Vasodilators in the Treatment of Hypertension

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Vasodilator drugs continue to interest research workers and clinicians alike. The evaluation of vasodilators in the management of congestive heart failure over the past few years has coincided with the general acceptance of the use of many of these agents as second and third choice drugs in the management of moderate and severe hypertension. In this paper we propose a classification of vasodilator antihypertensive drugs. As this group has grown considerably we have elected to concentrate on some areas of special interest, namely the pharmacology of minoxidil, calcium antagonists as hypotensive drugs and prazosin.

Classification

There is no agreement as to how these drugs should be classified. The narrowest definition would be to include only those drugs such as hydralazine and diazoxide which relax vascular smooth muscle but appear not to interact with "receptors". On the other hand, many drugs which lower blood pressure do so via receptors or specific sites on vascular smooth muscle and these produce haemodynamic responses not very different to those seen with non-specific vasodilators. We have, therefore, included angiotensin antagonists, calcium antagonists, prostaglandins and α-adrenoceptor blocking drugs in addition to non-specific vasodilators (Table 1). We rather arbitrarily excluded the converting enzyme inhibitor, captopril, because at least one of its important actions occurs remote from the vascular smooth muscle. However, an argument for its inclusion could be made on the basis that the end result is relaxation of vascular smooth muscle.

The pattern of response to a vasodilator is more importantly determined by the selectivity shown than by the precise mechanism of action. Thus the haemodynamic

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Table 1
Antihypertensive "vasodilators"

α-adrenoceptor Blocking Agents	
	Postsynaptic—prazosin
	Pre + postsynaptic—phenoxybenzamine, phentolamine
Angiotensin Blocking Agents	
	saralasin
Calcium Antagonists	
	nifedipine, verapamil
Prostaglandins	
	prostacyclin
Non-specific	
	selective—hydralazine, minoxidil, diazoxide
	non-selective—nitroprusside, tolmesoxide

response to a drug acting solely on arterioles such as hydralazine may be quite different to that observed with a non-selective vasodilator, such as nitroprusside which acts on both resistance and capitant blood vessels. With hydralazine, reflex tachycardia and increase in cardiac output accompany blood pressure lowering, whereas with a mixed arteriolar-venous dilator, cardiac output tends to remain unchanged or, indeed, to fall in hypertensive patients due to reduced venous return. The latter may indeed be associated with postural hypotension. The arteriolar selective drugs include hydralazine, diazoxide and minoxidil. The remaining vasodilator antihypertensives are non-selective and vary little in the balance of arteriolar versus venous effect and from the clinical point of view cannot be readily distinguished. Not surprisingly some of them (prazosin and nitroprusside) have an application in the management of congestive heart failure because they combine reduction of after-load with diminution in pre-load. In hypertension these drugs do not have a major effect on cardiac output, as stroke volume remains relatively constant in the face of a fall in outflow resistance (Cohn and Franciosa, 1977).

Minoxidil

Minoxidil has been under intense clinical scrutiny for the past decade and as it is likely to be approved shortly for clinical use in a number of countries it is perhaps timely to review the clinical pharmacology of this effective, non-specific vasodilator antihypertensive agent.

After oral administration the antihypertensive effect of minoxidil is maximal at 3–4 h and the duration of action depends *inter alia* on the severity of hypertension. While many patients can be controlled adequately with once daily administration, initially the drug should be given twice a day. The pattern of antihypertensive action does not relate in a simple manner with plasma levels, the concentration of parent drug being extremely low after 6 h. As with other vasodilators, the drug is taken up by blood vessels and its persistence there may explain the lengthy duration of

