Sustained Effects of Nitroglycerin Ointment in Patients with Angina Pectoris

By Nathaniel Reichek, M.D., Robert E. Goldstein, M.D., David R. Redwood, M.D., and Stephen E. Epstein, M.D.

SUMMARY

Cutaneous absorption of nitroglycerin is a well-documented phenomenon which may have unique advantages for the sustained prophylaxis of angina pectoris. Therefore, we have examined the effects of nitroglycerin ointment and placebo on exercise capacity in 14 patients with angina pectoris. Nitroglycerin ointment produced a significant increase in exercise capacity which persisted for at least three hours. Concomitant sustained changes in systolic blood pressure and resting heart rate were observed. Electrocardiographic evidence of myocardial ischemia was significantly reduced. Chronic administration in six patients did not reduce the effects of either nitroglycerin ointment or sublingual nitroglycerin. Nitroglycerin ointment appears to be a truly long-acting nitrate. While evidence of nitrate toxicity or tolerance was not observed in the present study, additional information is required before the widespread use of this agent can be recommended.

Additional Indexing Words:
Long-acting nitrates  Exercise capacity  Nitrate tolerance

Sublingually administered nitroglycerin provides marked symptomatic benefit in the treatment of angina pectoris due to occlusive coronary disease. Its brief duration of action, however, severely limits its usefulness as a prophylactic agent.1-3 Many attempts have been made to prolong the beneficial effects of nitroglycerin by altering its molecular configuration or mode of administration.4,5 Although successful demonstration of prolonged action has been claimed for some of these preparations,1,2,6-9 the results of such studies have been challenged.5,10,11 It is our conviction that evidence of substantially more prolonged prophylaxis than that achieved with sublingual nitroglycerin has not been presented.3,12

Sustained nitrate effects produced by cutaneous exposure to nitroglycerin have long been known to pharmacologists13 and industrial toxicologists.14,15 The cutaneous administration of nitroglycerin would thus appear to have a rational therapeutic potential. Although cutaneous administration of nitroglycerin ointment for the prophylaxis of angina pectoris was introduced by Davis and Wiesel in 1955,16 its efficacy has not been critically tested, and it has seen little use. To systematically assess the possibility that nitroglycerin ointment has sustained prophylactic efficacy, we have examined its effects on exercise performance in patients with angina pectoris.

Methods

Fourteen men, aged 38 to 61 years were studied. Each had experienced typical, stable exertional angina for at least six months. Coronary angiography in nine of the subjects revealed that each had one or more high-grade obstructive lesions. Well-documented myocardial infarction had occurred in seven patients, including all five not studied with coronary angiography. Thirteen subjects had been treated with propranolol, which was discontinued at least four days prior to study. Four patients were receiving "long-acting" nitrates, which were also discontinued prior to study. All patients reported prompt relief of angina by sublingual nitroglycerin. Average consumption of sublingual nitroglycerin was five tablets per day. None had previously received nitroglycerin ointment. Six patients were receiving digoxin.

The medications tested were 2% nitroglycerin ointment (Nitrol, Kremers-Urban) and a placebo consisting of inert ointment base. The dose of nitroglycerin ointment, individually selected for each patient, was the smallest amount that reproducibly increased heart rate at least 10 beats/min and/or decreased systolic blood pressure at least 10 mm Hg while the patient was seated at rest one hour after application. In one patient, the smallest dose of nitroglycerin ointment which changed heart rate and blood pressure also produced headache and a smaller dose was used for the study. Each dose of ointment was applied to the same 96 square inch area of the patient's back, covered with
plastic wrap and left in place until completion of exercise testing.

Patients were admitted to the Clinical Center, National Institutes of Health. Practice exercise was performed on hospital days three and four. On each practice day, control exercise testing was performed, placebo ointment applied and exercise testing repeated one and three hours after placebo application. Results derived from these preliminary tests were not incorporated into the study. Definitive testing was carried out on hospital days five and six with the sequence of exercise identical to that used on days three and four except that nitroglycerin ointment was substituted for placebo on one of the two definitive test days. The order of administration of nitroglycerin ointment and placebo was reversed in alternate patients. It was anticipated that, despite its physical resemblance to nitroglycerin ointment, both investigators and patients would be able to distinguish placebo from active drug by its lack of hemodynamic effects and their sequelae (flushing, tachycardia, etc.). Therefore, patients were told that the placebo was an agent different from nitroglycerin ointment; however, they were not told that this agent was pharmacologically inert.

Two patients developed mild headache during exercise after administration of active drug, but were able to complete their exercise bouts. No other adverse effect was noted. The average dose of nitroglycerin ointment contained five mg of nitroglycerin (range 1.5–19 mg), the amount present in a 0.4 inch ribbon of extruded ointment.

Six patients were restudied after administration of nitroglycerin ointment three times daily for 8–12 weeks. In these patients, administration of nitroglycerin ointment was continued throughout the second hospital admission and single dose of placebo was substituted on one of the test days. To evaluate the possibility of ointment-induced tolerance to sublingual nitroglycerin, the efficacy of a fixed dose (0.3 mg) was assessed in five patients before and during chronic administration of nitroglycerin ointment. Changes in heart rate, blood pressure, and exercise capacity were measured approximately three minutes after sublingual nitroglycerin.

