Nitrates in the Prophylactic Treatment of Angina Pectoris

It generally is recognized that prophylactically administered sublingual nitroglycerine exerts a potent yet short-lived beneficial effect on the exercise capacity of patients with coronary artery disease and angina pectoris. Efforts to achieve more prolonged therapeutic action have resulted in the introduction of a variety of nitrate preparations, some with altered molecular structure, others with altered route of administration, still others with both of these changes. Rather than providing a clear solution to a therapeutic problem, however, these preparations have posed a methodologic dilemma: how does one definitely evaluate long-acting agents given prophylactically for angina?

Measuring blood levels of nitrate esters or assessing the influence of nitrates on circulatory function will certainly contribute much to our understanding of nitrate effects. Nevertheless, the worth of an agent given primarily for the prevention of angina must ultimately rest upon data relating directly to the precipitation of ischemic chest pain. A drug that maintains suitable blood levels, hemodynamic alterations, or even improved ischemic electrocardiographic patterns for prolonged periods would still have only questionable value in the treatment of exertional angina if a concomitant increase in the patient's ability to perform exercise could not be demonstrated. Experience in our laboratory and elsewhere has shown that, when testing conditions are suitable, individuals consistently develop ischemic chest pain after a given duration of exercise, even when multiple exercise trials are performed. Measuring exercise capacity and the effects of a therapeutic intervention acutely in this manner avoids the variability that fluctuations in daily activity produce when efficacy of a therapeutic intervention is assessed by counting anginal episodes or recording the consumption of nitroglycerin tablets. However, exercise testing may not be as useful in identifying modes of therapy for angina precipitated by factors unrelated to exertion. For example, interventions, such as diuresis, that ameliorate nocturnal angina may not be equally effective in improving exercise performance.

Even when a suitable testing method is devised, care must be observed in choice of drug dosage—particularly when comparing two or more agents. Amplitude and duration of drug response are, in general, intimately related to the particular drug dose administered. Thus, a larger dose of a given drug may appear relatively "long-acting" simply because more drug and more drug effect were present at the outset. When comparing a single dose of each of two drugs with similar modes of action, one particular drug may appear superior, equivalent, or inferior relative to the second drug, depending on the particular dose chosen for each drug. For these reasons, broadly applicable conclusions cannot be made with certainty about the relative merits of two nitrate preparations based upon patient performance after a single arbitrarily chosen dose of each drug.

A number of different nitrate esters have been offered as sublingual substitutes for nitroglycerin in the hope that molecular alteration may prolong efficacy. A theoretical basis for this conjecture is lacking: the studies of Needleman, Blehm and Rotskoff have shown that susceptibility of the various nitrates to biological degradation parallels vasodilator potency. Thus, relative resistance of certain nitrates to metabolic destruction may be nullified by the necessity of these molecules to appear in higher concentration before the desired effect is achieved. When 16 different nitrate esters were given in doses producing an equal fall in blood pressure, the duration of action of each on blood pressure was indistinguishable. In contrast, a recent hemodynamic comparison of isosorbide dinitrate and nitroglycerin, in which fixed doses were employed, demonstrated reduction in pulmonary artery wedge pressure at one hour only after treatment with isosorbide dinitrate. In this study, however, the dose ratio of isosorbide dinitrate to nitroglycerin was 25:1, compared with an approximately 10:1 ratio required to produce equipotent circulatory effects at onset of action in the study of Needleman, Blehm and Rotskoff and in our own experience.
In exercise studies reporting a more long-lasting effect after sublingual isosorbide dinitrate\textsuperscript{5-7} or other sublingual nitrate esters\textsuperscript{7} as compared to nitroglycerin, single, arbitrarily chosen doses were usually examined. The studies did not exclude the possibility that similarly prolonged benefit might be duplicated by appropriate doses of nitroglycerin. Studies in our laboratory\textsuperscript{4} were performed using sublingual doses of nitroglycerin and isosorbide dinitrate specifically chosen so that each drug produced the same change in blood pressure at rest. Because equivalence of blood pressure reduction cannot, a priori, be equated with equivalence of beneficial influence on ischemic chest pain, it is important to note that both nitroglycerin and isosorbide dinitrate produced the same degree of improvement in exercise capacity at the beginning of exercise testing. Under these circumstances the improvement in exercise capacity diminished at the same rate after nitroglycerin and after isosorbide dinitrate, each drug having a half-time of about twenty minutes. Thus, there was no suggestion that sublingual isosorbide dinitrate favorably influenced exercise capacity for a longer period than a matched dose of nitroglycerin.

It also is interesting to note that persistence of hemodynamic change was not always correlated with a similar persistence of beneficial action on exercise capacity. For example, no patient tested two hours after isosorbide dinitrate manifested improvement in exercise capacity, yet four out of five continued to have a reduced blood pressure during exercise. Inferences made about the duration of action of isosorbide dinitrate on symptoms, based on duration of blood pressure changes, would therefore have been incorrect.