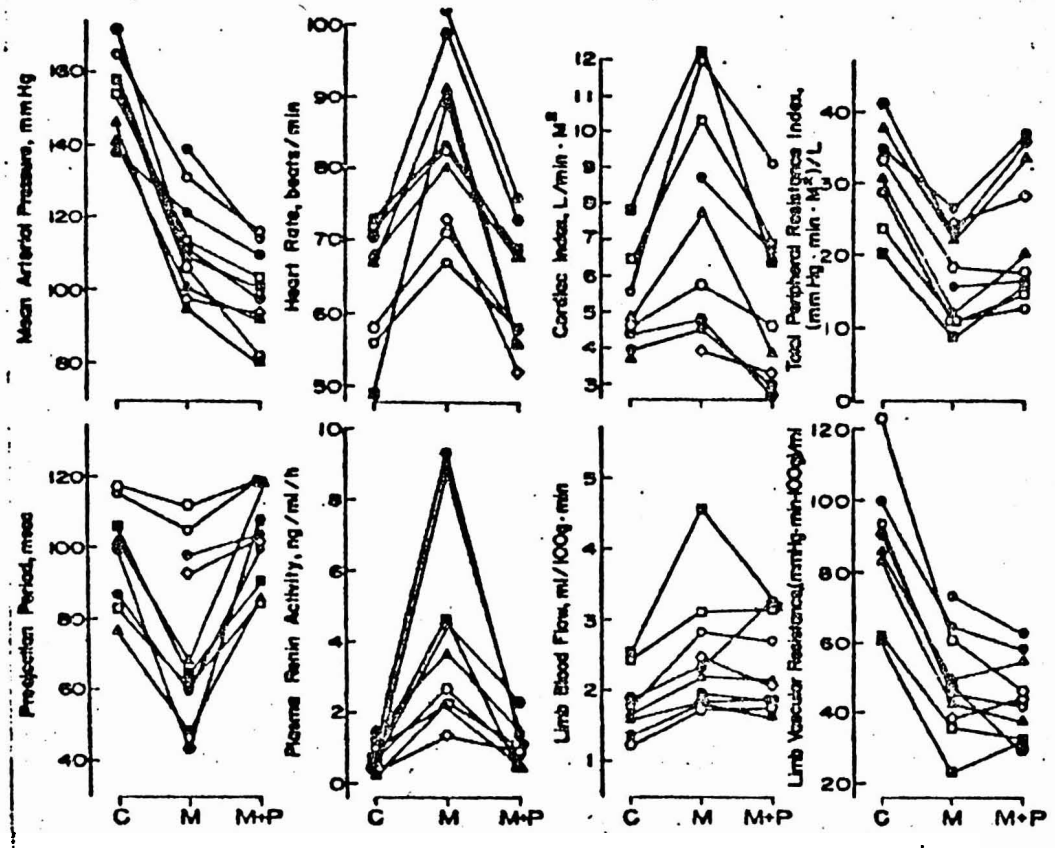

Figure 1. Haemodynamic responses to minoxidil (M) *and the combination of minoxidil and propranolol* (M + P) *in patients with essential hypertension* (*O'Malley* et al., *1976*)

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action and lack of correlation with plasma levels. The dose-response relationship is, however, relatively simple, there being a rather narrow range of slopes and threshold doses. Thus, it is easy to adjust dose and control blood pressure rapidly (O'Malley and McNay, 1975). When rapid control of blood pressure is required, 50% increments in dose may be administered every 6 h until goal pressure is reached.

Haemodynamic responses

The haemodynamic response observed (Fig. 1) is similar to that seen with other arteriolar selective vasodilators, most changes being reflexogenic in response to blood pressure reduction—tachycardia, increase in stroke volume, increase in plasma renin activity and sodium retention. These changes have the effect of offsetting the anti-hypertensive effect and it is invariably necessary to add a β-adrenergic blocking drug and a diuretic.

Unwanted effects

While minoxidil has been shown to be a highly effective antihypertensive agent, both in our own studies and in those of others (Gilmore *et al.*, 1970; Gottlieb *et al.*, 1972; Pettinger and Mitchell, 1973) this drug does have some serious unwanted effects. It causes hypertrichosis in a very high percentage of patients. In our experience, virtually all patients on treatment with this drug in a dose of more than 10 mg/day for more than 6 months developed some degree of hypertrichosis. The reason for development of hypertrichosis is not known. Another vasodilator agent, diazoxide, causes this problem with long-term therapy. The hair growth is lanugal in type and is not related to alterations in sex hormones. It may be related in some way to increase in skin blood flow. This unwanted effect severely limits the use of minoxidil in females.

A second unwanted effect of considerable importance is sodium retention. The degree of sodium retention is inversely related to renal function and many patients with poor renal function may prove quite resistant to treatment, even with high doses of frusemide. Particular care must be taken not to precipitate pulmonary oedema as sodium retention can be very marked.

There are several possible mechanisms involved in the sodium retention including stimulation of the renin–angiotensin–aldosterone system and alterations in distribution of renal blood flow (Zins, 1974). In addition, the marked lowering of blood pressure possible with this drug, could in itself lead to sodium retention in patients with nephrosclerosis and poor renal function.

Side-effects related to increase in sympathetic activity are readily controlled by the use of β-adrenergic blocking drugs. In addition, these agents potentiate the antihypertensive effect of the vasodilator by cutting out the contemporary reflex changes that tend to offset the hypotensive effect of the vasodilator. While relatively large doses of β-adrenoceptor blocking drugs may be required initially, with chronic use the dose requirement falls (Brunner *et al.*, 1978).

It seems likely, in view of the seriousness of the unwanted effects of minoxidil, that it will find a role only in the management of patients with severe hypertension who are resistant to conventional antihypertensive agents.

