Management of unstable angina at rest by verapamil

A double-blind cross-over study in coronary care unit

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SUMMARY A therapeutic trial with verapamil, a calcium-antagonist drug, was performed in 12 patients admitted to our coronary care unit because of frequent daily attacks of angina at rest attributed to coronary vasospasm. After a 48-hour run-in period, oral verapamil 480 mg/day and placebo were administered alternately during 4 randomised 48-hour periods. Transient ischaemic attacks with ST segment elevation or depression, with or without pain, were documented by continuous electrocardiographic monitoring. The number of attacks during the run-in and 2 placebo periods were 128, 123, and 130, respectively, and 31 and 23 during the 2 treatment periods ($P < 0.006$ and $P < 0.003$). This drug therefore appears to be effective in the management of patients with frequent attacks of angina at rest.

Although various forms of medical and surgical treatment have been proposed for the management of unstable angina at rest, the results are inconclusive (Cairns *et al.*, 1976) and often conflicting (Conti *et al.*, 1973; Bertolasi *et al.*, 1974; Hultgren, 1976; Selzer *et al.*, 1976; Clark *et al.*, 1977). This may be because the patients are selected on purely clinical criteria, rather than on criteria based on the pathogenetic mechanisms responsible for the onset of the anginal attacks; this method of selection leads to an inhomogeneous group of patients and treatment that is not rational. Rational therapy depends on recognition of the causes of the anginal attacks rather than on the clinical picture alone, which though it has prognostic significance has no clear pathogenetic implications.

Recent studies indicate that in patients with angina at rest, characterised by ST segment elevation or depression, the onset of the attacks cannot be attributed to an increase in the haemodynamic determinants of myocardial oxygen consumption (Guazzi *et al.*, 1971, 1975b; Maseri *et al.*, 1975a, b). In these patients myocardial scintigraphic studies have shown a massive transmural reduction of myocardial tracer uptake during the attacks, associated with ST segment elevation (Maseri *et al.*, 1976; Parodi *et al.*, 1978) or a diffuse or ill-defined reduction of tracer uptake during episodes of angina at rest with ST segment depression (Severi *et al.*, 1977). This reduction of myocardial perfusion appears to be related to either:

(1) severe vasospasm of a major coronary branch, when the perfusion deficit is transmural and the ST segment is elevated, or (2) less severe spasm or a spasm of a small branch or spasm in the presence of collaterals, when reduction of perfusion is not transmural and the ST segment is depressed (Marzilli *et al.*, 1977; Maseri *et al.*, 1977b; Parodi *et al.*, 1977).

Beta-blockers and coronary bypass surgery, which are the most commonly adopted therapeutic approaches (Cairns *et al.*, 1976), may not be the rational treatment in those patients with proven vasospastic angina with the clinical characteristic of 'unstable' angina at rest or of 'crescendo' angina.

In preliminary clinical trials we had the impression that verapamil¹, a calcium-antagonist with relaxing properties on large coronary arteries (Golenhofen and Lammel, 1972; Haeusler, 1972), was effective in reducing the number of anginal attacks in those patients. Hence we decided to undertake a double-blind cross-over study with this drug on patients having continuous electrocardiographic monitoring in a coronary care unit (CCU).

Subjects and methods

PATIENTS

We studied 12 patients (34 to 70 years old, average 54 years) admitted to our CCU because of recurrent, frequent daily episodes of angina at rest, which began from 3 months to 10 days before admission.

Table 1 *Physical, clinical, electrocardiographic, coronary arteriographic, and myocardial scintigraphic characteristics of patients*

Case no.	Age (y)	History		Electrocardiogram
		Onset of symptoms	Exercise tolerance	Basal
1	61	1 month (rest)	Good	Negative T V2-V5
2	70	10 days (rest)	Good	0.5 mm ST $\downarrow$ V4-V6
3	49	2 months (rest and effort)	Moderate	Negative T II, III, aVF
4	63	1 year (effort) 3 months (rest)	Moderate	Normal
5	61	6 years (effort) 10 days (rest)	Poor	Negative T I, II, III, aVF, V3-V6
6	60	7 months (effort) 1 month (crescendo)	Poor	Nondiagnostic (documented anterior and posterior infarction in previous tracing)
7	38	1 month (rest)	Good	Negative T I, II, aVL, V1-V2
8	50	2 months (rest)	Good	Normal
9	34	3 months (rest and effort)	Moderate	Incomplete RBBB and LAH
10	63	3 years (effort) 1 month (rest)	Poor	Q II, III, aVF, 0.5 mm ST $\downarrow$ V4-V6 I, aVL
11	48	3 months (effort) 1 month (rest)	Moderate	Negative T V1-V4
12	53	1 month (crescendo) 9 months (rest)	Good	Negative T V1-V4, aVL

