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The Clinical Pharmacology of Vasodilator Antihypertensive Drugs

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Abstract—Vasodilator antihypertensive agents are defined and classified according to their mechanism and site of action. The effects of minoxidil, in combination with propranolol and a diuretic, on renal blood flow and renal function were studied following acute and chronic therapy. Although renal blood flow is reduced after two weeks on minoxidil, renal blood flow and renal function are not compromised after one year. The haemodynamic effects and pharmacokinetic profile of acute dosing with tolmesoxide, a new vasodilator antihypertensive agent are described. Results suggest that the long-term efficacy and safety of this drug are worth studying.

Vasodilator antihypertensive agents may be defined as drugs which act on the arteriole to lower blood pressure. These drugs are currently of considerable research and therapeutic interest. There are three reasons for this. Firstly, the older vasodilators are being used in new ways. Secondly, a number of new vasodilator antihypertensive agents have become available, the characteristics of which have broadened the potential application of this group of drugs in hypertension. Thirdly, their mechanism and site of action are different from other groups of antihypertensive drugs and therefore they can be used effectively in combination with these.

Vasodilator antihypertensive agents may be classified as shown in Table 1. The vasodilator effect of the specific members of this group depends on their interaction with receptors. These include phenoxybenzamine and phentolamine which block both pre- and post-synaptic alpha-adrenoceptors and prazosin which selectively blocks post-synaptic receptors (Cambridge *et al.*,

TABLE I

Antihypertensive "vasodilators"

α-ADRENOCEPTOR BLOCKING AGENTS

post-synaptic – prazosin
pre + post-synaptic – phenoxybenzamine, phentolamine

ANGIOTENSIN BLOCKING AGENTS

saralasin

CALCIUM ANTAGONISTS

nifedipine, verapamil

PROSTAGLANDINS

prostacyclin

NON-SPECIFIC

selective – hydralazine, minoxidil, diazoxide
non-selective – nitroprusside, tolmesoxide

1977). Saralasin also falls within the definition of a vasodilator and acts as a competitive blocker of angiotensin II. However, this drug is usually the tool of investigators interested in the renin-agiotensin system and will not be considered further here. In contrast, a definitive mechanism of action has not been described for the non-specific group, although an effect on calcium flux in vascular smooth muscle has been suggested for some (Chidsey and Gottlieb, 1974).

The non-specific group of vasodilators can be divided into those that are selective for resistance blood vessels and non-selective agents which in addition dilate capacitance vessels. The term selective is a relative one and in the present context refers to clinically significant effects occurring on arterioles and/or veins. While diazoxide can be shown to possess vasodilatory action on veins using nonadrenaline-vasoconstricted vessels, the absence of a postural effect with this drug excludes a clinically important action on the venous side. Nitroprusside on the other hand has been shown to possess both arteriolar and venous dilatory action.

The haemodynamic consequences of selectivity are considerable (Table II). Whereas the selective dilators such as hydralazine increase cardiac output (Freis *et al.*, 1953; Crumpton *et al.*, 1953) the non-selective vasodilators may decrease or have only a minor effect on cardiac output (Schlant *et al.*, 1962). The effect of nitroprusside in uncomplicated hypertension should not be confused with its effect on cardiac output and cardiac function in conggestive heart failure. In the latter cardiac output is increased by reduction of after-load (Franciosa and Cohn, 1977).

TABLE II

Comparison of the Haemodynamic Effects of Selective and Non-Selective Vasodilator Antihypertensive Drugs

	Blood Pressure	Heart Rate	Cardiac Output
Selective (Hydralazine)	↓	↑	↑
Non selective (Nitroprusside)	↓	↑	↓ →

This paper is mainly concerned with some early work on the assessment of minoxidil—a highly effective antihypertensive drug, the emphasis being on the renal circulatory effects of prolonged use of minoxidil as part of an effective anti-hypertensive regimen. Work with a new vasodilator antihypertensive agent, tolmesoxide will be briefly discussed.

Minoxidil

Minoxidil has been under intensive investigation in the United States since the early 1970's and in Europe for a somewhat shorter period. It was released in June 1979 in the United States for restricted use in hypertension. The drug has an onset of action of 4–6 hours and the duration of action in most cases is at least 24 hours after a single dose and in some cases the hypotensive activity can be demonstrated for up to five days (Shen *et al.*, 1975). The dose response relationship (Fig. 1) is such that it is relatively easy to adjust the dose and to control blood pressure rapidly in severe hypertension.

The effect of antihypertensive drugs on renal function is often a matter of concern both in the acute and chronic situation. In most studies to date patients receiving minoxidil have severe hypertension and many have severe nephrosclerosis. It is therefore important to examine both the acute and chronic effects of therapy on renal blood flow. We carried out the present study in patients resistant to conventional antihypertensive drugs.

