

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***NITRATE THERAPY FOR STABLE ANGINA PECTORIS**

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THE organic nitrates are widely used in the management of coronary artery disease. They are given not only to patients with stable angina pectoris, but also to those with unstable angina, acute myocardial infarction, and heart failure. Although they are effective for the treatment of these disorders, their therapeutic value is compromised by the rapid development of tolerance during sustained therapy. This review will be limited to the use of organic nitrates in patients with chronic stable angina pectoris, but many of the principles enunciated are relevant to other clinical situations.

In 1879 Murrell reported that a 1 percent solution of nitroglycerin administered orally relieved angina and prevented subsequent attacks.¹ It was soon recognized that continued treatment resulted in the development of tolerance.² Subsequent experiments in animals confirmed that the short-term administration of organic nitrates had dramatic hemodynamic effects that rapidly diminished during sustained administration.³

PHARMACOLOGY OF ORGANIC NITRATES

The most commonly used organic nitrates are nitroglycerin (glyceryl trinitrate), isosorbide dinitrate, and isosorbide mononitrate (Fig. 1). These drugs are available in a variety of formulations with different routes of administration (Table 1). Although they are not commonly prescribed in North America, erythryl tetranitrate and pentaerythritol tetranitrate are widely used in certain parts of the world.

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The nitrates are rapidly absorbed from the gastrointestinal tract, skin, and mucous membranes.⁵ Isosorbide dinitrate and nitroglycerin undergo extensive first-pass hepatic metabolism when given orally.⁶ Nitroglycerin has a plasma half-life of approximately one to four minutes. It undergoes hepatic and intravascular metabolism, yielding biologically active dinitrate metabolites that have a half-life of approximately 40 minutes.^{5,7}

Experiments in animals showed that isosorbide administered through the portal vein had no hemodynamic effects.⁸ These results called into question the therapeutic efficacy of orally administered isosorbide, since they suggested that the drug was completely metabolized during its first pass through the liver. Subsequent studies in patients with coronary artery disease refuted these findings, because oral isosorbide dinitrate clearly had substantial hemodynamic and antianginal effects.⁹⁻¹¹ Isosorbide dinitrate, although it has hemodynamic and antianginal effects, is rapidly metabolized, with a plasma half-life of approximately 40 minutes. Its major metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, are both biologically active, with half-lives of approximately two and four hours, respectively.⁵ Isosorbide mononitrate (isosorbide-5-mononitrate), which has recently become available in North America, does not undergo first-pass hepatic metabolism and is completely bioavailable.

MECHANISMS OF ACTION OF THE ORGANIC NITRATES

The organic nitrates are prodrugs and must be biodegraded to have therapeutic effects. This biotransformation involves denitration of the nitrate, with the subsequent liberation of nitric oxide. Nitric oxide stimulates guanylyl cyclase, which leads to the conversion of guanosine triphosphate to cyclic guanosine monophosphate, which in turn causes vasodilation.^{12,13} The exact mechanism by which the organic nitrates undergo denitration and thus liberate nitric oxide remains controversial.^{14,15} Although it was originally proposed that reduced sulfhydryl groups were an essential substrate for bioconversion,^{16,17} they are probably required only as cofactors.^{14,15}

Nitric oxide is also known as endothelium-derived relaxing factor.¹⁸ In addition to exerting vasodilating effects, it reduces platelet adhesion and aggregation. The administration of nitrates has similar effects.¹⁹ Nitric oxide is also involved in the control of endothelial function and vascular growth¹⁸ as well as my-

ocardial contractility.²⁰ Since the availability of nitric oxide is decreased in a variety of conditions associated with endothelial dysfunction, it is possible that the organic nitrates, as exogenous donors of nitric oxide, might have beneficial effects in these conditions. Although this is an attractive hypothesis, it has yet to be tested in humans.

The hemodynamic and antianginal actions of the organic nitrates are mediated through vasodilatation of capacitance veins and conductive arteries. Dilatation of capacitance veins reduces ventricular volume and preload, thus lowering myocardial oxygen requirements and improving subendocardial blood flow. Dilatation of systemic conductive arteries in combination with the reduction of left ventricular volume lowers afterload, another determinant of myocardial oxygen consumption. Nitrates dilate epicardial coronary arteries, including stenotic segments, which can have beneficial effects.²¹ Nitrates also dilate collateral vessels, which can improve blood flow to areas of ischemia.²² In the doses used clinically, however, they do not affect coronary resistance vessels,¹⁵ thus reducing the risk of myocardial ischemia due to coronary steal, which can occur with drugs such as dipyridamole and short-acting dihydropyridines that cause arteriolar dilation.^{23,24} Therefore, the nitrates possess a unique combination of vascular effects that can favorably affect the mismatch between myocardial oxygen supply and demand in patients with coronary artery disease.

