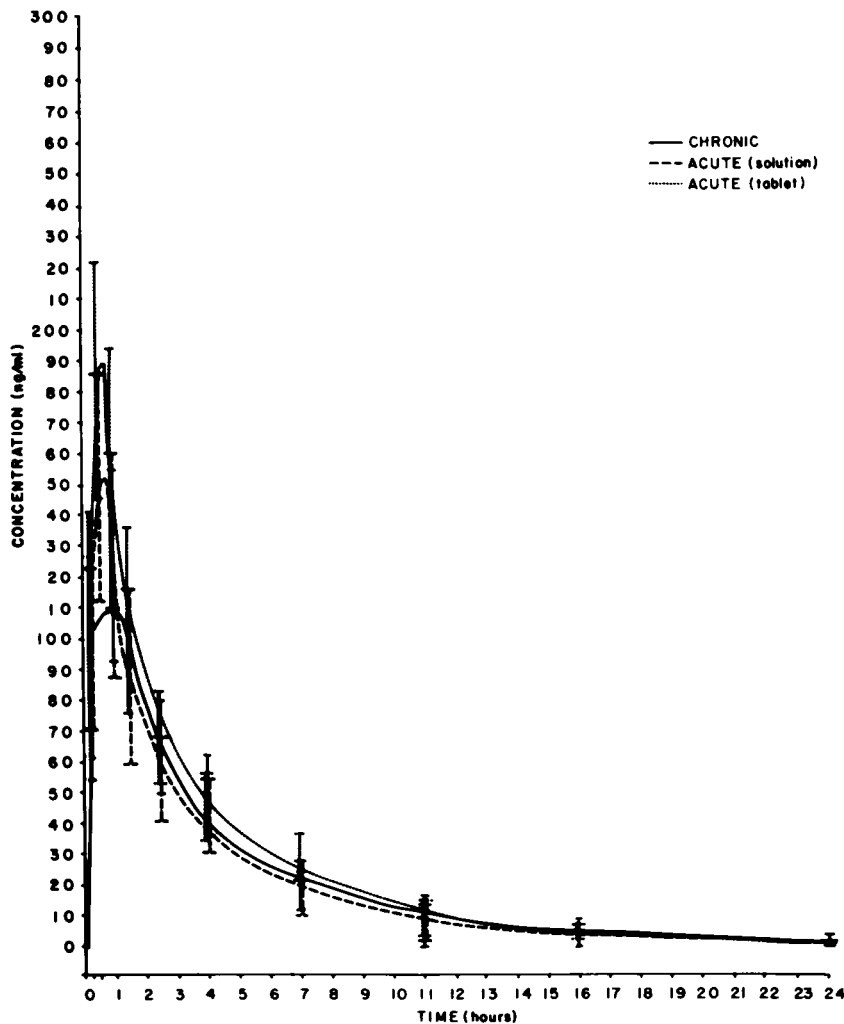


FIG. 1. Linear elimination curve comparing tablet and solution in single (acute) and multiple (chronic) dosing.

With an effective single oral dose, blood pressure may decline within 15 min, reaching a low between 2 and 6 hr and recovering at an arithmetically linear rate of 30% per day. The total duration of action of a single dose may exceed 72 hr (17,36,37). The supine diastolic blood pressure (SDBP) response to minoxidil is

TABLE 6. Percentages of total drug-related material in human urine over a 24 hr period