Renal blood flow was measured using the plasma clearance of bolus i.v. administration of I^{131} PAH (Pearson, 1979). Flow measurements were made prior to treatment, after seven days on minoxidil plus propranolol and after one year on minoxidil, propranolol and frusemide (Table III). There was a dramatic 45 mmHg fall in mean arterial pressure after seven days treatment and a further fall of 8 mmHg after one year. Although renal blood flow was significantly reduced from 505 ± 56 ml/min to 393 ± 44 ml/min after seven days of treatment, renal flow was not compromised in the long-term, with values similar to baseline values documented after 12 months treatment. Renal

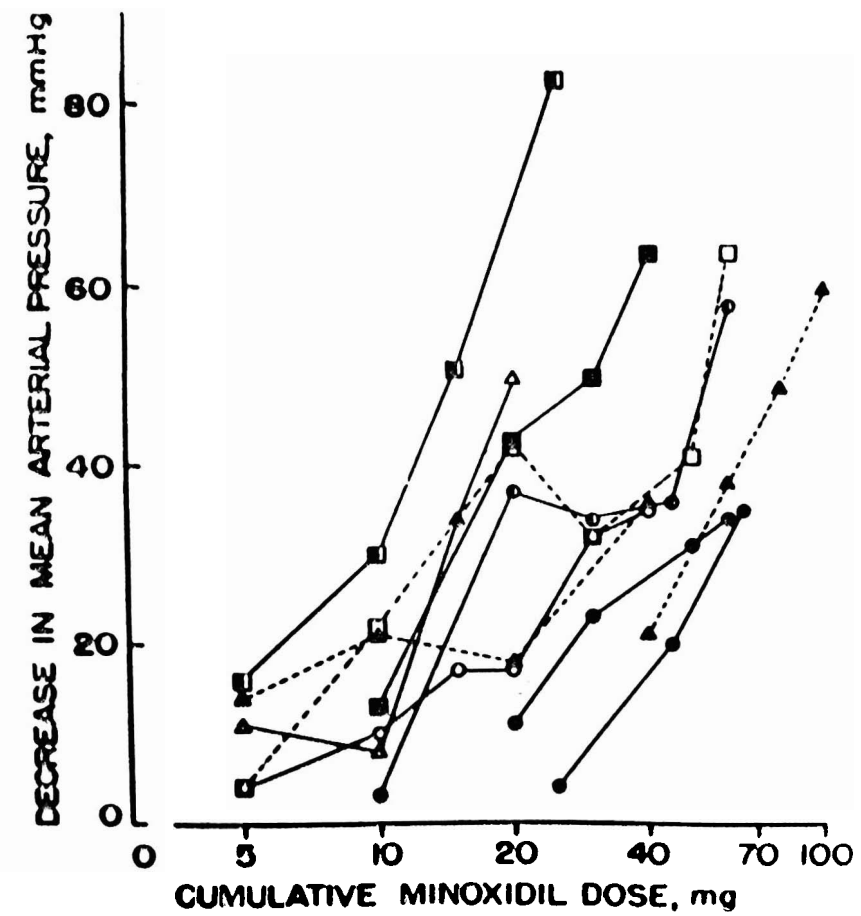


FIG. 1
Dose-response relationship of minoxidil.

conductance, which relates the renal blood flow to the mean arterial pressure, was unchanged after seven days but was significantly increased after one year from 3.6 to 5.3 $ml.min^{-1}$ $mmHg^{-1}$ ($P < 0.01$). There was a slight but non significant increase in serum creatinine after seven days and no change was observed over the remainder of the study.

This study confirms the value of minoxidil in severe hypertension with a fall of 34 % in the mean arterial pressure and documents the effect of minoxidil on renal function and renal blood flow. The disparity between renal blood flow or conductance after short-term and long-term treatment is important for two reasons. Firstly, it demonstrates that severely hypertensive patients may be treated with vasodilators on a long-term basis without unduly compromising

TABLE III

Effect of Blood Pressure "Normalization" on Renal Blood Flow and Serum Creatinine

