Glyceryl trinitrate ointment in angina pectoris

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Summary

Skin absorption of glyceryl trinitrate (GTN) has been recognized for a long time. The effect of GTN and a placebo ointment in prevention of chest pain has been assessed and compared by studying the exercise capacity in 17 patients with angina pectoris. The placebo cream was ineffective but the GTN ointment was found to have beneficial effect in relief of pain in 16 cases. This was established by the patients' capacity to exercise on a bicycle ergometer without chest pain. The beneficial effect was sustained for up to 3 hr in 12 patients. This preparation appears to act as a long-acting nitrate and may be valuable for patients in whom β -blocking agents are ineffective or contra-indicated, and surgery is not feasible.

Introduction

Sublingual glyceryl trinitrate (GTN) and isosorbide dinitrate relieve anginal chest pain briefly (Russek, 1966; Bunn and Chremos, 1963). A longer acting preparation of nitrates would be advantageous in patients with frequent anginal symptoms, especially when β -blocking agents are contra-indicated or ineffective and surgical treatment is not feasible. Claims for such longer acting oral preparations have been made (Russek, 1966) but the results have not been convincing (Goldberg *et al.*, 1969) and prophylactic oral nitrates are not widely used for the management of angina.

Nitrates in ointment can be used to provide absorption through the skin (Martindale, 1972); as with most cutaneous preparations, the effect should be longer lasting and sustained (Reichek *et al.*, 1974; Karsh *et al.*, 1978; Davidov and Mroczek, 1976). The aim of the present study was to compare the effect of a nitrate ointment with that of a placebo in patients with documented angina.

Patients and methods

Seventeen patients with typical exertional angina but not taking anti-anginal treatment were selected for the study. Eleven patients had previously documented myocardial infarctions. The resting ECG showed changes consistent with ischaemic

heart disease in 12 and the exercise ECG was abnormal in 5. Eleven patients who had been previously treated with β -blocking agents had their medication tailed-off at least 3 days before the study.

After a resting ECG the study was carried out in 3 stages:

- (1) Exercise with no medication.
- (2) After an interval of 30-45 min, similar exercise 30 min after application of placebo ointment over the right scapula.
- (3) Exercise 30 min after application of GTN ointment over the left scapula and at hourly intervals thereafter for up to 4 hr. This was carried out one hr after stage 2.

The patients were told that 2 different types of ointment would be used to discover which was more suitable for treating their symptoms. They were not informed that one was a placebo. However, they all invariably volunteered that the effect of one ointment (GTN) was similar to taking sublingual nitrates, either GTN or isosorbide dinitrate, which they had previously taken. This was because they experienced either some transitory throbbing sensation or actual headache.

The exercise was performed on a Godart ergometer pedalled at a constant speed of 70 rev/min against an initial work load of 500 kpm/min increased to 800 kpm/min after 30 sec and continued until the patient experienced typical angina. ECGs were obtained immediately after the onset of pain and again 3 and 6 min later.

1.8 cm of placebo ointment and ointment containing 2% GTN was applied to the patient's back and spread over an area 5×7.5 cm, which was then covered with a Melolin (S & N) dressing.

Results (Tables 1 and 2)

There were 16 men and one woman with ages ranging from 31 to 63 years (mean 50.2 years). All experienced typical angina on exercise at periods varying from 70 sec to 5.5 min with a mean of 2.83 min. Placebo ointment had no significant effect on the duration of exercise tolerance, the mean being 2.90 min.

TABLE 1. The effect of GTN ointment on exercise capacity in 16 patients with angina pectoris

Control		Placebo		After GTN									
				30 min		1 hr		2 hr		3 hr		4 hr	
min	sec	min	sec	min	sec	min	sec	min	sec	min	sec	min	sec
2	30	2	30	15		No pain		6	30	4		3	
2	30	4		No pain		No pain		No pain		No pain		11	
				15									
				No pain									
2		1	15	2	30	3		3	30	3	30	2	30
4	30	3		2	30	2	30	3		3		3	30
2		1	35	3		7	30	2	30	2	30	2	
3		3		3	30	4	30	7	30	5	30	4	
2		2	15	3	20	3	30	3		2	55	2	
4		5		6	30	5	30	5	30	4	30	4	30
2		1	20	3		3		2		2		2	
2	35	2	35	3		3	20	2	30	3	15	2	35
1	40	2		4		4		4		3		2	
1	25	2	15	3		4	30	8		6	30	5	30
								No pain					
5	30	5	30	15		15		12		7		5	30
				No pain		No pain							
5		4	30	15		15		8	30	6	10	5	30
				No pain		No pain							
2	55	3	10	5	30	6		4	30	4	15	4	
3		3		15		No pain		No pain		5	30	4	
				No pain									
1	10	1	25	1	20	1	20	3	5	2	45	2	15