Total polar	Minoxidil-O-glucuronide	4-OH-Minoxidil	Minoxidil
18%	67%	2.5%	12%

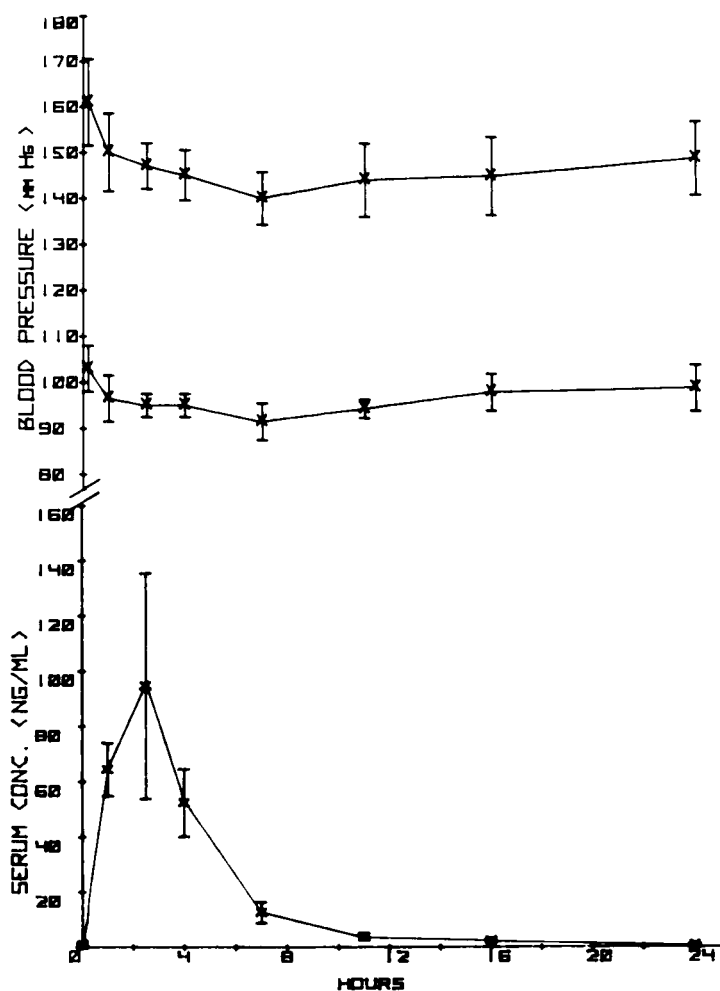


FIG. 2. Sensitivity of effects of minoxidil in chronic dosing: blood pressure response and serum concentrations versus time. Note that the maximum decreases in systolic and diastolic pressures are beyond the peak minoxidil concentration and $T_{1/2}$.

linearly related to the log of the dose administered, a semilog relationship intersecting the dosage axis at approximately 5 mg (23,27) (Table 7).

The slope of minoxidil's dose-response curve is proportional to the extent of the hypertension; it diminishes to zero at a SDBP of approximately 85 mm Hg. Thus, as SDBP declines with therapy, ensuing doses produce progressively smaller pressure reductions (Table 7). Because of this characteristic, minoxidil appears to be a purely antihypertensive drug, unable to reduce a normal blood pressure.

The plasma concentrations of several antihypertensive agents have been found to poorly correlate with antihypertensive effect [minoxidil (17), prazosin (38,39),

TABLE 7. Relationship between minoxidil dose-response curve and pretreatment supine diastolic blood pressure (BP) in hypertensive patients

Decrease in supine diastolic BP (mm Hg)	vs.	Pretreatment supine diastolic BP (mm Hg)
Dose (mg) × 2		
2.5		94
8.0		113
13.0		132
18.0		153

Adapted from Zins GR, Martin WB. The clinical pharmacology of minoxidil. In: *Symposium on Minoxidil*, Excerpta Medica, Amsterdam (in press).

hydralazine (40)]. This is true when the drug is given as a single dose or when chronically administered. It has been suggested that the reason for this poor correlation between clinical effect and plasma concentration is that the drug concentration is less in plasma because of its presence at the various receptor sites within the vascular tree (34). To test this hypothesis, group data were examined

