The patient's preference and grip strength indicate improvement on drugs which are anti-inflammatory or analgesic agents; under defined conditions joint size is an index of specific anti-inflammatory effect.

The reduction of joint size by prednisone, an anti-inflammatory agent, is contrasted with the absence of change on paracetamol.

High dosage of salicylate, unlike low dosage, is associated with reduction in joint size.

There is no detectable difference between low dosage of salicylate and placebo in their effect on joint size.

It is suggested that high dosage of salicylate, unlike low dosage, has a clinically measurable anti-inflammatory effect. If suppression of inflammation is desirable in rheumatoid arthritis high dosage of salicylate is indicated independently of symptoms.

Unlimited use of high dosage of salicylate in trials may affect the findings. Low dosage modifies the response if given in combination. Salicylate intake should be eliminated from comparative trials of anti-inflammatory agents.

It is suggested that the plan of this trial provides a simple method for the clinical assessment of the anti-inflammatory properties of a rapidly acting drug.

We wish to thank Dr. Peter Fowler for providing the millimetre gauge for the measurement of joint size; Dr. E. Lewis-Fanning for statistical advice; and Mr. J. A. Baker, chief pharmacist at the hospital, for organizing the provision of tablets suitable for the trials. Our thanks are also due to many members of the unit and to students for assisting in the assessment of error, in particular for the work illustrated in Fig. 2.

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Glyceryl Trinitrate in Angina Pectoris: Tablet or Aerosol?

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Though many drugs have been used in the symptomatic treatment of angina pectoris almost the only one which has been consistently shown to be of benefit in relieving the myocardial ischaemia is glyceryl trinitrate. In a previous study it was shown to be of considerable value when used prophylactically, but no better than a placebo when given after an attack of anginal pain had developed (Sandler *et al.*, 1963). It has been suggested that this lack of effect of glyceryl trinitrate in relieving established anginal pain might be due to the time it took to dissolve in the mouth (Evans, 1963), so that by then the angina had improved spontaneously. In relation to this possibility the development of an aerosol preparation of glyceryl trinitrate seemed of considerable interest, since such a preparation would be rapidly absorbed in the lungs with more rapid arrival in the myocardium. Preliminary observations (G. G. Gensini, unpublished; A. Black, unpublished) suggested that glyceryl trinitrate aerosol was of value in treating angina, and it was therefore decided to undertake an objective evaluation of the aerosol preparation (Cardamist) in treating angina pectoris and to compare it with the standard tablet trinitrate preparation.

Patients and Methods

Twenty-three patients with well-authenticated and typical attacks of angina pectoris were studied. These subjects, aged from 39 to 69 years, comprised 20 men and 3 women. In all of them the angina had settled down to a stable pattern, and the duration ranged from 3 to 72 months, with attacks occurring from 3 to 40 times weekly. The presumptive cause of the angina was coronary artery disease in all 23, but only four had evidence of previous myocardial infarction.

All the patients were admitted to hospital for a period of six days for the trial, and a daily exercise tolerance was carried out in each of them. The type of test has been described in detail in an earlier publication (Sandler, 1961), and is based on a modification of the Master two-step test, the patient exercising over two steps, each 9 in. (23 cm.) high, until he develops angina or completes 100 circuits over the steps; the test is stopped immediately if significant ischaemic change appears in the electrocardiogram during exercise. In addition to conventional electrocardiography, recording chest lead V5 before and after exercise, the patient is monitored continuously during exercise by means of a radiocardiograph. By this means ischaemic change can be detected immediately, even if unaccompanied by anginal pain, and the exercise terminated (Sandler, 1967). Depression of the ST segment of plane or sagging contour lasting at least 0.08 second, in either the radiocardiogram or the V5, was taken as evidence of myocardial ischaemia (Lloyd-Thomas, 1961; Master and Rosenfeld, 1961; Bellet *et al.*, 1962). Junctional depression, when it occurred, was accepted as significant of ischaemia only when the QX/QT ratio exceeded 50% (Master and Rosenfeld, 1961).