Sixteen patients showed considerable improvement with GTN ointment and only one showed no response, despite a fall in blood pressure and tachycardia indicating adequate absorption of the ointment. The comparison with placebo in this study is the 30-min result and the findings later than this on GTN relate only to the control time and provide no comparison with placebo at one to 4 hr.

TABLE 2. Mean BP recordings (mmHg) in various stages of testing

Resting	Placebo	After GTN		
		30 min	3 hr	4 hr
139/96	138/96	114/82	116/81	126/91

Thirty min after application of the ointment 5 patients experienced no pain after 15 min of continuous exercise, which was stopped because of exhaustion. The remaining 11 all showed considerable improvement compared with their control values. The mean duration of exercise tolerance was 6.5 min.

At one hr the number of pain-free patients remained the same, and there was a further increase in the exercise tolerance of the remaining 11, with a mean duration of 6.8 min.

At 2 hr 3 of the 5 patients who had had no pain experienced mild discomfort but still showed marked improvement on their control times. The other 2 remained pain-free. Of the remainder, 4 continued to show improvement and one became pain-free; 4 had similar exercise times as at one hr; and 3 had

exercise tolerance comparable with their control values.

At 3 hr there was only one patient who was pain-free. Three had pain at control times while 12 still continued to show considerable benefit from GTN. The mean duration of exercise was 5.22 min.

At 4 hr all patients had pain; 10 at control times and 6 still showing improvement. The mean duration of exercise was 4.03 min (Table 1).

Blood pressure was recorded during the resting phase, after application of placebo and after 30 min, 3 and 4 hr after GTN cream (Table 2). The mean pulse rate at rest was a little over 78 and at 30 min after GTN cream just under 93/min.

Discussion

The 16 patients with angina on effort who responded favourably to GTN ointment at 30 min showed a significant rise in pulse rate over their control values and a significant fall in blood pressure (the mean control being 139/96 and at 30 minutes 114/82 Table 2). This suggests that absorption of the ointment had started before this period. It would be difficult to be certain of the exact time when GTN entered the blood stream, however, because BP and pulse rate were not monitored continuously, nor were blood levels of GTN estimated. The effect appeared to last up to 3 hr in the majority of patients, although in some there was a fair response even at 4 hr. The ECG, which had shown ischaemic changes during rest and in the control period of exercise,

remained normal at 30 min and up to 3 hr in 3 patients—this further confirmed the clinical impression that this ointment was effective.

It is surprising that, although the use of GTN ointment was first described in 1955 (Davis and Wiesel, 1955), its use has not yet gained popularity. The widespread use at one time of longer-acting oral preparations of nitrates may have prevented clinicians from trying the ointment. In recent years, β -blocking agents and surgery in selected patients have become standard prophylactic treatment for patients with angina pectoris. Beta-blocking agents may, however, be ineffective or cause unpleasant side effects, or are contra-indicated because of the presence of obstructive airways disease, cardiac failure or intermittent claudication. The authors feel that in these individuals and in patients who are unfit for surgery GTN ointment merits a trial. The main problem with this form of therapy is headaches, encountered in 3 of the patients, and individuals who get headaches with sublingual GTN tablets should not be prescribed the ointment. The ointment is readily absorbed through the skin and, if someone other than the patient is applying it, he or she should be advised to use gloves.

Oral nitrates have been used in patients with severe heart failure to reduce the work load of the ventricles, their action is relatively short and absorption may not be smooth (Williams *et al.*, 1976).

The authors have used GTN ointment with clinical improvement, either in conjunction with or in place of oral nitrates to achieve more sustained and longer action in patients with intractable cardiac failure.

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