Exercise was performed on a constant-load, upright Godart bicycle ergometer that was pedaled steadily at 40 to 50 rpm. Workload was increased by 20 watts every three minutes. The initial workload was preselected individually for each patient so that angina began between the third and sixth minutes of exercise when no drug was administered. Exercise was stopped at the onset of angina. Continuous electrocardiographic monitoring was performed using the CM₅ lead. Statistical analyses were made with Student's t-test for paired data.

**Results**

Placebo failed to alter exercise capacity one and three hours after its administration (fig. 1). Similarly, control values for duration of exercise at onset of ischemic chest pain did not differ significantly on the two test days. Thus, there was no tendency for exercise capacity to change in the absence of effective anti-anginal medication.

In contrast, exercise capacity following administration of nitroglycerin ointment was markedly greater than following administration of placebo (fig. 2). At one hour, mean exercise duration was 5.0 minutes following placebo but 8.0 minutes following nitroglycerin ointment (P < 0.001). All patients exercised longer and 10 of 13 were able to perform at a higher workload before onset of angina when tested after nitroglycerin ointment. At three hours, mean exercise duration was still 7.4 minutes after nitroglycerin ointment, a value that again was significantly above levels achieved after placebo. Twelve of 13 patients exercised for longer periods prior to angina and eight following placebo.
of 13 exercised to a higher workload. Values of exercise capacity measured three hours after nitroglycerin ointment did not differ significantly from values measured one hour after nitroglycerin ointment.

Chronic administration in six patients did not significantly alter the exercise prolongation produced by nitroglycerin ointment. In all five patients tested with sublingual nitroglycerin, exercise prolongation following administration of 0.3 mg sublingual nitroglycerin was not impaired by prior chronic administration of nitroglycerin ointment (fig. 3). Liver function tests and methemoglobin levels remained within normal limits in all chronic recipients of nitroglycerin ointment.

When present, exercise-induced ST segment depression provides an objective index of myocardial ischemia. In four patients not receiving digitalis, exercise electrocardiograms repeatedly demonstrated ST depression prior to the onset of angina. Neither repeated testing nor the administration of placebo influenced ST depression measured after equal duration of sublingual exercise loads. However, ST depression after equal exercise was an average of 1 mm less ($P < 0.05$) one hour after nitroglycerin ointment than it was after placebo (fig. 4); at three hours the difference was 0.9 mm ($P < 0.05$).

Persistent changes in resting heart rate and blood pressure were noted following administration of nitroglycerin ointment (fig. 5). Mean heart rate increased from 83 to 98 beats/min three hours after nitroglycerin ointment. One and three hour values differed significantly from control, but not from each other. In contrast, administration of placebo failed to alter heart rate and blood pressure. In the six patients studied before and after chronic nitroglycerin ointment, heart rate and blood pressure responses produced acutely by nitroglycerin ointment did not differ significantly from those observed following its chronic administration. Moreover, in the five patients so tested, changes in heart rate and blood pressure produced by 0.3 mg of sublingual nitroglycerin did not differ significantly in the acute and chronic phases of the study. Thus, there was no evidence that patients became tolerant to the circulatory effects of nitroglycerin.

**Figure 3**

Change in exercise duration at onset of angina produced by sublingual administration of nitroglycerin (vertical axis) is compared before (left column) and after (right column) chronic administration of nitroglycerin ointment. Results from the same patient are connected. As indicated by the mean values (circled bars) there was no significant change.

**Figure 4**

Amplitude of ST segment depression in lead CM5 (vertical axis) after placebo (left of each panel) and after nitroglycerin ointment (right of each panel) measured after equal amounts of sublingual nitroglycerin. Data from the same individual are connected. Mean values (numbers and circled bars) indicate a significant diminution in ischemic electrocardiographic change one hour (left panel) and three hours (right panel) after nitroglycerin ointment.

**Figure 5**

Values of heart rate (left panel) and systolic blood pressure (right panel) at rest are shown prior to nitroglycerin ointment (control) and one and three hours after nitroglycerin ointment. Results from the same patient are connected. As indicated by mean values (numbers and circled bars), a significant rise in resting heart rate and a significant fall in resting systolic blood pressure were observed one and three hours after nitroglycerin ointment. The P values refer to differences from control; one and three hour results did not differ from each other.
nitroglycerin as a result of repeated cutaneous exposure under the conditions of this study.

Discussion

The data obtained in the present investigation demonstrate that nitroglycerin ointment produced sustained enhancement of exercise capacity and attenuation of ischemic electrocardiographic changes in patients with angina pectoris. Changes in both exercise capacity and the electrocardiographic response to exercise remained undiminished for at least three hours. Concomitant long-lasting changes in heart rate and blood pressure typical of nitrate effect were also observed. Following chronic administration of nitroglycerin ointment, sustained enhancement of exercise capacity persisted, while nitrate tolerance and toxicity were not observed.