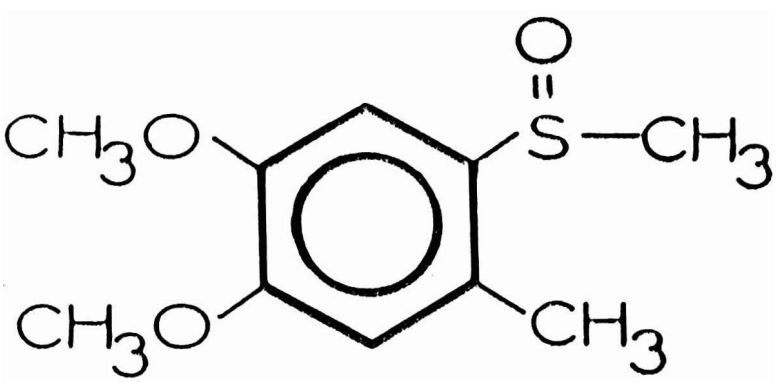
	Mean Arterial Pressure mm Hg	Renal blood flow ml/min 1.73 M^2	Renal conductance RBF/MAP	Serum Creatinine mg %
Control	155 ± 6	505 ± 56	3.3 ± 0.4	1.2 ± 0.1
7 days	110 ± 3*	393 ± 44*	3.6 ± 0.4	1.4 ± 0.2
12 months	102 ± 2*	538 ± 81	5.3 ± 0.8*	1.4 ± 0.2

* $P < 0.01$ vs control.

renal blood flow or function—a clinically important consideration in drug selection for hypertensives, who may have significant renal impairment prior to treatment. Secondly, it underlines the importance of repeated review of haemodynamic measurements in long-term assessment of drug effects.

Tolmesoxide

Since the advent of beta adrenoceptor blocking agents the use of vasodilators for the treatment of hypertension has become widespread.



TOLMESOXIDE

FIG. 2

Structure of tolmesoxide.

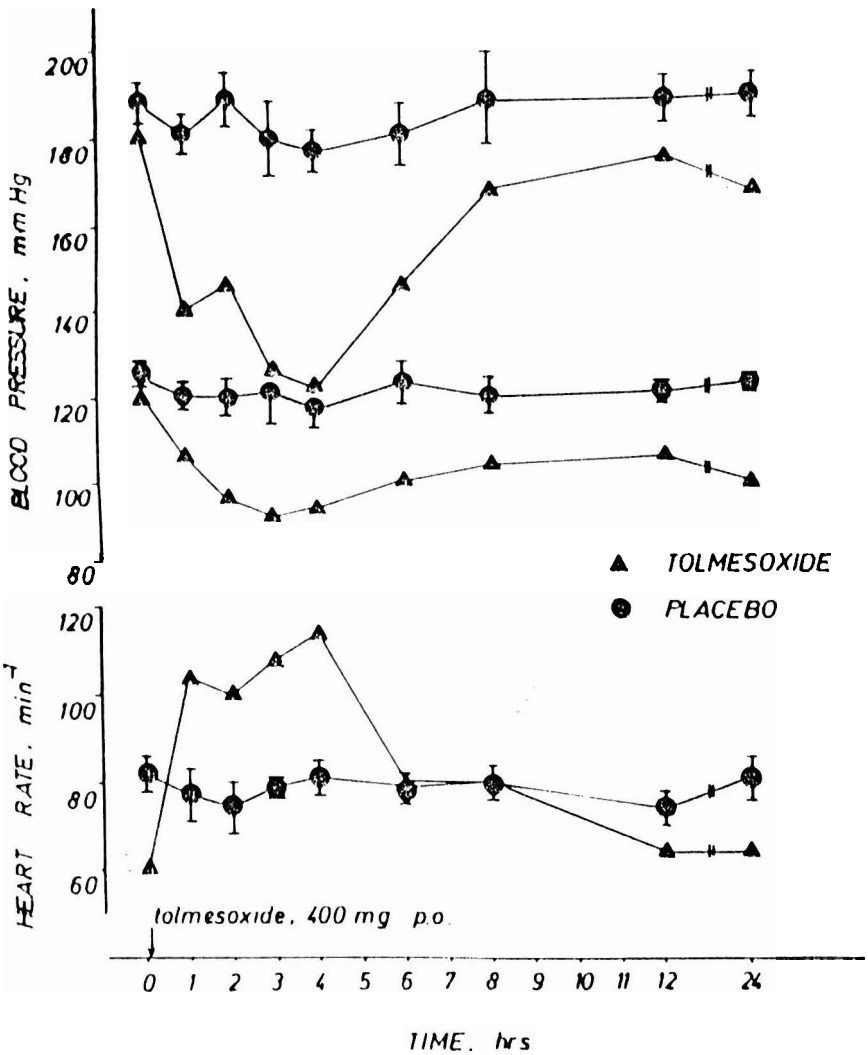


FIG. 3
Antihypertensive effects of tolmesoxide.

Although beta adrenoceptor blocking agents and diuretics may minimise the reflex effects associated with vasodilators, many of these drugs have shortcomings. Consequently newer vasodilators are being assessed in the hope of finding a drug which is effective and safe in the long term.

Tolmesoxide (Fig. 2) is a new vasodilator and is a member of a class of sulphoxides chemically dissimilar from existing vasodilators. The relevant cardiovascular properties of tolmesoxide have been demonstrated in a variety of

animal models and in preliminary human studies. Results suggest that tolmesoxide achieves its effects by acting directly on the vascular smooth muscle, probably by influencing the contractile process through an action on calcium (Doxey, 1978).

