Tolerability of combined treatment with verapamil and beta-blockers in angina resistant to monotherapy

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Summary: We have used a combination of a beta-blocker and verapamil to treat 42 consecutive patients with angina resistant to either agent alone. Patients with heart failure, heart block or uncontrolled hypertension were excluded. The mean duration of follow-up was 6.5 months. Thirty-six patients (81%) reported an improvement and the number of angina attacks was reduced from 17/week to 5/week. Side effects necessitated withdrawal of one or both drugs in 6 patients, 2 of whom developed bradyarrhythmias not solely related to drug treatment. The most common complication was mild left ventricular failure (6) treated by reducing or stopping the beta-blocker. The data suggest that the combination of verapamil and a beta-blocker may be used in a relatively unselected group of patients with difficult angina. However, as dosage adjustment and close observation may be necessary to minimise side effects, the use of this combination should be limited to hospital practice.

Introduction

Beta-adrenoceptor antagonists have been considered the cornerstone of anti-anginal therapy. More recently, calcium antagonists such as nifedipine and verapamil have offered an alternative form of treatment. When a single agent is used to treat angina of effort verapamil is at least as effective as a beta-blocker and both may be superior to nifedipine (Livesley *et al.*, 1973; Lynch *et al.*, 1980; Bala Subramanian *et al.*, 1982a; Leon *et al.*, 1981; Johnson *et al.*, 1981). However, when symptoms are resistant to a beta-antagonist alone most authorities recommend the addition of nifedipine (Opie, 1980a; Lewis, 1981; Geddes, 1983). This is because of the theoretical risk of an interaction between beta-blockers and verapamil which may predispose to cardiac failure or heart block. Although such complications have occurred particularly after intravenous use of these agents (Lewis, 1981; Packer *et al.*, 1982a; Packer *et al.*, 1982b; Kieval *et al.*, 1982) recent short-term studies have suggested that combined oral therapy is both safe and effective (Leon *et al.*, 1981; Bassan *et al.*, 1982). However, there is little information on the long-term tolerability of this combination in a relatively unselected group of patients. Therefore we report our ex-

perience with long-term combined use of beta-blockers and verapamil in consecutive patients with effort angina not controlled with either agent alone. The results suggest that the tolerability of the combination is sufficiently good to permit its use in hospital practice.

Patients and methods

Forty-two consecutive patients were treated with beta-blocker and verapamil when their anginal symptoms had not responded adequately to treatment with optimal dose monotherapy with either agent. There were 32 men and the mean age was 59 y (range 42–77 y). No patient had evidence of heart failure, uncontrolled hypertension or heart block (PR interval >0.24 s). Fifteen patients (36%) complained of episodes of chest pain at rest and 2 of these were admitted for the addition of verapamil (120 mg t.d.s.) because of the severity and frequency of symptoms. Twenty-nine patients had a past history of hypertension, 26 of whom were receiving diuretics. Initial daily drug treatment was atenolol 100 mg (31), or 50 mg (2), propranolol 160 mg (4), pindolol 20 mg (1), metoprolol 100 mg (1), or verapamil 360 mg (3). The decision to add verapamil was taken if patients were receiving the British National Formula recommended ceiling dose of atenolol (100 mg) or if they were taking a maximum tolerated dose of beta-blocker. Sitting

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heart rate in the clinic (see Results) suggests adequate compliance.

Unequivocal evidence of coronary artery disease in 33 patients was demonstrated by at least one of the following criteria; transmural myocardial infarction (17), abnormal coronary arteriography (4) or a positive stress test on treadmill exercise, (> 1 mm ST depression) (17). In 9 patients exercise tests were either non-diagnostic (2), terminated because of claudication (2) or not performed (5) (2 of these had left bundle branch block).

Protocol

All but 2 patients were treated as out-patients. Those taking a beta-blocker were generally commenced on verapamil 80 mg t.d.s. and were instructed to increase the dose to 120 mg t.d.s. after one week if symptoms had not resolved and if they were free from side effects. Atenolol 100 mg daily was added to verapamil monotherapy in 3 cases. Patients were seen initially every 2 weeks to assess symptoms of angina and heart failure and to exclude conduction disturbances on ECG. The PR interval was measured from lead II of the ECG recorded at 50 or 100 mm/s on monotherapy and after 4 weeks on dual therapy with a view to withdrawing patients on heart block as defined above.