ORGANIC NITRATES IN THE TREATMENT OF ANGINA

Treatment of Episodes of Angina

Nitroglycerin is the drug most frequently used for treating anginal attacks. It is usually given as a sublingual tablet but is also available as a sublingual spray. The advantage of the spray is that the sublingual tablets deteriorate in an unpredictable fashion once exposed to air. The tablets should be replaced every three months, whereas the spray is stable for at least three years. Isosorbide dinitrate is also available as a sublingual tablet, but its onset of action is slower than that of the nitroglycerin preparations.

Prevention of Angina with Nitroglycerin

Sublingual Nitroglycerin

The beneficial effect of sublingual nitroglycerin tablets in the prophylactic treatment of angina is often overlooked. Many patients can predict which activities will induce angina and are able to prevent it by using sublingual nitroglycerin two to five minutes before undertaking these activities. In some patients this obviates the need for other antianginal therapy.^{25,26}

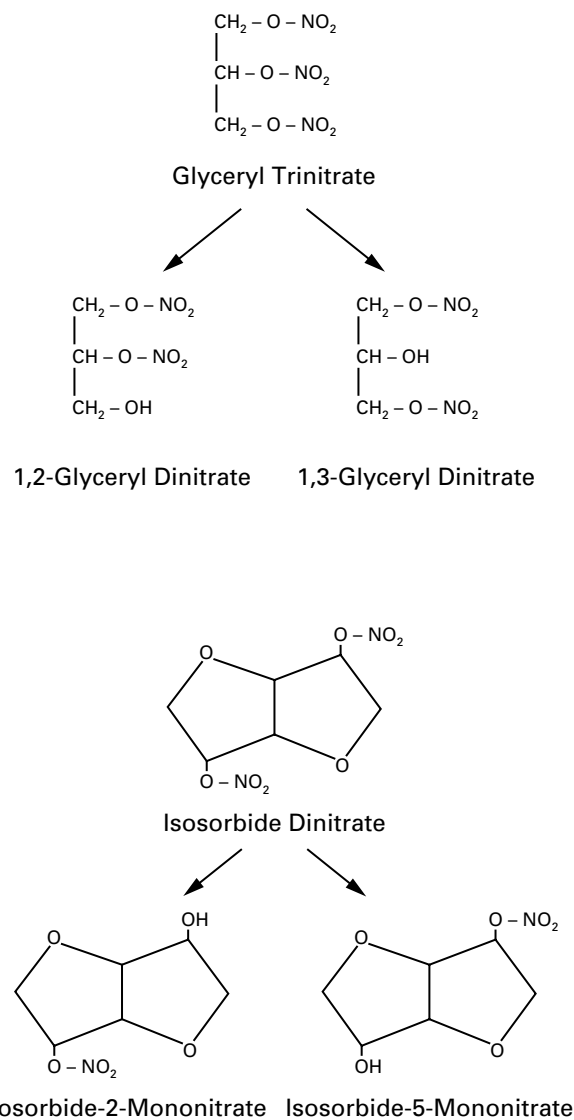


Figure 1. Chemical Structures of the Commonly Used Organic Nitrates.

1,2-Glyceryl dinitrate and 1,3-glyceryl dinitrate are biologically active metabolites of nitroglycerin. Isosorbide-2-mononitrate and isosorbide-5-mononitrate are biologically active metabolites of isosorbide dinitrate. Modified from Torfgard and Ahlner.⁴

Oral Nitroglycerin

Nitroglycerin is available as an oral preparation that is given every 8 to 12 hours. This dosing regimen increases exercise tolerance for up to four hours after a morning dose, but there are no well-designed studies demonstrating efficacy throughout the dosing interval.²⁷ Because of the limited data on efficacy during sustained therapy and the absence of data on efficacy throughout the dosing interval, we do not recommend oral nitroglycerin.