The preparations studied were glyceryl trinitrate aerosol delivering 0.13 mg. of the drug per inhalation—the dose investigated being 0.26 mg. (two inhalations)—an identical placebo aerosol, and standard tablets of 0.5 mg. of glyceryl trinitrate. Study of the aerosol preparations was made on a double-blind basis, and the distribution of active and placebo preparations in each pair of aerosols was randomized. It was not thought necessary to include a placebo tablet with the glyceryl trinitrate tablet, since a previous double-blind study had confirmed the effectiveness of the latter in this type of trial (Sandler *et al.*, 1963). Each of the three preparations—glyceryl trinitrate aerosol, placebo aerosol, and glyceryl trinitrate tablet—was assessed when given both before exercise was

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undertaken and after, so that altogether six exercise-tolerance tests were carried out in each patient, each acting as his own control. Each exercise test was made at the same time in the morning, in the same environment, and with the same medical and technical staff present. To minimize the effects of progressive rest in hospital on the performance of the exercise-tolerance tests, the three preparations were varied in their order of administration in successive patients as they came under trial; this scheme is shown more clearly in Table I. All patients were fully ambulant between the exercise tests.

TABLE I.—Varying Order of Administration of Aerosol Preparations and Glyceryl Trinitrate Tablets to Successive Patients

Patient	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	A.1 B/E	A.1 A/E	A.2 B/E	A.2 A/E	Tab B/E	Tab A/E
2	A.1 B/E	A.1 A/E	Tab B/E	Tab A/E	A.2 B/E	A.2 A/E
3	Tab B/E	Tab A/E	A.1 B/E	A.1 A/E	A.2 B/E	A.2 A/E
4	A.1 B/E	A.1 A/E	A.2 B/E	A.2 A/E	Tab B/E	Tab A/E
5	A.1 B/E	A.1 A/E	Tab B/E	Tab A/E	A.2 B/E	A.2 A/E
6	Tab B/E	Tab A/E	A.1 B/E	A.1 A/E	A.2 B/E	A.2 A/E

A.1 = First aerosol
A.2 = Second aerosol
Tab = Glyceryl trinitrate tablet. B/E = Before exercise. A/E = After exercise.

In addition to the inpatient assessment all patients were asked to use the aerosols as outpatients after discharge from hospital, again on a double-blind basis, and were subsequently questioned on several aspects of their use—which of the two aerosols was found more effective, whether the aerosol was better than the glyceryl trinitrate tablets previously used in relieving anginal pain, whether there was any difficulty in using the aerosol in public, and, finally, if any side-effects had been encountered with the aerosols.

Results

Table II shows the mean number of circuits undertaken by the patients with the three preparations. The control observations in this and subsequent tables are those recorded when the drugs were given after exercise had been completed, so that no medication had been taken before the exercise. In addition to calculation of the mean values for the whole group, the differences in individual patients resulting from each of the three preparations have been analysed statistically, so that variation between different subjects was eliminated and any changes produced by the drugs would have become more apparent. In Table II there were no significant differences, either in the mean number of circuits or in the mean change in the number of circuits, between any of the three preparations when given before exercise.

Table III shows the influence of the three preparations given before exercise on the number of patients developing angina, the time taken for the angina to develop, and the duration of

TABLE II.—Mean Number of Circuits and Mean Change with Administration of Active Aerosol, Placebo Aerosol, and Glyceryl Trinitrate Tablets Before Exercise (23 Patients)

	Glyceryl Trinitrate Tablets	Active Aerosol	Placebo Aerosol
Control No. of circuits	80.0	81.5	80.9
Mean No. of circuits with drug	80.9	83.5	83.0
Mean change in No. of circuits	+0.6	+2.0	+2.1

TABLE III.—Incidence, Exercise Time, and Duration of Angina (Mean Values)

	Glyceryl Trinitrate Tablets	Active Aerosol	Placebo Aerosol
No. of patients with angina	8	8	7
Exercise time before angina (sec.)	332.7	350.3	280.9
Duration of angina (sec.)	371.3	339.1	404.0
	+68.2	+14.5	+64.9
Duration of angina (sec.)	158.9	158.9	218.0

the angina (no control value was available for the duration of angina, since the control observations are those recorded when drugs are given after exercise). No significant differences were apparent between the three preparations in the number of patients developing angina, the time taken for angina to occur, or in the duration of the angina.