The assessment of anti-anginal response to treatment was made on the history alone (including angina diary cards in those studied prospectively). Tolerability of the combination was determined from the need for an alteration in drug dosage. Patients were seen by only one of the 3 co-authors who were alert to the theoretical risks of cardiac failure and bradyarrhythmias. Data from the first 31 subjects was analysed retrospectively but the last 11 patients have been studied prospectively. The protocol was approved by the Hospital Ethics Committee.

Results

The patients have been followed for up to 15 months (mean 6.5 months). The maximum daily dose of verapamil was 240 mg in 11, 360 mg in 29 and 480 mg in 2 patients.

Angina symptoms were improved in 34 patients (81%). In those tolerating the combination for one month, the mean number of anginal attacks decreased from 17 per week on monotherapy to 5 per week on dual treatment. Six patients were resistant to additional treatment.

Heart rate tended to fall with dual therapy, but this reduction was not statistically significant (paired 't' test, $n = 38$, Table I). The mean resting heart rate on monotherapy was 62 ± 12 beats/min suggesting that patients were probably receiving adequate beta-

Table I Mean values (s.d.) of blood pressure, heart rate and PR interval measured before and after one month's dual therapy in 38 patients.

	<i>Monotherapy</i>	<i>Dual Therapy</i>
Systolic blood pressure – mmHg	143(24)	137(25)
Diastolic blood pressure – mmHg	84(7)	78(10)
Heart rate beats/min	62(12)	56(15)
PR interval (s)	0.16(0.02)	0.18(0.03)

blocker therapy. Nine patients had a sinus bradycardia < 50 beats/min on dual therapy compared to 4 on beta-blocker alone. None of the latter 4 patients experienced any further reduction in heart rate with the addition of verapamil. No alteration in drug dosage was necessary for sinus bradycardia.

Blood pressure and PR interval did not change significantly (paired 't' test) after one month's dual therapy (Table I). No patient was withdrawn because of PR interval prolongation > 0.24 s.

Tolerability

There were 2 early withdrawals. Verapamil was withdrawn in one patient after 2 days of dual treatment because of non-specific symptoms. The second patient had been admitted for addition of verapamil 360 mg daily to metoprolol 50 mg b.d. because of crescendo angina. He developed an inferior myocardial infarction complicated by complete atrioventricular dissociation within 2 days of admission. He responded to temporary cardiac pacing and withdrawal of both drugs.

Of the remaining 40 patients an alteration in drug dosage was necessary in 10, because of mild left ventricular failure (6), nodal bradycardia (1), postural hypotension (1) or tiredness (2). The last 2 symptoms resolved on a reduction in the dose of beta-blocker. Nodal bradycardia occurred in a man who had been symptom free for 6 months on atenolol 100 mg and verapamil 360 mg daily. He 'collapsed' and was found to have a nodal bradycardia (rate 44 beats/min) on admission to another hospital where both drugs were discontinued. He returned to sinus rhythm and is now receiving verapamil alone. Coronary arteriography subsequently performed for uncontrolled angina has shown inoperable 2 vessel coronary artery disease.

Heart failure

Six patients complained of increased exertional dyspnoea on combined treatment and 3 of them had signs

of left ventricular failure. Symptoms invariably occurred within 2 weeks of increasing drug dosage. Factors which may have been related to left ventricular failure were previous hypertension (despite good control) (6), previous diuretic therapy (5), high drug dosage (verapamil 360 mg + atenolol 100 mg (5) and verapamil 480 mg + atenolol 200 mg (1)). However, previous myocardial infarction (3) and increased cardiothoracic ratio (3) were not more common in this group. Symptoms resolved on decreasing (3) or stopping (3) the beta-blocker.

Outcome

Five patients have suffered a myocardial infarction during dual therapy. Three occurred within 2 weeks of commencement, reflecting prior unstable features; one occurred at 9 months and one during coronary arteriography for drug resistance. Two other resistant patients have undergone coronary bypass surgery. There have been no deaths during the follow-up period.