LMS, left main stem; LAD, left anterior descending; LCA, left circumflex artery; LMB, left marginal branch; LDB, left diagonal branch; RCA, right coronary artery; RBBB, right bundle-branch block; LAH, left anterior hemiblock.

--- Not performed.

We excluded from the study patients with anginal episodes of long duration (more than 10 to 15 minutes).

The main physical, clinical, and electrocardiographic characteristics of the patients, the results of coronary angiography, and of thallium-201 myocardial scintigraphic studies are reported in Table 1. Two had had a documented old myocardial infarction, 7 and 25 months before admission. None had a history or clinical signs of congestive heart failure on admission. The electrocardiographic abnormalities during the anginal attacks were ST segment elevation in 6 patients, ST segment depression in 4, and alternate episodes of ST segment elevation and depression in the same leads in 2. Seven patients had in addition asymptomatic episodes of ST segment changes similar to those accompanied by pain. Coronary arteriography was performed by the Judkins technique (1968) in 9 patients. In 6 patients in whom contrast injections could be made during an anginal attack, coronary artery spasm was shown angiographically. The attack occurred spontaneously in 2 and was induced by ergonovine in the other 4. In 1 patient the ergonovine test (0.2 mg in 2 doses of 0.05 mg and 0.15 mg at 10-minute intervals) was negative, while the other 2 did not consent to the test. A massive reduction of myocardial perfusion during a spontaneous anginal attack was documented

in all the 8 patients in whom thallium-201 could be injected at the beginning of an ischaemic episode. In 3 patients no direct evidence of a sudden reduction of myocardial blood supply was obtained, as the appropriate studies could not be performed because of failure of the equipment or lack of isotope. However, these patients had no history of effort angina, and repeated measurements of heart rate and systemic blood pressure at the very beginning of the ST segment changes or before the onset of pain failed to show any consistent change relative to control state. No haemodynamic change was observed at the onset of pain in the 3 patients (cases 9, 10, and 11) in whom left ventricular pressure was continuously monitored (Chierchia *et al.*, 1977).

DESIGN OF INVESTIGATION

Following the diagnostic evaluation, the 12 patients selected were kept in the CCU throughout the trial with continuous electrocardiographic monitoring of the lead showing the most obvious changes during the anginal attacks. After a 2-day control period on diazepam (2 to 5 mg 3 times daily), they entered the trial. This was composed of 4 2-day treatment periods, according to the following double-blind cross-over plan:

spontaneous attacks	Exercise	Asymptomatic episodes	Coronary arteriography		Myocardial scintigraphy
			Control	During angina	Location of cold areas during ischaemia at rest
T V2-V5	Positive T V2-V5	No	----	----	----
ST ↓ V4-V6	-----	Yes	-----	-----	-----
V4 ↑	2 mm ST ↓ V2-V5	Yes	75% LAD	LAD, LCA spasm	Anteroseptal, inferior
V4 ↓			75% LCA		
III, aVF ↑					
V5 ↑	3 mm ST ↑ V2-V4	Yes	50% + 75% LAD	LAD spasm	Anterior
			50% RCA		
ST ↓ I, II, III, aVF	-----	No	-----	-----	Anterior
ST ↓ V2-V6	3 mm ST ↓ V2-V6	No	90% LMS		Anterior, inferior
			75% LAD		posterior
			90% 1° LDB		
			75% LMB		
VL ↑ V1-V3	-----	No	90% LAD	-----	-----
VL ↑ V2-V6	Normal	Yes	90% LAD	LAD spasm	
			75% 2° LDB		
			50% LCA		
V5 ↓	3 mm ST ↓ V2-V6	Yes	90% LAD	LAD incomplete spasm	Anteroseptal
V6 ↓					
ST ↓ V4-V6	-----	No	75% LAD	-----	Anterolateral
			100% LCA		
			100% RCA		
V4 ↑	2 mm ST ↑ I, aVL	Yes	75% LAD	LAD spasm	Anteroseptal
			75% LMB		
V4 ↑ LAH	Positive T V1-V3	Yes	90% LAD	LAD spasm	Anterior
			100% RCA		