Table IV compares the degree of ST depression occurring during exercise in the radiocardiogram and after exercise in both radiocardiogram and V5; it shows the mean values for the different groups and the mean of the changes produced in individual patients by all three different preparations administered before exercise was undertaken. Considering first the changes in the radiocardiogram during exercise, the least ST depression occurred when a tablet of glyceryl trinitrate was given before exercise, and when compared with the mean ST depression after placebo administration before exercise the difference was seen to only just exceed the 5% probability level. Though the mean ST depression following glyceryl trinitrate aerosol before exercise was also less than that with the placebo, the difference was not significant ($0.15 < P < 0.2$). The mean change in ST depression during exercise did not differ significantly between the three preparations. When the changes in the radiocardiogram after exercise are considered there was significantly less depression in the ST segment with glyceryl trinitrate tablets than with the placebo ($P < 0.05$), and again there was no significant difference between the active and placebo aerosols. The changes in V5 after exercise did not show any significant differences between the three preparations.

TABLE IV.—Comparison of Degree of ST Depression in Radiocardiogram and V5

	Glyceryl Trinitrate Tabs		Active Aerosol		Placebo Aerosol	
	No. with Changes	Mean ST Depression (mm.)	No. with Changes	Mean ST Depression (mm.)	No. with Changes	Mean ST Depression (mm.)
Mean ST Depression						
R.C.G. { D/E	11	0.91	12	1.12	11	1.32
A/E	11	0.59	15	0.87	11	1.08
V5—A/E	8	0.75	14	0.71	13	0.79
	No. of Patients	Mean Change in ST Depression (mm.)	No. of Patients	Mean Change in ST Depression (mm.)	No. of Patients	Mean Change in ST Depression (mm.)
Mean of Changes in ST Depression						
R.C.G. { D/E	19	0	22	+0.02	22	+0.34
A/E	19	-0.24	23	-0.07	22	+0.18
V5—A/E	22	0	23	+0.05	22	+0.07

D/E = During exercise.

The duration of ST depression in the radiocardiogram and V5 is shown in Table V. When the three drugs were given before exercise no significant differences in the duration of ST depression were apparent between the glyceryl trinitrate, either in tablet or in aerosol form, and the placebo. Similarly, when the three preparations were given at the end of the exercise neither of the two active preparations significantly influenced the duration of the ST depression compared with the placebo.

Outpatient assessment showed that 10 patients regarded the active aerosol as more effective in relieving anginal pain, 11

TABLE V.—Duration of ST Depression in Radiocardiogram and V5 With Drug Administration Before and After Exercise

	Glyceryl Trinitrate Tablet		Active Aerosol		Placebo Aerosol	
	No. with Changes	Mean Duration ST Depression (sec.)	No. with Changes	Mean Duration ST Depression (sec.)	No. with Changes	Mean Duration ST Depression (sec.)
Drugs { R.C.G.						
B/E	10	384	15	306	11	344
V5	8	405	15	490	13	308
Drugs { R.C.G.						
A/E	11	368	16	317	10	360
V5	12	365	15	350	13	288

chose the placebo aerosol, while two regarded active and placebo aerosols as equally effective. When asked to compare the aerosol preparation with glyceryl trinitrate tablets five patients thought the active aerosol more effective than the tablets, and seven thought the placebo aerosol the more effective. Only two patients thought that tablets were better than aerosol. The only side-effect encountered with the active aerosols was headache, which occurred in six patients. Only one patient, a woman, thought that use of an aerosol preparation in public was embarrassing.

