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VASODILATORS IN THE MANAGEMENT OF HYPERTENSION

Desmond Fitzgerald, Eoin T. O'Brien, Kevin O'Malley

Department of Clinical Pharmacology, Royal College of Surgeons, St. Stephen's Green, Dublin 2. and The Hypertension Clinic, The Charitable Infirmary, Dublin 1, Ireland

In the majority of hypertensive patients the major haemodynamic abnormality is a raised systemic vascular resistance. Vasodilators would therefore, be a logical choice of treatment in most patients. Further, this group of drugs lacks the sympathoplegic effects of the ganglion blockers. However, their use as first line therapy in the treatment of hypertension is limited because of the reflex haemodynamic changes they induce. Further, when used alone their blood pressure lowering effect is generally no greater than occurs with a beta-blocker. They are most effective in combination with a diuretic and a beta-blocker when these drugs have failed to control blood pressure adequately. However, newer vasodilators, such as captopril and verapamil, which have little or no reflex effects, may be shown eventually to have a role as monotherapy in patients intolerant of beta blockers.

Vasodilators in the management of hypertension are reviewed with special reference to classification and their use in hypertensive crisis and in elderly patients. In addition, the effect of vasodilators, and more specifically minoxidil, on renal plasma flow and renal function is described.

Vasodilators are agents which directly or indirectly relax vascular smooth muscle. The result of this action depends on the vascular bed affected. Therefore, vasodilators can be further classified as predominantly arteriolar dilators such as hydralazine, minoxidil and

diazoxide; predominantly venodilators, such as nitrates and diuretics; or combined arteriolar and venodilators such as nitroprusside, captopril and prazosin. Further, nitrates and calcium antagonists act not only as afterload (arterial) and pre-load (venous) reducing agents but also directly relax coronary artery smooth muscle.

The dose hypotensive-response relationship of the vasodilators is variable. For captopril and prazosin it is complex and not easily predictable. Some workers have found no relationship between the degree of hypertension and the effective dose of prazosin[1]. Further, at higher doses the dose-response curve tends to flatten and the maximum response may be delayed for weeks. In contrast, minoxidil and nitroprusside have a linear log-dose response relationship[2,3]. Further, with minoxidil the threshold dose and the slope of the dose response curve positively correlate with mean arterial pressure[2]. This linear dose response relationship allows for rapid control of blood pressure in a predictable manner[4].

Vasodilators have a duration of action in excess of that predicted from their plasma half-lives. For this reason, hydralazine[5] and captopril are effective in twice daily doses, despite having very short half-lives. Minoxidil also has a prolonged duration of antihypertensive action which is usually about 24 hours but may be as long as 2-5 days[2] in contrast with a plasma half-life of 4.2 hours[6]. The rate of decay in antihypertensive effect is closely correlated with the pre-treatment blood pressure so that more severely hypertensive patients require twice daily doses. In less severely hypertensive patients once-daily administration suffices[2].

The role of vasodilators in the long-term treatment of hypertension has only become apparent with the introduction of so called triple therapy. Predominantly arterial vasodilators cause a reflex increase in sympathetic activity which, by increasing cardiac output and vasoconstriction, limit the blood pressure lowering effect of these drugs. Further more, the increased renin release stimulates angiotensin II production and release of aldosterone. A further consequence is that altered renal haemodynamics increase sodium absorption from the proximal tubule leading to fluid retention. The addition of beta blockers to vasodilators limits the reflex tachycardia and prevents the increase in cardiac output[7]. Furthermore, 85% of the increase in renin secretion which occurs with minoxidil is prevented by beta blockers[8]. This decrease in renin release may be important in producing the additional fall in

blood pressure which occurs when beta blockers and minoxidil are given together. Presuming that the findings for minoxidil can be extended to other vasodilators, the importance of beta-blockade in patients on vasodilators is apparent. Not all vasodilators induce reflex sympathetic activity, however; nitroprusside, prazosin and captopril are notably free of this effect at least in the supine position.

Fluid retention is common in patients on vasodilators and beta blockers and can be prevented by adding a diuretic. In patients with impaired renal function fluid retention may be a difficult problem and aggressive diuretic therapy is required[6,9]. Oedema may occur in the absence of fluid retention with drugs which are predominantly arteriolar dilators because, in the absence of venodilators, pre-capillary pressure rises leading to interstitial oedema[10].

TABLE I : Classification of Vasodilators.

1.	Alpha-adrenoceptor blocker	
	a. Post-synaptic e.g. prazosin.	
	b. Pre-and post-synaptic e.g. phentolamine, phenoxybenzamine, trimazosin	
	c. Combined alpha and beta receptor blocker e.g. labetalol	
2.	Non-specific vasodilators	Nitroprusside Minoxidil Hydralazine Diuretics
3.	Angiotensin II blockers	
	a. Angiotensin II receptor blockers	Saralasin
	b. Angiotensin I convertine enzyme inhibitors	Captopril Teprotide
4.	Calcium antagonists	Verapamil Nifedipine Perhexilene
5.	Prostaglandins	
6.	Drugs with combined effects:	
	Captopril:	Angiotensin blockade Direct vasodilation Inhibits bradykinin metabolism Increases plasma prostaglandins
	Indapamide:	Predominantly diuretic Mild vasodilator.

