Combination therapy with β -adrenoceptor blockers and calcium antagonists

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- 1 Verapamil and nifedipine enhance the hypotensive and anti-anginal effects of β -adrenoceptor blocking drugs.
- 2 The combination of β -adrenoceptor blocking drugs with nifedipine may pose fewer safety problems than the combination with verapamil especially in ischaemic heart disease when left ventricular function is suspect.
- 3 Verapamil as a single agent may be as effective as a β -adrenoceptor blocking drug in angina and provide a suitable alternative.
- 4 Careful supervision is required when verapamil is combined with β -adrenoceptor blockers for both angina and hypertension but reported clinical problems in hypertension are few.

Keywords β -adrenoceptor antagonists verapamil nifedipine

Introduction

Verapamil was the first 'calcium antagonist'. This term was applied by Fleckenstein to compounds that inhibited the slow influx of calcium necessary for the contraction of myocardial and vascular smooth muscle cells. From their coronary and peripheral vasodilatory properties together with their negative inotropic effect he predicted their future use in hypertension and in angina pectoris (Fleckenstein, 1971, 1977). At that time β -adrenoceptor blocking drugs were becoming established as the first line treatment for both conditions and, in general, they have proved to be effective and safe in long term use (Symposium on beta blockers in the 1980s, 1983). The modes of action of β -adrenoceptor blockers and calcium antagonists clearly are very different and, recently, new concepts about the pathophysiology of angina and hypertension has led to a reappraisal of traditional therapeutic strategies (Dargie *et al.*, 1981). Thus, calcium antagonists are now being used with increasing frequency as single agents to treat both conditions and the differing and possibly complementary pharmacologic profiles of β -adrenoceptor blockers and calcium antagonists have pointed to a potentially beneficial drug interaction. Since calcium influx

is important also in the generation of normal pacemaker activity in the sinus node and in the conduction of these impulses through the atrio-ventricular node (Fleckenstein, 1971) and since sympathetic activity also facilitates these mechanisms and promotes myocardial contractility the possibility of adverse cardiac interactions arises. However, the calcium antagonists are a heterogeneous group of compounds and this is reflected in their differing effects on contractility, conduction and arterial tone in man (Henry, 1980; Nayler, 1980).

In this paper the current status of β -adrenoceptor blocker/calcium antagonist combinations in hypertension and angina is reviewed with particular reference to verapamil and nifedipine.

Hypertension

Although β -adrenoceptor blocking drugs have been a first line therapy in hypertension for many years, their mode of action remains disputed though it is clear that they do not reverse the primary haemodynamic abnormality (at least directly) which is increased peripheral vascular

resistance. Prior to the advent of β -adrenoceptor blockers the peripheral vasodilators such as hydralazine had largely been abandoned not only because of specific drug toxicity but also because reflex tachycardia and increased myocardial contractility opposed their hypertensive effect (Koch-Weser, 1974). But the arrival of the β -adrenoceptor blockers which could prevent these effects of increased sympathetic activity encouraged the reappraisal of hydralazine and facilitated the introduction in refractory hypertension of the more powerful vasodilator, minoxidil (Dargie *et al.*, 1977; Mackay *et al.*, 1981) as third drugs in a stepped care approach. Thus the concept of combined vasodilator/ β -adrenoceptor blocker therapy was well established before calcium antagonists were introduced. They seemed particularly attractive because they had the potential to dilate the coronary as well as the peripheral circulation thus enhancing the 'cardio protective' image already established with β -adrenoceptor blockers in anti-hypertensive therapy, though this may have been more imaginary than real.

Nifedipine

In a double-blind controlled study in patients with angina the potential use of the combination in hypertension was evident (Harris *et al.*, 1982). The individual and combined effects of nifedipine and propranolol were investigated in a double-blind placebo controlled trial in which the order of treatments was determined by a balanced latin square. Propranolol and nifedipine each lowered supine and standing blood pressure to a similar extent but the effects of the combination were additive and significantly greater than either drug alone (Figure 1). The blood pressure responses to cold pressor stimulation and to mental arithmetic also were blunted especially by the combination.

