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Clinical Trial

A CONTROLLED TRIAL OF LONG-ACTING GLYCERYL TRINITRATE FOR THE PREVENTION OF ANGINA PECTORIS

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NITROGLYCERIN sublingually remains the drug of choice for the relief of the acute anginal episode (Bunn and Chremos, 1963). Correctly used it has no competitor in this field (Evans, 1963) and is the only therapy necessary or desired by the great majority of patients with angina of effort.

In the search for an effective long-term prophylactic, glyceryl trinitrate swallowed in slow-release tablet form (Sustac) seemed likely to be successful if absorption of the active principle, once released from the tablet, proved adequate. Huppert and Boyd (1955), Jablons, Schilero, Sicam and Estrellado (1956), and Kutschera and Perger (1957) thought this preparation clinically useful, but other reports (Russek, Zohman and Dorset (1955), Russek, Zohman, Drumm, Weingarten and Dorset, (1955); Riseman, Altman and Koretsky (1958); Parry and Wells (1960); Pilkington and Purves (1960)) were not encouraging. In an attempt to decide the place of Sustac in the management of those patients with angina for whom sublingual nitroglycerin alone seemed inadequate, we undertook a double-blind controlled trial in selected patients.

Material and Methods

During the course of two years, 50 patients with coronary artery disease were selected from several hundred anginal subjects attending a cardiac clinic. Selection for the trial was governed by apparent stability of the attack-rate, a stated average requirement of at least four glyceryl trinitrate tablets sublingually per day, and a degree of intelligence sufficient to cope with the rather complicated recording system. Each patient was asked to record, on cards provided, the number of attacks of angina pectoris experienced during the waking hours each day, the number of any such attacks while in bed at night, and the total number of sublingual trinitrate tablets consumed in each 24-hour period. Patients were specifically and repeatedly asked not to use sublingual trinitrate prophylactically during the six-week period but were urged to suck or chew these tablets as usual at the first onset of recognized anginal pain. All other anti-anginal therapy was suspended during the trial.

Weekly totals of 'day' and 'night' attacks, and of sublingual nitroglycerin tablets taken, were thus obtained from the completed cards. Information was also sought in regard to any intercurrent illness, changes in activity or exposure to cold and wind, and any side-effects thought to be due to the trial tablets. An additional question concerned the amount of breathlessness on exertion, where present.

During the first fortnight of the trial either Sustac 1/10 gr. (6.5 mg.) or an inactive tablet of identical appearance was swallowed by each patient three times daily. The first dose was taken on rising and the last on retiring. During the second fortnight no trial tablets were taken. During the third fortnight each patient took whichever of the trial tablets, active drug or placebo, he had not received during the first fortnight. Initial random allocation to drug or placebo was made by the pharmacist who knew the tablets only as A or B. The clinician was unaware, throughout the whole period of the trial and until the final analysis was completed, which of these tablets any patient was receiving.

The average age of the patients was 56.3 years (range 38 to 70 years). Thirty-nine of them were male (average age 55.3 years) and 11 female (average age 59.6 years). Eighteen patients had electrocardiographic evidence of myocardial infarction and 9 of these were considered to have suffered such episodes within the preceding 12 months. Only 2 patients were on anti-coagulant therapy (phenindione). None was taking hypotensives. Duration of angina ranged from 2 months to 13 years (average 37.5 months).

Results

Thirty-seven of the 50 patients completed the trial. Non-completion was due to occurrence of side-effects in 4 cases; 3 patients were excluded because of inadequate records, 5 others defaulted, and one was admitted to hospital with a myocardial infarction during the third week of the trial.

The 37 completed records were first analysed with a view to separating those patients in whom there was a statistically significant difference at the 5% level between either the first or third fortnight and each of the other two fortnights in respect of:

(*a*) total consumption of sublingual trinitrate tablets,
(*b*) number of attacks of nocturnal angina,
(*c*) number of attacks whilst up and about.

It was evident when the records were first examined that certain patients had suffered very few attacks of pain during the trial, and that some had required only a minimal number of nitroglycerin tablets. It was calculated that it would be impossible to demonstrate any significant benefit from any treatment given unless a patient had suffered four or more attacks of angina or had required four or more sublingual trinitrate tablets in at least one of the three fortnightly

periods. All patients with fewer attacks, or lower requirements for sublingual nitroglycerin, than this were therefore excluded from the relevant sub-groups.

Total consumption of sublingual trinitrate tablets

In addition to the 13 patients who failed to complete the trial, 2 were excluded having required less than 4 sublingual trinitrate tablets per fortnight throughout the trial.

There remained therefore 35 patients, 18 of whom were given tablet A during the first fortnight. In 6 instances tablet A proved statistically superior, whilst tablet B was significantly better in 8 cases.

Number of attacks of nocturnal angina

In addition to the 13 patients who failed to complete the trial, 23 were excluded having experienced less than 4 attacks of nocturnal pain per fortnight throughout the trial, and one patient did not keep a record for the middle fortnight.

There remained therefore 13 patients, 6 of whom were given tablet A during the first fortnight. Statistical analysis showed that in one instance tablet A proved superior whilst tablet B was better in 6 instances.

Number of attacks of anginal pain whilst up and about

In addition to the 13 patients who failed to complete the trial, 2 were excluded having experienced less than 4 attacks of diurnal pain per fortnight throughout the trial.

There remained therefore 35 patients available for analysis in this group. 18 patients were given tablet A first. In 5 instances tablet A proved significantly better, whilst in 6 cases tablet B was superior.