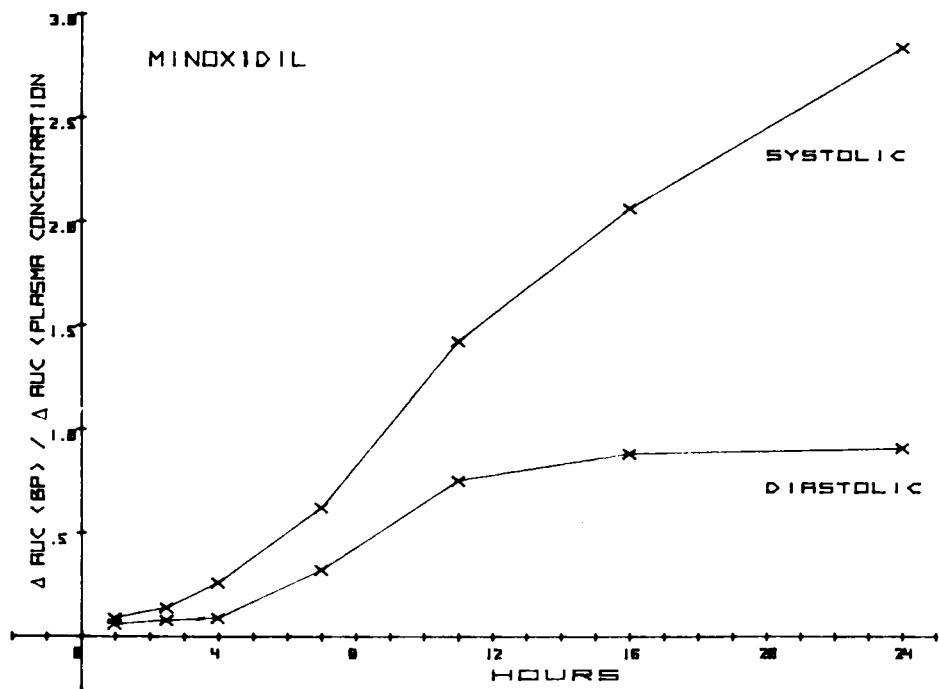


FIG. 3. Change in area under the curve blood pressure (systolic and diastolic) to change in plasma concentration versus time ratio curves during chronic minoxidil dosing.

comparing the responses to minoxidil and prazosin by examining the area under the curve of plasma concentration versus time sequence and relating them to the area under the curve of the changes in systolic and diastolic blood pressure response versus the time sequence. It can be seen from the Fig. 3–5 that two characteristic trends are apparent. First, Fig. 3 describes a slope which rapidly increases with time, suggesting maintenance of antihypertensive effect while the drug is rapidly shifting to its site of action (drug concentration, or denominator, falls). This would be a type I curve (Fig. 3 and 4). A type II curve demonstrates a decreasing slope with time, indicating the development of tolerance, decreased receptor affinity, or decreased receptor sensitivity (Fig. 5). Type I plots are seen for all the subjects, regardless of the level of renal function, in the systolic and diastolic pressure responses to minoxidil. Patients receiving prazosin at low dosage, i.e., 3–8 mg/day also have a type I response (Fig. 4). On the other hand, patients receiving high-dose prazosin, regardless of renal function, had type II curves (Fig. 5). Those patients requiring prazosin in high dosage, that is, 9–20 mg/day, tend to have an inadequate antihypertensive response to the drug and may require additional adrenergic blocking therapy, that is, clonidine or propranolol. Thus, the pharmacologic sensitivity of response can be derived by relating the plasma area under the curve to the area under the change in blood pressure response.