The additive effects on blood pressure have since been confirmed in patients with hypertension; for example in a double-blind study in which nifedipine was added in patients whose blood pressure was inadequately controlled on a combination of β -adrenoceptor blockers and diuretics, the combination significantly improved blood pressure control (Bayley *et al.*, 1982).

Verapamil

In the current wave of enthusiasm for calcium antagonists in hypertension it is salutary to remember that the efficacy of verapamil in hypertension was established in a well designed double-

Figure 1 Average falls in supine systolic (SBP) (■) and diastolic (DBP) (□) blood pressure on propranolol 480 mg day⁻¹ (P), nifedipine 60 mg day⁻¹ (N) and the combination (N+P), compared with placebo, $n = 18$. (Harris *et al.*, 1982). * $P < 0.01$ vs placebo, ** $P < 0.01$ vs propranolol.

blind placebo controlled study several years ago (Lewis *et al.*, 1978). Although this has been confirmed in more recent studies there are few double-blind controlled studies of the combination of verapamil and β -adrenoceptor blockers in hypertensive patients. The efficacy and safety of verapamil in combination with propranolol was investigated in patients with mild to moderate hypertension; some of these data have been reported elsewhere (McInnes *et al.*, 1985). The falls in erect and supine blood pressures are shown in Figure 2 and while all treatments significantly reduced the diastolic blood pressure the effect of the combination of verapamil and propranolol was significantly greater than either drug alone. Propranolol reduced the resting heart rate and the addition of verapamil to propranolol reduced this further from 63.3 ± 9 beats min⁻¹ to 56.9 ± 8.4 ($P < 0.005$) when compared to propranolol alone. All treatments increased the PR interval slightly but this was significant only on the combination which increased it from 154 ± 27.7 ms on placebo to 185.5 ± 35.3 . During 24 h ambulatory monitoring the minimum heart rate was reduced by all active treatments but heart rates less than 50 beats min⁻¹ were seen in some subjects in all phases including placebo.

The combination significantly increased the echocardiographic left ventricular end diastolic and end systolic dimensions though this effect was small and no change in the echo ejection phase indices occurred.

Figure 2 Falls in supine systolic (■) and diastolic (□) blood pressure on propranolol 240 mg day⁻¹ (P), verapamil 360 mg day⁻¹ (V) and the combination (V+P), *n* = 14. (McInnes *et al.*, 1985). *P < 0.01 vs placebo, **P < 0.01 vs propranolol.

Angina pectoris

In the past decade β -adrenoceptor blockers have dominated the medical treatment of angina because they are very effective in exercise induced myocardial ischaemia. β -adrenoceptor blockers do not improve coronary blood flow. It could be argued that calcium antagonists would be a more appropriate treatment for angina since they have the potential to increase coronary blood flow (Fleckenstein, 1971; Engel & Lichtlen, 1981; Singh *et al.*, 1978). Indeed, the concept that transient increases in coronary arterial tone could cause myocardial ischaemia was a principal reason for the initial interest in calcium antagonists. However in angina the coronary arterioles are believed to be maximally dilated, at least during exercise, and there is considerable debate about the degree to which the atheromatous large main stem coronary arteries are susceptible to vasoconstrictor stimuli or indeed vasodilation by calcium antagonists (Kaltenbach *et al.*, 1979). Nonetheless the potential for coronary vasodilation by the calcium antagonists either in promoting better myocardial perfusion during exercise or preventing vasoconstriction, together with the favourable effects of peripheral arteriolar dilation in reducing left ventricular afterload, promise an important anti-anginal effect; it also suggests a beneficial drug interaction with β -adrenoceptor blockers whose primary action is to reduce myocardial oxygen demands.