Treatment A₁: verapamil (80 mg) 1 tablet every 4 hours for 2 days (480 mg/24 h)

Treatment B₁: placebo 1 tablet every 4 hours for 2 days

Treatment A₂: verapamil (80 mg) 1 tablet every 4 hours for 2 days (480 mg/24 h)

Treatment B₂: placebo 1 tablet every 4 hours for 2 days.

The two sequences of treatments A₁, B₁, A₂, B₂ or

B₁, A₁, B₂, A₂ were randomised. Each period of treatment was started at 6 a.m.

During the whole period of the trial the paramedical CCU personnel were instructed to record the monitored lead during each episode of ST segment change and, whenever possible, a 12-lead electrocardiogram. Blood pressure was recorded every 4 hours and heart rate every 2 hours during periods free of ischaemic episodes and whenever

Table 2 Number of episodes per hour during run-in (C), treatment (A₁, A₂), and placebo periods (B₁, B₂)

Case no.	C		A ₁		B ₁		A ₂		B ₂	
1	5	2	0	0	1	1	0	0	1	1
2	2	3	0	2	1	2	0	0	3	3
3	3	3	2	0	7	4	1	0	2	8
4	6	8	0	4	0	4	0	0	0	5
5	1	3	0	0	0	2	0	0	3	1
6	1	2	0	0	3	2	1	1	2	4
7	4	4	1	3	6	1	1	0	1	5
8	8	6	0	1	4	18	5	0	8	7
9	23	6	1	1	20	11	4	0	14	21
10	4	7	0	0	7	5	4	0	7	7
11	10	4	1	3	6	6	1	0	7	8
12	5	8	2	10	6	6	2	3	10	2
Total in 24 hours	72	56	7	24	61	62	19	4	58	72
Total in 48 hours	128		31		123		23		130	

┌ P < 0.006 ─┘ ┌ P < 0.003 ─┘

there were ST segment changes. Serum enzymes (LDH, CK, SGOT (AST)) and creatinine, haemoglobin and blood count, chest x-ray films, standard electrocardiogram, and body weight were obtained every fourth day.

The patients were informed that neither the rationale nor the effectiveness of treatment of this syndrome were yet established and that, given the large spontaneous variability in the frequency of symptoms, the choice of a drug for long-term treatment would require objective demonstration of its efficacy. All gave their written consent to the trial.

A statistical evaluation of the significance of the results was carried out by the Wilcoxon matched-pair signed-rank test (Snedecor and Cochran, 1964).

Results

During the trial symptomatic and asymptomatic episodes of ST segment elevation or depression were recorded and were pooled in the statistical analysis. For each patient the total number of ischaemic attacks during the control, treatment, and placebo periods is reported in Table 2. Detailed results of the trial in the 12 patients are presented in Fig. 1 and 2.

No episodes were observed during both periods of treatment in 2 patients and during 1 of the 2 periods in 4. All the others except case 12 consistently showed an obvious reduction in the number of episodes.

For the group as a whole, the number of episodes during the 48-hour run-in period was not statistically different from that during the placebo periods (128 versus 123 and 130). By contrast, during each period of verapamil treatment, a highly significant reduction in the number of episodes was observed (31 and 23, $P < 0.006$ and $P < 0.003$). The reduc-

Fig. 1 Number, type, and time of occurrence of ischaemic episodes in 6 patients. C indicates run-in period; A₁ and A₂ treatment periods; B₁ and B₂ placebo periods. The broken line divides each 2-day placebo period into 2 24-hour periods. Circles and squares indicate episodes with ST segment elevation and depression respectively; closed and open symbols indicate symptomatic and asymptomatic ischaemic episodes respectively. The time (from 0600 hrs) is shown on the scale on the left of each set of data.