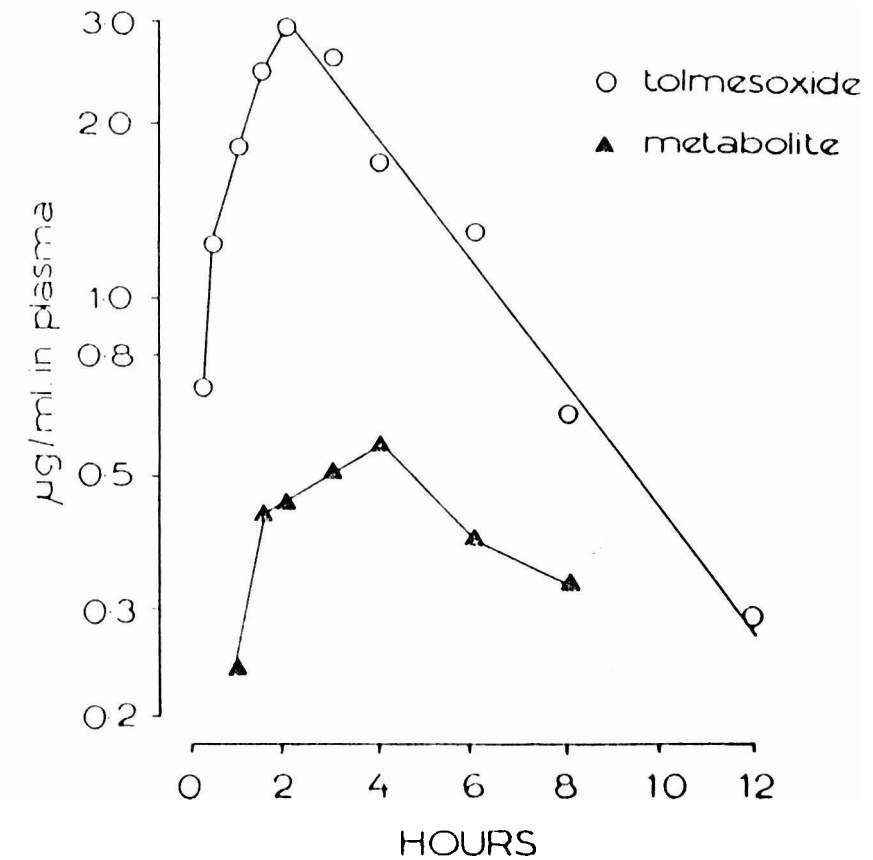


FIG. 4

Plasma levels of tolmesoxide and metabolite (RX 71112) following administration of 100 mg orally to a hypertensive patient.

The antihypertensive effect seen in normal volunteers (Buylla *et al.*, 1979) has been confirmed in severe hypertensive patients following acute oral dosing. A typical vasodilator response is observed with a significant fall in systolic and diastolic blood pressure and a coinciding reflex tachycardia (Fig. 3) and rise in plasma renin. The onset of antihypertensive effect is rapid, often within one hour, and the duration of effect of single doses studied last up to 12 hrs. A variable postural effect suggests that tolmesoxide is a non-selective vasodilator and clinically confirms previous forearm flow studies indicating a balanced

action on arteriolar and venous smooth muscle tone (Collier *et al.*, 1978). Initial results in our laboratory also suggest that by reducing pre-load and after-load tolmesoxide may be beneficial in refractory cardiac failure.

Tolmesoxide is rapidly and completely absorbed, fasting peak concentrations are often achieved in less than one hour after oral dosing (Fig. 3). There is a good correlation between dose and peak concentrations. A short half-life, ranging from two to five hours, is similar to that of other members of the vasodilator group and highlights the disparity between half-life and duration of effect which is so characteristic of this group of drugs. However the half-life in congestive heart failure may be considerably increased (greater than eight hours) and this may be related to poor hepatic perfusion consequent on a low cardiac output.

Initial results, which characterise tolmesoxide as a typical vasodilator antihypertensive agent, are encouraging and indicate a significant antihypertensive effect in acute dosing. However, further evaluation with chronic dosing will be necessary before the value of this new addition to the vasodilator group of drugs is established.

Conclusion

Vasodilator antihypertensives are becoming increasingly important in the treatment of hypertension and a classification based on their mechanism and site of action is now possible. Interest in these drugs is reflected in the development of new members of the group. Tolmesoxide is being assessed for its long-term efficacy and safety while minoxidil is established in the management of severe resistant cases. We have shown that in combination with propranolol and a diuretic, minoxidil lowers blood pressure effectively but renal blood flow and renal function are maintained.

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