Prazosin

Prazosin is one of the newer "vasodilator" compounds and is certainly one of the most interesting. Clinically its effectiveness has been demonstrated in hypertension and congestive heart failure.

Prazosin was initially synthesized for its phosphodiesterase inhibitory effect. Not only does its structure include the dimethoxybenzo moiety of papaverine, a potent phosphodiesterase inhibitor, but it also has some features of cyclic AMP and cyclic GMP, both of which are important in the regulation of vascular smooth muscle tone. Initial assessment confirmed its vasodilator activity and hypotensive effect in dogs (Constantine *et al.*, 1973). However, further studies in rats, cats and dogs demonstrated the need for an intact sympathetic nerve supply. This finding, coupled with the clinical observations of an absence of reflex tachycardia or increase in plasma renin activity, indicated that it is not a non-specific vasodilator.

The bulk of evidence now points to an α-adrenoceptor blocking mechanism of

action although direct vascular smooth muscle relaxation may occur at very high doses in animals. In addition to the need for an intact nerve supply for prazosin to decrease vascular resistance (Wood *et al.*, 1975) it has been shown that prazosin attenuates the pressor response to noradrenaline and cifezoline, a specific α-agonist (Cavero and Lefevre, 1976), and sympathetic stimulation, but does not reduce the pressor response to serotonin, vasopressin (Wood *et al.*, 1975) or angiotensin II (Graham *et al.*, 1977; Stokes and Oates, 1977), suggesting an α-adrenoceptor level of action rather than direct vasodilation. Reversal of the pressor response to adrenaline, which occurs with α-adrenoceptor blocking agents has been demonstrated with prazosin (Stokes and Oates, 1977; Graham *et al.*, 1977). Its adrenoceptor-blocking action is confirmed by abolishing its effect by prior blockade with conventional α-adrenoceptor blocking agents such as phentolamine (Stokes and Oates, 1977) and phenoxybenzamine (Commarato *et al.*, 1978).

Although prazosin fulfils the criteria for an α-adrenoceptor blocking agent, and is more potent than phentolamine in this respect, it does not demonstrate the typical reflex changes of conventional α-adrenoceptor blocking agents. Langer's (1974) concept of presynaptic α-receptors prompted further studies of the nature of the α-blockade associated with prazosin.

Cambridge *et al.* (1977) compared the effect of prazosin and phenoxybenzamine on the stimulation-induced overflow of tritiated noradrenaline (^{3}HNA) in rabbit pulmonary artery. Prazosin, in concentrations which produced similar antagonism of postsynaptic function to that seen with phenoxybenzamine, caused no significant increase in the overflow of ^{3}HNA, while phenoxybenzamine caused a marked increase in overflow. Graham *et al.* (1978) demonstrated a disproportionately greater (300%) increase in plasma noradrenaline response to equipressor doses of phenoxybenzamine and prazosin, thereby confirming a relative selectivity of prazosin for postsynaptic adrenoceptors.

Prazosin does not cause an overflow of noradrenaline owing to lack of interference with presynaptic inhibition of noradrenaline release, which is the postulated theory for the absence of reflex tachycardia and rise in plasma renin activity. Similarly, in the majority of animal studies, prazosin causes either no change or a reduction in plasma renin activity. Massingham and Hayden (1975) demonstrated no significant increase in plasma renin activity in conscious hypertensive dogs, given i.v. or oral prazosin. In anaesthetized dogs given prazosin i.v., plasma renin activity was significantly lowered to 62% of the control value with prazosin, in contrast to a rise in activity of 180% of control value when diazoxide was administered. Similar findings apply in man (Rosenthal, 1978).

Although the selectivity of α-blockade exhibited by prazosin may reduce circulating noradrenaline, this is not the only pathway for reflex effects. Baroreceptor reflex function should normally compensate for falls in blood pressure. As demonstrated by Buzzeo (1978) sympathetic responsiveness remains intact in the face of a challenge but yet the hypotension induced by prazosin is inadequate to stimulate the expected response.

It would seem from *in vitro* and *in vivo* animal studies that prazosin is a selective postsynaptic α-adrenoceptor blocking agent in doses studied, although the pharmacodynamic picture is not complete. It is of interest that the selectivity varies among species. Its lack of effect on plasma renin activity and heart rate are suggestive, but not conclusive proof, of its selective postsynaptic α-adrenoceptor blocking action in man, a probable explanation that has so far been difficult to prove. In any event the absence of an increase in sympathetically mediated response accounts, partly at least, for the greater efficacy of prazosin compared to older α-adrenoceptor blocking drugs such as phentolamine and phenoxybenzamine in essential hypertension.