Fig. 2 Results of the trial in the other 6 patients (shown as in Fig. 1).

Fig. 3 The total number of episodes in 12 patients in each 48-hour period of the trial. C indicates run-in period; A₁, A₂ verapamil periods; B₁, B₂ placebo periods. Control and placebo periods show similar number and type of ischaemic episodes, while during treatment with verapamil there is a conspicuous reduction in frequency of all types of episodes.

tion was similar for the number of episodes with ST segment elevation and depression and for symptomatic and asymptomatic episodes (Fig. 3). Within each period the number of episodes during the first 24 hours was never significantly different ($P < 0.05$) from that observed during the second 24 hours.

There were no consistent changes in heart rate (average of 12 daily measurements) or length of PQ interval, and no conduction disturbances were observed. No significant biochemical changes

occurred. A slight reduction of arterial blood pressure (average of 4 daily measurements) was seen in 2 patients (cases 2 and 10) with mild systolic hypertension (Table 3).

SIDE EFFECTS

Muscle cramps and weakness were observed in case 10, constipation in cases 1 and 10, and transitory mental confusion in case 5.

FOLLOW-UP OF PATIENTS

All patients were maintained on verapamil (320 to 400 mg/day). One patient (case 7) had a small myocardial infarct in hospital after completion of the trial, while on verapamil (80 mg 3 times a day) and oral nitrates. Eight patients were discharged free of symptoms; the others had occasional anginal attacks (from 1 to 3 episodes per week). During follow-up (average 47 weeks), 7 patients were free of pain, 3 showed a reduction in the number of ischaemic attacks (cases 3, 4, and 6) (average 2 attacks/week); the follow-up of the last 2 patients is still in progress.

Discussion

Patients categorised clinically as unstable angina at rest constitute a heterogeneous group. Some with extremely limited exercise tolerance develop angina with any minimal increase of myocardial metabolic demand; in others with normal or variably reduced exercise tolerance, the anginal episodes at rest are caused by transient coronary vasospasm. Of all patients with angina at rest, those with extremely reduced coronary reserve (class IV angina pectoris of the Canadian Cardiovascular Society (Crochet *et al.*, 1975)) are a relatively small number. In fact, patients with 'variant' angina, for whom vasospasm can be con-

Table 3 Effects of verapamil on blood pressure, heart rate, and PQ interval, and side effects

Case no.	Blood pressure (mmHg)				Heart rate (beats/min)		PQ interval (s)		Side effects
	Placebo S	D	Verapamil S	D	Placebo	Verapamil	Placebo	Verapamil	
1	120	75	125	75	60	57	0.20	0.22	Constipation
2	175	100	160	100	56	62	0.20	0.20	
3	150	100	135	85	59	58	0.16	0.16	Transitory mental confusion
4	140	85	145	85	72	75	0.14	0.14	
5	110	70	115	70	73	69	0.14	0.18	
6	130	80	130	80	64	62	0.20	0.22	
7	120	85	140	85	82	72	0.20	0.22	Constipation, muscle cramps
8	130	85	130	80	69	68	0.12	0.12	
9	125	70	120	75	86	65	0.12	0.14	
10	170	90	150	90	76	74	0.14	0.15	
11	120	80	115	80	75	77	0.18	0.20	
12	125	85	120	80	76	71	0.16	0.16	

sidered a 'proven hypothesis' (Meller *et al.*, 1976), are found to be a sizeable fraction of those with angina pectoris at rest if appropriately searched for (Maseri *et al.*, 1977a, b). In addition, vasospasm has also been shown to be a cause of angina at rest with ST segment depression in patients with a variable degree of coronary atherosclerosis (Marzilli *et al.*, 1977; Maseri *et al.*, 1977a). Finally, it has been shown by continuous ambulatory electrocardiographic monitoring that the majority of patients with 'stable' angina have ischaemic episodes at rest or at considerably lower work loads than can be achieved during an exercise test; it was suggested that in these patients functional impairment of coronary blood supply capable of causing these anginal attacks may be superimposed (Schang and Pepine, 1977). The evaluation of the effectiveness of drugs on vasospastic angina is thus of practical interest.