Definitive comparison of nitroglycerin ointment with other modes of nitrate therapy requires a breadth of factual information that is not available either in the present study or in the literature. There is no generally accepted value for "maximal efficacy" or "maximal duration of action" for any nitrate, including sublingual nitroglycerin. Although the degree and duration of improvement in exercise performance after nitrates may increase when progressively larger doses of the nitrate are administered, there are physiologic limits of nitrate dosage that should not be exceeded because of potentially adverse effects such as excessive hypotension and reflex tachycardia. Hence, because of safety limitations, it is unlikely that the maximal efficacy and duration of action of nitrates can ever be determined in patients with angina. For these reasons, we examined the effects of a dose of nitroglycerin ointment that was judged physiologically effective by purely arbitrary criteria. It is possible that a larger dose would produce even greater and more prolonged benefit than that observed in the present study. Lack of knowledge of the full dose-response relation inevitably introduces an element of uncertainty into every comparison of the efficacy of nitrates.

Nevertheless, nitroglycerin ointment exhibited a consistently prolonged beneficial influence that, in practice, has never been demonstrated for any other nitrate used in the therapy of angina. One hour after application of nitroglycerin ointment, exercise capacity was increased significantly (i.e., by one minute or more) in 12/13 patients. More importantly, exercise capacity continued to show increases of greater than one minute in 10/13 patients studied three hours after treatment (fig. 2). Using similar testing techniques, studies from this laboratory previously demonstrated that "ordinary," physiologically effective doses of either sublingual nitroglycerin (0.6-0.8 mg) or the allegedly "long-acting" sublingual agent, isosorbide dinitrate (5-10 mg) produced comparable degrees of improvement in only 2/8 patients and 4/11 patients, respectively, when testing was performed one hour after treatment, neither sublingual agent produced any measurable increase in exercise capacity two hours after administration. Other studies of sublingual isosorbide dinitrate and other sublingual "long-acting" nitrates tend to confirm a lack of demonstrable beneficial influence on exercise capacity two hours after treatment with "usual" doses. Certain oral agents, such as pentacetythrol tetranitrate, have been thought to yield benefit for more than three hours. The degree of improvement observed after oral agents, however, is often less than that seen after sublingual agents. In contrast, the magnitude of observed benefit after nitroglycerin ointment (3.0-2.4 min mean increase in exercise capacity) is indistinguishable from the peak benefit (2.7 min mean increase) after "ordinary" doses of sublingual isosorbide dinitrate. Hence, nitroglycerin ointment, in the doses used in the present study, appears equally efficacious and far more long lasting than commonly employed doses of sublingual isosorbide dinitrate.

As previously discussed, the comparison just presented undoubtedly depends heavily upon the particular techniques used to choose drug dosage. Larger doses of either sublingual or oral (or cutaneous) agents may be significantly more beneficial and long lasting. Thus, although the precise place of nitroglycerin ointment within the armamentarium of antianginal agents must be defined by further testing and clinical experience, the results obtained in the present study indicate that at least one nitrate preparation now available can consistently produce marked improvement in exercise capacity and in the exercise electrocardiogram for at least three hours.

While data concerning the time course of transcutaneous nitrate absorption are lacking, presumably the differences in duration of improved exercise performance produced by sublingual and cutaneous nitroglycerin reflect differences in the rate of entry of nitroglycerin into the bloodstream. It is probable that cutaneous administration of nitroglycerin permits gradual absorption of larger doses of nitrate than would be tolerated if administered by the sublingual route. In addition, it should be noted that cutaneous administration of nitrates may be particularly advantageous relative to the oral route of administration. Oral nitrates, carried to the liver in relatively high concentrations by the portal circulation, may experience particularly rapid hepatic degradation. In contrast, cutaneous administration, like sublingual administration, permits...
direct introduction of nitrate esters into the systemic circulation.

The availability of a truly long-acting nitrate raises important questions about nitrate tolerance and dependence. Tolerance to circulatory effects of organic nitrates has been experimentally demonstrated in animals and in man,19-20 but tolerance to the beneficial influence of nitrates on exercise capacity was not found after isosorbide dinitrate was taken sublingually by patients four times daily for periods lasting up to seven months. Similarly, tolerance was not observed in the present study in the patients receiving chronic nitroglycerin ointment therapy. Nonetheless, a more extensive evaluation of nitrate tolerance is clearly required.

Nitrate dependence has been hypothesized to explain the excess morbidity and mortality related to angina, myocardial infarction and sudden death in heavily exposed populations of industrial nitrate workers.21-22 Symptoms in this group of patients occur during periods of withdrawal from nitrate exposure. No evidence of nitrate dependence was observed in the present study. Before the widespread use of nitroglycerin ointment can be recommended, however, greater assurance must be obtained that nitrate dependence does not develop as a result of nitroglycerin ointment therapy.

Finally, it should be emphasized that use of nitroglycerin ointment can expose the patient to very large doses of nitroglycerin. Careful individual adjustment is required to prevent manifestations of nitrate overdose. When used in the manner we have described, the doses of nitroglycerin ointment recommended by the manufacturer may be excessive in some patients and smaller initial doses are advisable.

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References

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