Calcium Anatagonists in Hypertension

While vasodilating drugs have long been of use in the treatment of systemic hypertension, the mechanism of action of these drugs is still unclear. It has been suggested that hydralazine (Koch Weser, 1976a) and diazoxide (Koch Weser, 1976b) exert their effect by chelating certain trace metals required for smooth muscle contraction. It has also been postulated that diazoxide competes with calcium to lower smooth muscle tone (Wohl *et al.*, 1967). Minoxidil may exert its effect by blocking calcium entry at the plasma membranes. Sodium nitroprusside is thought to either inhibit calcium release in the cell or calcium activation on the contractile protein.

In view of the putative links between the established vasodilating drugs and calcium, it is not surprising that there has been interest in the hypotensive effect of the calcium antagonist group of drugs. The most commonly used calcium antagonist drugs are nifedipine, a pyridine derivative, and verapamil, a synthetic papaverine derivative. These drugs combine a peripheral and coronary artery vasodilating effect with a negative inotropic effect on the heart, thus diminishing myocardial oxygen requirement (Nayler, 1967; Nayler and Szeto, 1972; Ross and Jorgensen, 1967). These drugs are in common use for the treatment of angina (Andreasen *et al.*, 1975) and are particularly useful in the treatment of coronary artery spasm or Prinzmetals angina, where β-adrenoceptor blocking drugs may be contraindicated (Hansen *et al.*, 1978). Theoretically, the calcium antagonist group of drugs should be free of some of the side-effects of the established vasodilating drugs and therefore might be of particular value in the treatment of hypertension where it is associated with angina pectoris.

Splitting of ATP is required for the energy delivery process of muscle contraction and this process is dependent on calcium. Calcium antagonists act by blocking the passage of extracellular calcium from the superficially located membrane storage areas of the sarcoplasmatic reticulum into the cell plasma, where the ATP-ase of the myofibrils is located. In the heart, inhibition of calcium displacement produces a negative inotropic effect. In addition, reduction of the amount of calcium available at the myofibril, leads to a diminution in turnover of high energy phosphates, thus reducing myocardial oxygen demand.

Nifedipine

Nifedipine has a rapid onset of hypotensive action after both oral (20 min) and sublingual (5 min) administration (Guazzi *et al.*, 1977). The hypotensive effect is accompanied by increses in heart rate (21%), stroke index (7%) and cardiac index (30%) with a 40% reduction in total peripheral resistance. No change occurs in mean right atrial pressure suggesting that nifedipine does not significantly diminish venous tone. In chronic dosing (Olivari *et al.*, 1979) the pattern is rather similar with the response to each dose lasting 8–12 h. Side-effects include headache and palpitations but postural hypotension is not seen.

Of particular interest is the failure of nifedipine to markedly perturb the renin–angiotensin system. Modest increases (50%) in plasma renin activity have been observed (Lederballe-Pedersen *et al.*, 1979). This contrasts with the five- to ten-fold increases observed with minoxidil (O'Malley *et al.*, 1975). In addition to reflecting a slightly smaller hypotensive effect, these differences most likely indicate that nifedipine attenuates renin responsiveness.

Verapamil

The antihypertensive efficacy of verapamil in the acute situation is documented in a number of studies as reviewed by Lewis (1978). Lederballe-Pederson (1978) studied the antihypertensive effect of verapamil on six hypertensive patients whose diastolic pressures were greater than 100 mmHg, and found that the drug given i.v., produced a significant reduction in blood pressure which was accompanied by an increase in heart rate. Chronic dosing (320–640 mg/day) produced a modest reduction in blood pressure (mean reduction 14/12 mmHg) but it is obvious that full evaluation of the hypotensive potential of this drug would require more extensive studies. There is insufficient information available at present to assess the clinical potential of verapamil in hypertension. In addition, the marked effect on impeding A-V conduction (Husaini, 1975) seen after verapamil, but not with nifedipine (Rowland *et al.*, 1979) may preclude its use in patients with conduction disturbances. Fatal bradyarrhythmias have been reported following the use of verapamil i.v., especially when it is combined with the use of β-adrenoceptor blocking drugs (Benaim, 1972). It seems likely, therefore, that verapamil may have little to offer over other vasodilators because of this troublesome effect. There are studies currently under way on various other calcium antagonists, including RO 11–1781 which resembles verapamil in its antiarrhythmic qualities.

Summary

The major advantage of the use of calcium antagonist drugs in the treatment of hypertension lies in their use in the patient with concomitant ischaemic heart disease, in whom the use of conventional vasodilators may be contraindicated. In addition, the lack of a major effect of these drugs on the renin–angiotensin system and sodium balance requires further long-term study, as this may prove to be an important advantage over older vasodilators and raise the possibility that these drugs may be used as monotherapy.

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