TABLE 1. NITRATE PREPARATIONS, ROUTES OF ADMINISTRATION, AND DOSING STRATEGIES.*

DRUG AND INDICATION	ROUTE	DOSE RANGE	FREQUENCY
Treatment of anginal attacks			
Nitroglycerin tablets	Sublingual	0.3–0.6 mg	1–3 times†
Nitroglycerin spray	Sublingual	0.4–0.8 mg	1–3 times†
Nitroglycerin buccal tablets	Buccal	1–3 mg	Once
Prevention of anginal attacks			
Nitroglycerin tablets	Sublingual	0.3–0.6 mg	2–5 min before activity
Nitroglycerin spray	Sublingual	0.4–0.8 mg	2–5 min before activity
Nitroglycerin buccal tablets	Buccal	1–3 mg	2–5 min before activity or 3 times/day, tablet removed overnight
Nitroglycerin SR	Oral	2.6–10.4 mg	2–3 times/day‡
Nitroglycerin ointment	Transdermal	1–10 cm	3–4 times/day, remove for 12 hr§
Nitroglycerin patch	Transdermal	0.2–0.8 mg/hr	Once daily, 12-hr patch- free interval
Isosorbide dinitrate SF	Sublingual	2.5–10 mg	5–10 min before activity
Isosorbide dinitrate SF	Oral	10–45 mg	3 times/day, 14-hr tab- let-free interval
Isosorbide dinitrate SR	Oral	20–80 mg	1–2 times/day¶
Isosorbide mononitrate SF	Oral	10–20 mg	2 times/day, 7 hr be- tween doses
Isosorbide mononitrate SR	Oral	30–240 mg	Once daily

*SR denotes sustained-release formulation providing therapeutic plasma concentrations for 12 hours, and SF standard formulation.

†Dose may be repeated after five minutes for a total of three doses. If pain persists, patient should seek medical care.

‡There are no data supporting the efficacy beyond four hours during sustained therapy with sustained-release oral nitroglycerin.

§There are no data supporting the efficacy of intermittent use of transdermal nitroglycerin ointment.

¶There are no data supporting the efficacy of the sustained-release isosorbide dinitrate formulation marketed in the United States. If used, these preparations should be given as a single daily dose or eccentrically with a 16-to-18-hour tablet-free interval.

Nitroglycerin Ointment

Single doses of nitroglycerin ointment have clinically important antianginal effects,^{28,29} but only one study has documented efficacy during sustained therapy.²⁸ Nevertheless, given the efficacy of other transdermal preparations, we believe that nitroglycerin ointment is effective if an intermittent regimen with a 12-hour dose-free interval is followed.

Nitroglycerin Transdermal Patches

Nitroglycerin patches were introduced in the United States in the early 1980s, on the basis of the demonstration of therapeutic plasma nitroglycerin concentrations throughout a 24-hour period. The results of studies of transdermal nitroglycerin therapy demonstrate loss of effects during continuous therapy.^{30,31} For example, in a study of continuous transdermal nitroglycerin therapy in 562 patients, tolerance developed in most patients within 24 hours, with loss of antianginal effects that could not be overcome by larger doses.³² The provision of a patch-free period is effective in preventing, or at least reducing, tolerance.^{33–36} The most compelling evidence suggests

that a 12-hours-on, 12-hours-off schedule is effective in improving exercise performance in patients with chronic stable angina pectoris.^{34,36}

Prevention of Angina with Isosorbide Dinitrate

Sublingual Isosorbide Dinitrate

Sublingual isosorbide dinitrate is also useful in the prevention of angina. With its longer half-life, sublingual isosorbide dinitrate can provide effective antianginal prophylaxis for up to one hour.³⁷

Standard-Formulation Isosorbide Dinitrate

A wide range of doses of standard-formulation isosorbide dinitrate have clinically significant antianginal effects when given over the short term.¹⁰ Standard-formulation isosorbide dinitrate is rapidly absorbed and must be given every four to six hours to maintain therapeutic plasma concentrations. During long-term therapy with isosorbide dinitrate given four times daily, with the last dose given at bedtime, partial tolerance to its hemodynamic and antianginal effects developed.¹¹ Tolerance occurred despite higher plasma concentrations of the parent