Discussion

Beta-adrenoceptor antagonists and verapamil are probably the 2 most powerful agents used to treat effort angina (Livesley *et al.*, 1973; Bala Subramanian *et al.*, 1982a; Johnson *et al.*, 1981). They have different modes of action and hence their combined use should be effective in patients with symptoms resistant to monotherapy. However, experience with the combination is limited because of fears that it may be associated with serious cardiac side effects. Short-term studies have confirmed the efficacy of this combination without significant toxicity (Leon *et al.*, 1981; Bassan *et al.*, 1982). The only reported chronic study using this combination in angina supports the findings of shorter studies with drug withdrawal in only one of 14 patients because of mild heart failure (Bala Subramanian *et al.*, 1982b). That study was of necessity highly selective excluding patients with severe or unstable angina, recent myocardial infarction, those receiving diuretics and the elderly. Furthermore the follow-up period was only 4 weeks. Ours is a large, long-term study reflecting the tolerability of the combination in a relatively unselected group of patients. Exclusions were based only on symptoms and signs of heart failure, uncontrolled hypertension and on electrocardiographic evidence of atrioventricular conduction delay.

The combination appeared more effective than a single agent. However, the finding that 81% reported a clinical improvement must be interpreted with caution since there were no controlled data and the assessment was purely subjective with no confirmation by objec-

tive tests such as treadmill exercise tolerance.

In contrast the absence of control data is likely to over-estimate the number of drug related withdrawals since some may have been due to the disease itself or to the use of a single agent. This is particularly so with the 2 serious arrhythmias encountered. One patient developed a nodal bradycardia after 6 months successful treatment. The other developed complete arterio-ventricular dissociation with the addition of verapamil in association with an acute inferior myocardial infarction. Although inferior myocardial ischaemia alone may be associated with this arrhythmia, it seems likely that it was precipitated by the combined use of verapamil plus a beta-blocker. Hence, extreme caution should be employed when prescribing these drugs concurrently in clinical situations known to predispose to such events. However, both published studies on multiple dose treatment with propranolol plus verapamil (Leon *et al.*, 1981; Bassan *et al.*, 1982) suggest that the incidence of serious conduction disturbances (i.e. requiring withdrawal or > 1st degree heart block) is no more frequent than that observed with verapamil alone. In common with these workers we observed no significant increase in PR interval or in the incidence of symptomatic sinus bradycardia with additional treatment.

The most frequent adverse effect complicating this form of dual therapy was mild heart failure. It occurred in 15% of patients emphasising the need for close observation, particularly in the initial period. In all cases symptoms resolved on reducing or stopping the beta-blocker. High drug dosage seems the major factor responsible but providing patients are seen soon after increasing drug treatment the risk of severe symptoms is small. All patients reporting dyspnoea had hypertension. This may reflect the population studied or the poorer prognosis of ischaemic heart disease when complicated by hypertension, treated or untreated (Graham *et al.*, 1978; Frank *et al.*, 1968).

It is important now to determine the place of this drug combination in patients resistant to monotherapy. They are unlikely to respond to nifedipine alone but may do so with the combination of beta-blocker and nifedipine which is more effective than either drug alone (Lynch *et al.*, 1980). Whether this combination is superior to that of beta-blocker plus verapamil is unknown. There is definitely no increased risk of conduction abnormalities with nifedipine which must encourage its use in combination with a beta-blocker. However, it is not clear whether the need for careful dose titration (Deanfield *et al.*, 1983) and the precipitation of angina (Bala Subramanian *et al.*, 1982a; Deanfield *et al.*, 1983) encountered with nifedipine monotherapy, remain when a beta-blocker is added. In addition anecdotal reports of cardiovascular side effects with this combination (heart failure, hypotension and angina) (Opie and White 1980b;

Anastassiades, 1980)) suggest that close observation may be necessary.

In summary therefore, we have shown that the combination of a beta-blocker and verapamil may be used in a relatively unselected group of medical out-patients with difficult angina. Withdrawal of one of these drugs was necessary in 6 (14%) and 5 of these

patients had cardiac side effects. This figure is similar to that reported anecdotally by Subramanian in a series of 40 patients (Bala Subramanian *et al.*, 1982b). However, greater experience is required and the use of this combination must be restricted to hospital practice and probably to patients intolerant of other drug combinations.

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