Nifedipine

There are few double-blind placebo controlled trials in which the combined effect of nifedipine and β -adrenoceptor blockers have been studied but of these, three are of special interest because they illustrate some general points about anti-anginal trials, in addition to defining the role of nifedipine in the practical management of angina. In the first (Kenmure & Scrutton, 1980), recording of the simple but important clinical variables of angina frequency and nitrate consumption showed that although combination therapy with propranolol and nifedipine was significantly more effective than placebo or nifedipine alone it was only slightly better than propranolol alone. The second study (Ekelund & Oro, 1979), also suggested a small improvement in symptoms on the combination compared with β -adrenoceptor blockers alone. Exercise tolerance was greater during the combination though no data on electrocardiographic indices of ischaemia were reported. The combination phase came at the end of the trial in each patient so an order effect may have contributed to the apparent improvement. In the third study (Lynch *et al.*, 1980), the objective indices used (24 h ambulatory monitoring of the ST segment and exercise testing using precordial ST segment mapping) allowed clear separation of individual drug effects and identification of the added effects of the combination (Figure 3). These data showed conclusively that the combination, which reduced exercise ischaemia and episodes of ischaemia on ambulatory monitoring (many of which are painless) by 90 and 95%, respectively, was better than either drug alone. Propranolol was better than nifedipine and there was no difference in the two doses of propranolol which were 240 and 480 mg day⁻¹. By contrast the subjective indices of chest pain and nitrate consumption were only slightly (but significantly) better on the combination than on propranolol alone which in turn was superior to nifedipine alone. These studies underline the difficulty in demonstrating an improvement when combination therapy is compared with an effective treatment like β -adrenoceptor blockade in effort related angina pectoris and the importance of using objective techniques which detect ischaemia electrocardiographically rather than relying solely on the subjective data. Moreover it is important to record the severity of ischaemia during exercise as well as the exercise time or work done which could be influenced by factors other than ischaemia such as tiredness of the legs on β -adrenoceptor blockers. Also they suggest that rather than being prescribed as a single agent in chronic stable angina nifedipine may

Figure 3 Episodes of ST segment depression during 48 h ambulatory monitoring on placebo, nifedipine 60 mg day⁻¹ (N), propranolol 480 mg day⁻¹ (P) and the combination (N+P), $n = 16$. (Lynch *et al.*, 1980). * $P < 0.005$ vs placebo, ** $P < 0.0025$ vs placebo, *** $P < 0.01$ vs propranolol.

be used to best advantage in combination with a β -adrenoceptor blocker.

Verapamil

Four placebo controlled studies of verapamil and propranolol have shown that the combination is superior to either drug alone (Leon *et al.*, 1981; Balasubramanian *et al.*, 1982; Winniford *et al.*, 1983; Findlay *et al.*, 1984). The doses of verapamil ranged from 320 to 480 mg day⁻¹ which is much higher than recommended initially. In three of these studies (Leon *et al.*, 1981; Balasubramanian *et al.*, 1982; Winniford *et al.*, 1983) the combination was used when monotherapy had failed to control the symptoms. All these studies confirmed that combination therapy had additive effects and was superior to either drug alone using both subjective and objective criteria of efficacy. In the fourth study verapamil, atenolol and that combination were compared in a double-blind placebo controlled study of identical design to that with nifedipine already described (Findlay *et al.*, 1984). The objective indices confirmed the superiority of the combination and also confirmed earlier studies showing that verapamil was as effective as the β -adrenoceptor blocker in reducing exercise induced ischaemia (Figure 4).

Potential adverse effects

Myocardial depression

While all the currently available calcium an-

Figure 4 Episodes of ST segment depression during 24 h ambulatory monitoring on placebo, verapamil 360 mg day⁻¹ (V), atenolol 100 mg day⁻¹ (A) and the combination (V+A), $n = 15$. * $P < 0.05$, ** $P < 0.01$.