Discussion

The effectiveness of glyceryl trinitrate in the management of angina pectoris depends primarily on its route of administration. The sublingual route has been found to be most useful clinically (Riseman *et al.*, 1958); for when the drug is swallowed, even in greatly increased doses, it is much less effective and the onset of activity is considerably delayed (Russek *et al.*, 1953; Russek, 1956). The introduction of aerosol administration of glyceryl trinitrate theoretically offers more rapid absorption through the alveolo-capillary membrane, and enables more rapid access to the myocardium and coronary vessels by eliminating the mouth-to-lung circulation time, usually 10 to 12 seconds. In addition, more consistent and concentrated absorption is possible, since sublingual administration may be modified by local oral factors. In a comparative trial of the aerosol and sublingual routes of glyceryl trinitrate administration in 31 anginal patients, A. Black and M. Black (unpublished observations) found that the aerosol gave more rapid relief of angina than the tablets in 27 patients, but assessment was made solely on subjective criteria.

In the present objective study the aerosol preparation given before exercise was no more effective than the placebo aerosol in influencing the amount of exercise possible, the incidence and duration of angina, or the degree and duration of the ischaemic ST depression induced by exercise. On the other hand, sublingual glyceryl trinitrate given before exercise did significantly improve the amount of ST depression occurring both during and after exercise. Though the doses of the aerosol and tablet preparations were not similar, the dose of 0.26 mg. of glyceryl trinitrate in the aerosol form was regarded as a potentially effective dose, since an earlier study had shown that a 0.25-mg. tablet of glyceryl trinitrate favourably influenced exercise-tolerance tests in anginal patients (Sandler *et al.*, 1963). The lack of effect of the aerosol preparation in this study is unlikely to have been associated with defects in absorption from the lungs, since care was taken to exclude any patient with clinical or radiological evidence of pulmonary disease, and the development of headache in six patients using the active aerosol indicates that adequate absorption has occurred, at least in these subjects.

The mode of action of glyceryl trinitrate in angina still remains controversial. Though coronary vasodilatation occurs in normal subjects, doubt has been expressed on whether it develops in atherosclerotic subjects (Gorlin *et al.*, 1959). However, more recent work with radioactive flow techniques and cineangiography has confirmed that coronary vasodilatation can occur in anginal patients (Johnson and Sevelius, 1960; Sones and Shirey, 1962). It is likely, however, that production of coronary vasodilatation by glyceryl trinitrate is beneficial only when the drug is used before exercise, since maximal coronary vasodilatation has probably already occurred when angina has developed owing to release of powerful local vasodilator meta-

bolites by the hypoxic myocardium (Wiggers, 1954; Friedberg, 1966). Gorlin *et al.* (1959) believe that the main benefit of glyceryl trinitrate in angina is due to peripheral pooling in the venocapillary system, leading to a diminished venous return and consequent reduction of cardiac work. The earliest concept of the mechanism of action of glyceryl trinitrate is reduction of cardiac work owing to systemic hypotension (Brunton, 1897), but assessment of blood-pressure changes after glyceryl trinitrate administration, both in the present study and in a previous one (Sandler *et al.*, 1963), has shown that this is an inconstant and very variable factor. It is likely that the beneficial effects of this drug are due to a combination of its two main actions—coronary vasodilatation and reduction of external cardiac work.

Summary

A controlled double-blind objective evaluation of the use of an aerosol preparation of glyceryl trinitrate was made in 23 patients with typical angina pectoris, and the results are compared with a standard 0.5-mg. tablet of glyceryl trinitrate administered sublingually. Assessment was made by exercise-tolerance tests with continuous radiocardiographic monitoring during and after exercise, as well as a conventional pre- and post-exercise electrocardiogram. The dose of aerosol studied was 0.26 mg. delivered in two inhalations, and both aerosol and tablet preparations were assessed before and after exercise.

The active aerosol was no more effective than the placebo aerosol in favourably influencing the amount of exercise performed, the incidence and duration of angina, or the degree and duration of the ischaemic change in the electrocardiogram; these results applied to administration both before and after exercise. On the other hand, glyceryl trinitrate tablets significantly improved ischaemic changes in the electrocardiogram when given before exercise, but not when given after it.

It is concluded that the aerosol preparation of glyceryl trinitrate used in the present trial is ineffective, and prophylactic sublingual administration of glyceryl trinitrate tablets still remains the treatment of choice.

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