Effect of various factors on therapeutic response

The results were analysed in order to ascertain whether certain factors were associated with differing therapeutic response. It was found that no difference could be detected when sex, age, duration of history of angina, or evidence of a previous myocardial infarct were taken into consideration.

No meaningful information could be derived from patients' answers to the ancillary questions which had been included in the record charts.

At this stage the hitherto secret key to the identity of the trial tablets was revealed and it was found that tablet B was the active (Sustac) tablet. Table 1 summarizes the results obtained in each group.

It is seen that Sustac was effective in reducing the frequency of nocturnal angina in 6 out of 13 cases and that in this respect it was statistically superior to placebo ($\chi^2 = 5.2786$, $0.02 < p < 0.05$). No beneficial effect could be demonstrated in relation to diurnal attacks or total sublingual nitroglycerin consumption.

Side-effects

The side-effects reported are shown in Table 2. Headache occurring in 13 patients whilst on Sustac, and in 5 patients whilst on placebo, was the most frequent side-effect. This table is based on the 37 patients who completed the trial and the 4 patients who defaulted because of side-effects.

TABLE 1

	Significant ($p < 0.05$) reduction in		
	Sublingual trinitrate consumption	Frequency of nocturnal attacks	Frequency of diurnal attacks
Sustac	8	6	6
Placebo	6	1	5
No. of patients studied	35	13	35
Difference between Sustac and placebo	Not signi.	$\chi^2 = 5.2786$ $0.02 < p < 0.05$	Not signi.

Table showing the difference in therapeutic effect of Sustac and placebo on total sublingual trinitrate consumption, frequency of nocturnal anginal attacks, and frequency of diurnal anginal attacks.

TABLE 2

	Sustac	Placebo	No trial tablets	Number of patients reporting symptoms
Headache	13	5	3	17
Abdominal complaints	3	4	—	7
Giddiness	2	1	—	3
Others	3	2	—	5

Table showing the incidence of side-effects.

Discussion

In so far as angina pectoris is a symptom, it is apparent that it cannot be objectively evaluated (Oram and Sowton, 1961). It is a pity, therefore, that some authors have recently claimed objectivity in their assessment of glyceryl trinitrate, and other so-called coronary dilators, for the relief of ischæmic cardiac pain. Most of the early trials of Sustac were similarly pseudo-objective or inadequately controlled subjective assessments. A more recent trial (Meciani and Brina, 1962) comes within the latter category.

We decided that the value of Sustac, or any other long-acting angina prophylactic, could be demonstrated only by its ability to reduce the frequency of patients' anginal attacks. This widely shared point of view has recently required reiteration (*Brit. med. J.*, 1963). We therefore selected for trial a number of patients who, from their own statements, appeared to need a sufficiently large number of sublingual nitroglycerin tablets regularly to allow the effect of a potent long-acting prophylactic to be shown. The patients were asked, as were those of Pilkington and Purves (1960), to eschew the use of sublingual nitroglycerin to prevent pain during the trial, and this may account for the much lower consumption of tablets during the control period (second fortnight) than had been

expected. Indeed, in 2 patients, this 'base-line' consumption proved to be so low that no long-term prophylactic could have effected a significant reduction and, unless there was more than usual restriction of activities during this period (which did not appear to be the case), there could hardly have been any advantage to be gained from any prophylactic other than sublingual nitroglycerin. It is of interest that only 4 patients failed to complete the trial on account of side-effects attributed to active drug or placebo.

Our final total of 37 patients satisfactorily completing the six-week course is much smaller than had been anticipated and reflects the difficulty of obtaining suitable subjects even from a busy cardiological out-patient department. Nevertheless the number of those experiencing angina while in bed at night has proved large enough to demonstrate a clear-cut reduction in such attacks while Sustac was being taken. On the other hand, the differences in regard to day-time attacks and total sublingual nitroglycerin consumption are not large enough to suggest that diurnal use of Sustac is advantageous. Such differences as were found in diurnal attack rate and total tablet consumption are entirely explicable on the basis of chance variations in climate, activity, stress and other such uncontrollable factors.

Prevention of night pain is presumably attributable to the dose of Sustac taken on retiring. Peripheral vaso-dilation is still detectable six hours after ingestion of 13 mg. of Sustac (Mann, 1958) and it seems reasonable to regard this as about the upper limit of duration of the angina-preventing effect of the usual (smaller) therapeutic dose (Pilkington and Purves, 1960). It may be that nocturnal angina is prevented because the mechanism of its production differs from that of the day-time attack. More probably, however, since sublingual trinitrate seems equally effective for both day and night attacks, the success of the swallowed bed-time prophylactic depends upon factors favouring absorption of the glyceryl trinitrate released from the tablet during the hours of sleep.

Headache was the only common side-effect noted by patients taking Sustac and was reported by 13 of them (32%). Various non-specific symptoms were reported while on active drug and placebo. As anticipated, the group as a whole showed the expected tendency to decreased frequency of attacks during the later weeks of the trial period (Cole, Kaye and Griffiths, 1958). In this respect it was fortunate that of those finally qualifying for analysis, as many had first received Sustac as had first received placebo.

Summary

A double-blind controlled trial of long-acting glyceryl trinitrate (Sustac) was carried out in fifty selected out-patients with angina pectoris due to coronary artery disease. The dose of Sustac was 6.5 mg. in the early morning, about midday, and on retiring.

There were no significant changes in diurnal attack-rate or total requirement of sublingual nitroglycerin for pain, but in 6 of 13 patients with nocturnal angina the administration of Sustac coincided with a significant reduction in the number of night-time attacks.

It is concluded that Sustac taken on retiring is of value in the prevention of nocturnal angina.

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