tagonists nifedipine, verapamil and diltiazem share vasodilatation as their main pharmacological property nifedipine is the most potent in this respect both experimentally and clinically (Fleckenstein, 1971; Henry, 1980). In patients with normal left ventricular function this results in a rise in cardiac output when nifedipine is given alone (Kurnik *et al.*, 1984) while the acute administration of verapamil usually does not increase cardiac output despite peripheral vasodilation, implying a negative inotropic effect; indeed a fall in left ventricular dp/dt can be seen transiently after intravenous injection (Singh & Roche, 1977). These haemodynamic differences probably reflect both the more potent arteriolar dilating effects of nifedipine and the greater intrinsic negative inotropic effect of verapamil and may assume greater importance when calcium antagonists are added to a background of β -adrenoceptor blockade; a small increase in cardiac output occurs with nifedipine despite a fall in LV dp/dt (Joshi *et al.*, 1981) while indices of contractility decrease with verapamil (Winniford *et al.*, 1982). The potential for myocardial depression during long term oral combination therapy may be greater with verapamil than with nifedipine and indeed in a double-blind study with verapamil and atenolol one patient in whom left ventricular function was impaired prior to treatment developed frank left ventricular failure on the combination (Findlay *et al.*, 1984); this complication seems less common in patients with normal left ventricular function prior to treatment in whom ejection fraction responses have remained unchanged (Leon *et al.*, 1981; Winniford *et al.*, 1983). In such patients an increase in echocardiographic dimensions has been demon-

strated in a double-blind placebo controlled study in hypertensives though no change in the echo ejection phase indices occurred (McInnes *et al.*, 1985). In most studies both in hypertension and ischaemic heart disease doses of β -adrenoceptor blockers and verapamil which conventionally could be described as maximal have been used. In clinical practice the addition of lower doses of one drug to the other would be more usual and probably safer.

There are anecdotal reports of cardiac failure with the combination of nifedipine and β -adrenoceptor blockers (Gillmer & Kark, 1980; Anastassiades, 1980) though studies in patients with good left ventricular function have been reassuring (Rowland *et al.*, 1983). There are few data with this combination in patients with impaired left ventricular function in whom removal of the sympathetic drive by concomitant β -adrenoceptor blockade could be disadvantageous.

Moreover there is little evidence that the addition of nifedipine might improve cardiac function in patients with poor left ventricular function who are already receiving a β -adrenoceptor blocker.

Conduction effects

In vitro, sinoatrial automaticity and atrioventricular nodal conduction are depressed by both nifedipine and verapamil but only verapamil affects these in man (Rowland *et al.*, 1979). Since sympathetic activity enhances both functions the combination of β -adrenoceptor blockers and verapamil could depress sinoatrial and AV nodal function further. This has been documented in patients with ischaemic heart disease in some studies (Findlay *et al.*, 1984; Winniford *et al.*, 1982) but not in others (Leon *et al.*, 1981). There is very little information avail-

able on electrophysiological variables in patients with hypertension but in a double blind study the combination of verapamil and propranolol significantly prolonged the PR interval though ambulatory monitoring revealed no important bradyarrhythmias or heart block (Findlay *et al.*, 1984).

Conclusion

Combination therapy with β -adrenoceptor blockers and calcium antagonists is very effective both in hypertension and angina and double-blind controlled studies have confirmed that this is more effective than β -adrenoceptor blockers alone. When safety aspects purely are considered, the more obvious combination is that of nifedipine and a β -adrenoceptor blocker. But in patients with good left ventricular function and normal sinoatrial and atrioventricular nodal function, as in the majority with hypertension, serious clinical problems directly related to combination therapy with either nifedipine or verapamil and β -adrenoceptor blockers are likely to be few. In those patients in whom left ventricular function is impaired great caution is required especially with verapamil and β -adrenoceptor blockers though in some refractory patients appropriate dosing and monitoring of the effects can result in substantial improvement.

In general the results of clinical studies with calcium antagonists alone are consistent with the predictions made from observations on their basic pharmacology many years ago. The recent and increasing use of these drugs in combination with β -adrenoceptor blockers has posed a new set of problems that will be answered only by further clinical experience which, thus far, is promising; perhaps surprisingly, there have been few serious clinical problems.

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