There were several reasons for believing that anginal attacks at rest in our group of patients were not caused by an increase of myocardial demand: (1) Five patients had no history of exertional angina; of these 1 had a normal electrocardiographic stress test and 2 developed electrocardiographic signs of ischaemia only at high work loads; (2) in 3 patients continuous haemodynamic monitoring showed that no consistent increase of heart work preceded the onset of the ischaemic episodes; (3) in all patients systematic measurements of blood pressure and heart rate during asymptomatic electrocardiographic ischaemic episodes or at the onset of ST segment changes showed no consistent increase relative to the control periods.

Direct evidence for a vasospastic origin of the attacks was obtained in 9 patients: by both angiography and by myocardial scintigraphy in 5, by myocardial scintigraphy alone in 3, and by angiography alone in 1. In the other 3 patients there was no history of exertional angina, and no consistent increase in heart rate or blood pressure at the onset of anginal attacks. Two had typical 'variant' angina. Thus, all these patients appear to have a common mechanism responsible for the onset of their anginal attacks at rest, which cannot be attributed to an increase of myocardial metabolic demand beyond their coronary reserve. Though we cannot exclude other so far unidentified mechanisms, it is reasonable to infer that their attacks were caused by coronary vasospasm, in spite of the difference in the time of onset of angina, the extent of coronary atherosclerosis, and type of electrocardiographic ST segment change during ischaemia.

The study was carried out in the CCU both because of the severity of the patients' symptoms and because in this environment treatment could be

closely supervised and an objective unbiased record obtained of the response to treatment. We selected patients who were having several anginal episodes per day and studied 2 treatment periods alternating with 2 placebo periods, with the aim of comparing the extent and the consistency of the response of the individual patients with that of the group as a whole. We selected 48-hour periods, because of the 2 to 3 hour half-life in blood of the drug after its oral administration (Schomerus *et al.*, 1976), and because of possible carry-over effects of the drug. Longer periods of treatment were not adopted in view of the frequent spontaneous waxing and waning of the disease. We chose a higher than usual dose of the drug in order to overcome possible differences in absorption and to be reasonably certain that an adequate blood level was attained.

A non-parametric test was selected for the statistical evaluation of the results because of the possible lack of homogeneity of response among patients, as it should tend to reduce the influence of a few exceptional responders.

PREVENTION OF ISCHAEMIC EPISODES

A study of Fig. 1 and 2 shows that verapamil appears to be consistently effective in reducing the number of ischaemic episodes in patients in whom angina was predominantly associated with ST segment elevation, in those with angina and ST segment depression, and in those with asymptomatic ST segment changes. The reduction was more obvious in the patients with frequent episodes during the placebo periods. We could not find an explanation for the inconsistent effects observed in case 12 but have previously observed in a trial of intravenous isosorbide dinitrate (Maseri *et al.*, 1976; Distanti *et al.*, 1978) that in some patients it is not possible to prevent ischaemic attacks completely, probably because of the very acute phase of their disease.

In the group as a whole, the reduction in number of ischaemic episodes during verapamil treatment was highly significant. Therefore, this drug seems to have a potent effect in preventing attacks of vasospastic angina. Because of the design of our trial (randomised, short-term, cross-over), it is not possible to compare our results with those obtained in other trials with less sophisticated experimental designs (Papazoglov, 1971; Guazzi *et al.*, 1975a). The remarkable effects of verapamil during this trial appear to be maintained during long-term treatment of these patients, with doses of 80 mg 3 to 5 times a day. In fact their course so far appears very favourable, considering the severity of their symptoms initially and the severity of their coronary atherosclerotic disease. Although the number of

patients studied is small and the average duration of follow-up is relatively short, the results of this treatment compare favourably with the results reported in similar types of patients of coronary bypass surgery (Miller *et al.*, 1973; Gaasch *et al.*, 1974; Heng *et al.*, 1976) and of other surgical procedures such as cardiac denervation or autotransplantation which have been performed in selected patients with proven coronary vasospasm (Clark *et al.*, 1977).

In conclusion, verapamil is an effective drug for the management of those patients in whom unstable angina at rest is not the result of an excessive increase of myocardial metabolic demand.

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