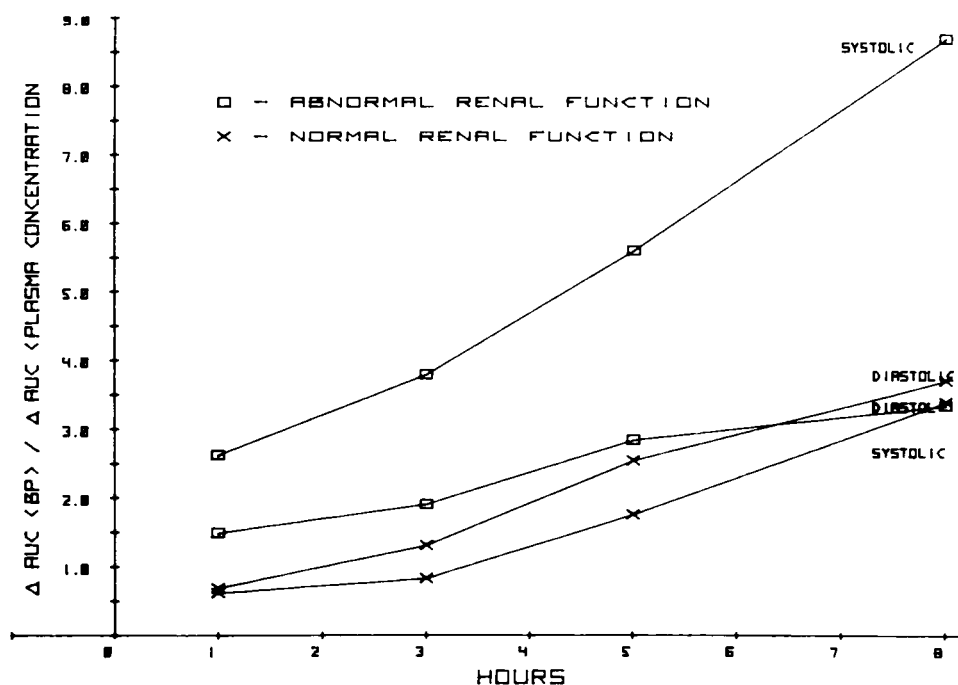


FIG. 4. Change in area under the curve blood pressure to area under the curve plasma concentration versus time for chronic low-dose prazosin (3–8 mg/day).

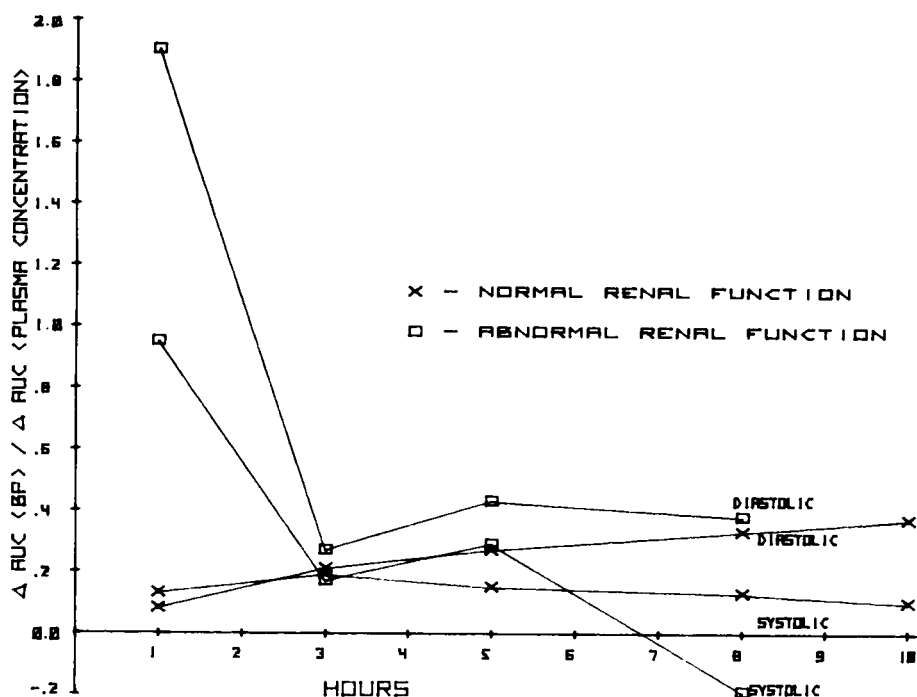


FIG. 5. Change in area under the curve blood pressure to area under the curve plasma concentration versus time for chronic high-dose prazosin (9-20 mg/day).

ADVERSE CLINICAL RESPONSE

The adverse effects seen with minoxidil are mainly related to vasodilator-induced hemodynamic changes and can be ameliorated pharmacologically. In addition, hypertrichosis, especially on the forehead, sides of the face, and extremities may be treated with depilatory agents. Following the initial dosing with minoxidil over the first 7-9 days, 30% of patients may show some ischemic ST-T wave changes, which are reversible even when the drug is continued. This may be related to a coronary-steal syndrome associated with the reduction in blood pressure. Long-term use of minoxidil has been associated with pericardial effusion, especially in patients with end-stage renal disease. It is unclear whether this is drug related or part of the natural history of chronic renal failure. In our experience, we have obtained serial echocardiograms in 10 patients with varying degrees of renal impairment prior to and following 2 years of minoxidil therapy. No pericardial effusion has developed.

CONCLUSION

In conclusion, the antihypertensive effect following a single dose is seen within 15 min, reaches a nadir by 2 to 6 hr, and returns to baseline at an arithmetic linear rate of about 30% per day. The total duration of action of the single dose may exceed 72 hr. The adverse pharmacological effects of minoxidil can be reversed with

furosemide or dialysis and with a beta adrenergic blocker and/or clonidine. Standard depilatory agents may relieve the hirsutism. Because of hirsutism, it is recommended that when used in women minoxidil be given only for severe refractory hypertension, especially in younger women.

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