Setting aside the relative merits of the various nitrate compounds, it is important to note that none of the highly effective sublingual preparations offers truly long-lasting benefit. Even if a particular nitrate could be shown to exert a beneficial effect with a half life of 30 minutes—50\% greater than that empirically found for isosorbide dinitrate—the patient's exercise capacity would exceed 25\% of the peak nitrate-induced increase for only an hour after each dose, and during the night he would receive essentially no protection.

Oral administration of a variety of nitrate esters, including nitroglycerin, has been advanced as a method of achieving long-lasting prophylactic benefit. However, this route of administration may be uniquely disadvantageous: delivery of these drugs via the portal vein may favor rapid degradation by hepatic enzymes with consequent loss of vasodilator action.\textsuperscript{8} Despite their widespread use relatively little is known concerning the clinical or circulatory actions of orally administered nitrates. Exercise testing revealed either no benefit\textsuperscript{6} or an inconsistent improvement\textsuperscript{5,10} after oral isosorbide dinitrate, in marked contrast to the consistent and unequivocal improvement following the same drug given sublingually. Modest improvement has been noted after oral penterythritil tetranitrate.\textsuperscript{5} Long-lasting hemodynamic alterations and reduction of ischemic electrocardiographic changes have been reported after oral nitroglycerin,\textsuperscript{11,12} but data describing changes in exercise capacity after oral nitroglycerin are lacking.

It should be noted that evaluations of oral nitrate therapy generally employ a relatively narrow, arbitrarily chosen dosage range. Perhaps larger doses (in some individuals) may yield more dramatic degrees of improvement. It is probably premature to arrive at a final judgment concerning the therapeutic value of oral nitrates on the basis of data currently available. Nevertheless, it appears unwise at present to set aside clearly effective modes of nitrate therapy in favor of the oral agents, whose beneficial effects, at best, seem marginal and inconsistent.

Another approach to achieving long-lasting nitrate benefit, well known to older clinicians, has been the administration of nitroglycerin cutaneously.\textsuperscript{12} Although this mode of therapy has been available for nearly two decades, little precise evidence has been obtained concerning its efficacy. We therefore evaluated the influence of cutaneously administered nitroglycerin in the exercise laboratory.\textsuperscript{14} When nitroglycerin ointment was applied in amounts sufficient to produce distinct changes in blood pressure and heart rate at rest, a marked and consistent beneficial effect was observed on exercise capacity and the exercise electrocardiogram one hour after application, which persisted essentially undiminished three hours after application. Our results do not prove that cutaneous administration is a uniquely superior mode of nitrate therapy. Nonetheless, these studies do document that cutaneously administered nitroglycerin is capable of conferring benefit for at least three hours. Thus, it is possible that change in route of administration, rather than alteration in the organic portion of the nitrate molecule, might be a more successful means of approaching a sustained and potent nitrate response.
Even if it were possible to devise a reliable means of obtaining a truly long-acting nitrate effect, certain important reservations remain concerning the desirability and safety of such treatment. For example, the possibility that repeated use of organic nitrates will lead to an eventual loss of efficacy has been suggested repeatedly. Huge doses of nitroglycerin appear to produce tolerance to circulatory effects in experimental animals, and a preliminary report suggested reduced venodilator response to nitroglycerin in patients chronically receiving isosorbide dinitrate. Our own studies, however, failed to demonstrate tolerance to nitrate-induced increases in exercise capacity after several weeks of therapy with regular doses of either nitroglycerin ointment or sublingual isosorbide dinitrate.

A second (and even more alarming) possible result of effective chronic nitrate therapy is physiologic drug dependence. Toxicologists have postulated that the chronic nitroglycerin exposure experienced by workers in the explosives industry may lead to a compensatory increase in vasomotor tone which, they suggested, could produce excessive constriction of coronary and other vascular beds when the vasodilatory influences of nitrates are suddenly removed. This coronary vasoconstrictor action during nitrate withdrawal was offered to explain the disturbingly high frequency of otherwise unexplained myocardial infarctions among nitrate workers. There is no evidence that dependence is a problem in patients receiving usual therapeutic doses of nitrates. It is possible, however, that dependence might become a problem among patients with coronary artery disease if a more effective means were devised for delivery of nitrates to the blood stream.

To summarize, the complexities of evaluating antianginal agents have led to much confusion regarding the various nitrate preparations. The resulting controversies are probably best resolved by appreciating very real differences in the approach employed by different investigators and by applying sound principles of pharmacology and physiology. At present, the weight of evidence suggests that most sublingual nitrates, though very effective, are not particularly long-lasting with regard to symptomatic improvement. Recent exercise data, however, suggest that nitroglycerin ointment may be distinctly superior to either sublingual or oral nitrates in angina prophylaxis. The use of nitroglycerin ointment certainly deserves careful reassessment. Before pursuing this course, however, one must give serious consideration to the possibility of untoward effects, in particular the possibility of nitrate tolerance and nitrate dependence.

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