Calcium antagonists are an interesting group still under assessment in the management of hypertension. Verapamil does not cause a reflex tachycardia or a rise in plasma renin[11]. Further, it appears to have a post-capillary vasodilator affect which prevents fluid retention and oedema[12]. However, it has profound depressive effects on AV-conduction and pacemaker function and has a negative inotropic action[13]. In contrast, nifedipine causes oedema[10], and an increase in catecolamines and heart rate[14]. It has little affect on myocardial smooth muscle. Verapamil is as effective in lowering blood pressure as a beta-blocker[11] and these drugs have a place in the treatment of hypertension in patients suffering from angina. Further, nifedipine has a rapid onset of action when given sublingually and may have a role in the treatment of severe hypertension. The hypotensive effect of oral nifedipine is short, at present four daily doses are used to control blood pressure[10], and this may limit it's usefulness.

The rapid onset of action of parenteral vasodilators has led to their use in the treatment of hypertensive emergencies. However, studies in renal and spontaneously hypertensive rats have demonstrated that rapid reduction of blood pressure to levels at which autoregulation of cerebral flow fails causes ischaemic brain damage[15]. The range of mean arterial pressure over which auto-regulation occurs is 60-120 mmHg in normotensives rising to 120-160 mmHg in patients with hypertension. When blood pressure rises above these limits, cerebral oedema may occur. Thus, this mechanism protects the hypertensive patient. Below these limits, ischaemic brain damage occurs due to a fall in cerebral blood flow. Although protected from cerebral oedema, the hypertensive patient is susceptible to cerebral oedema, the hypertensive patient is susceptible to cerebral ischaemia with acute reduction of blood pressure[16,17]. Gradual reduction of blood pressure may allow return of some autoregulatory control.

Diazoxide is one of the agents frequently used in the treatment of hypertensive crisis. However, the highly variable duration of action (2-12 hours) and abrupt onset of effect with this drug when given by bolus injection makes its use hazardous[16]. Similarly, hydralazine has a rapid onset (15 mins) and prolonged duration of action after intravenous injection but there is a considerable individual variation in response to hydralazine and both hydralazine and diazoxide cause a reflex tachycardia. In contrast, nitroprusside, a combined venous and

arterial vasodilator with a rapid onset of action, is rapidly metabolized so that discontinuation of an infusion results in return to pre-treatment blood pressure within 5 minutes. It's action can, therefore, be terminated at will. Furthermore, there is a linear log-dose response relationship so that blood pressure can be maintained at the desired level, and reflex tachycardia does not occur in the supine position[3].

The high prevalence of raised blood pressure in patients over 65 years of age (approximately 50% have a blood pressure in excess of 160/95 mmHg) and the high mortality in elderly hypertensives from cardiovascular disease, points to possible benefits of antihypertensive treatment in this group[18]. Previous studies suggest that a reduction in hypertensive complications may occur with treatment in elderly subjects but a number of multicentre trials are now under way. Disproportionate systolic hypertension is more common in elderly than young hypertensives, as a result of reduced large vessel compliance[18]. Drugs which reduce systolic and diastolic pressure equally may compromise blood flow so that drugs which have a greater effect on systolic pressure may be particularly appropriate in this age group. Nitroprusside reduces systolic blood pressure possibly through an increase in aortic compliance[19]. Furthermore, response to vasodilators is partly determined by activity of the baroreflex which is depressed in elderly subjects[20]. We compared heart rate responses in elderly and young hypertensives to a nitroprusside infusion. The increase in heart rate was much less marked in the elderly group. Thus, vasodilators may have a particular role in the treatment of elderly hypertensives.

The effect of antihypertensive therapy on renal function is of concern not least in patients with pre-treatment renal impairment. To date neither hydralazine nor prazosin have been shown to have an adverse effect on renal function. Nitroprusside has a variable affect on PAH clearance and reduces GFR slightly[21]. In a few cases renal impairment has disimproved on captopril. In studies with minoxidil, renal blood flow was shown to be impaired acutely but with chronic treatment renal blood flow improved despite large reductions in blood pressure[22].

In conclusion, vasodilators continue to be of practical and theoretical interest in the management of hypertension. Most current interest centers on the calcium antagonists whose efficacy as

antihypertensive agents has been documented. Their use is facilitated by their lack of significant reflex effects and their effectiveness in the treatment of some cases of angina. The role of vasodilators in the management of hypertensive emergencies is being reassessed in view of the evidence that they are being used too aggressively. The position of minoxidil is now well established as being in resistant hypertension, a role also suited to captopril. The promise of vasodilators that combine dilatation with additional properties such as beta-blockade or a diuretic effect generates continued interest in this group of drugs.

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