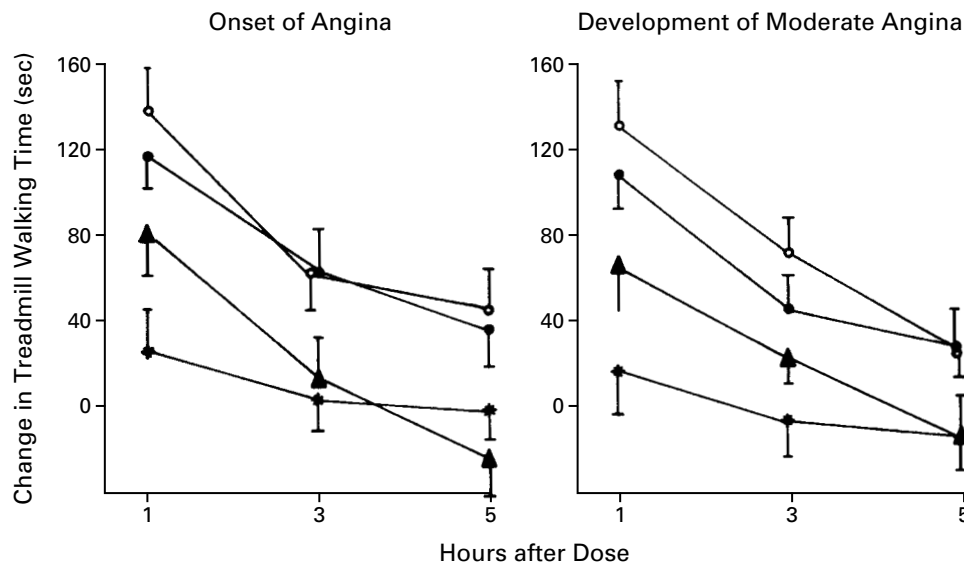


Figure 2. Changes in Mean (\pm SE) Treadmill Walking Time until the Onset of Angina and the Development of Moderate Angina during Sustained Therapy with Isosorbide Dinitrate Twice Daily (Solid Circles), Three Times Daily (Open Circles), and Four Times Daily (Triangles), and with Placebo Four Times Daily (Asterisks) in 12 Patients with Coronary Artery Disease.

Modified from Parker et al.³⁸

drug and active metabolites during sustained therapy than during short-term administration.¹¹

In a subsequent study in which isosorbide dinitrate was given three times daily, with a tablet-free period of 14 hours, tolerance did not develop (Fig. 2).³⁸ In this study, exercise testing was performed only after the morning dose, and the effects of the second and third doses were not reported. In another study of eight patients with stable angina who were following a similar dosing regimen, the anti-anginal effects decreased progressively after the second and third daily doses.³⁹ Therefore, it remains unclear whether therapy with isosorbide dinitrate provides sustained antianginal effects throughout the day.

Sustained-Release Isosorbide Dinitrate

Sustained-release isosorbide dinitrate has a slower rate of absorption and results in therapeutic plasma concentrations for 12 hours. When given in doses of 80 mg every 12 hours, it leads to the development of tolerance.⁴⁰ In contrast, when given once daily, or twice daily with less than 12 hours between the two doses (that is, in an eccentric fashion), it has continued antiischemic effects.⁴⁰ The sustained-release preparation of isosorbide dinitrate approved in the United States is marketed as a twice-daily preparation in doses of 20 to 80 mg, but there are no data from controlled clinical trials documenting efficacy.

Prevention of Angina with Isosorbide Mononitrate

Standard-Formulation Isosorbide Mononitrate

In clinical studies of patients with angina pectoris, the standard formulation of isosorbide mononitrate in doses of 20 and 40 mg induced tolerance when given every 12 hours for one week.^{41,42} In contrast, when given in an eccentric fashion — that is, twice daily with 7 hours between doses — its antianginal efficacy lasted for 12 hours.^{43,44}

Sustained-Release Isosorbide Mononitrate

A sustained-release formulation of isosorbide mononitrate has been developed that provides therapeutic plasma drug concentrations for up to 12 hours each day and low concentrations during the latter part of the 24-hour period. In a recent multicenter clinical trial, sustained therapy with large doses (120 and 240 mg) was effective for up to 12 hours each day.⁴⁵

Nitrates as Initial Preventive Therapy

Nitrates have been proved effective in patients with stable angina. Their safety profile, with few serious side effects, makes them an attractive choice as initial therapy (Table 2 and Fig. 3). This is particularly true if the angina responds well to sublingual nitroglycerin. The use of nitrates should be considered in patients with a variable anginal threshold,

TABLE 2. SIDE EFFECTS OF ORGANIC NITRATES.

DRUG AND ROUTE	SIDE EFFECTS	COMMENTS
Sublingual Nitroglycerin Isorbide dinitrate Erythryl tetranitrate	Headache, postural hypotension, syncope	Dose reduction may be required
Oral Nitroglycerin Isorbide dinitrate Isorbide-5-mononitrate Erythryl tetranitrate Pentaerythritol tetranitrate	Headache, postural hypotension, syncope, nausea	Headache and postural hypotension often resolve after several days of therapy; resolution of headache does not necessarily mean loss of efficacy
Transdermal Nitroglycerin	Headache, postural hypotension, syncope, nausea, skin erythema and inflammation at site of patch application	Initiate treatment with small doses and increase as necessary; vary application site

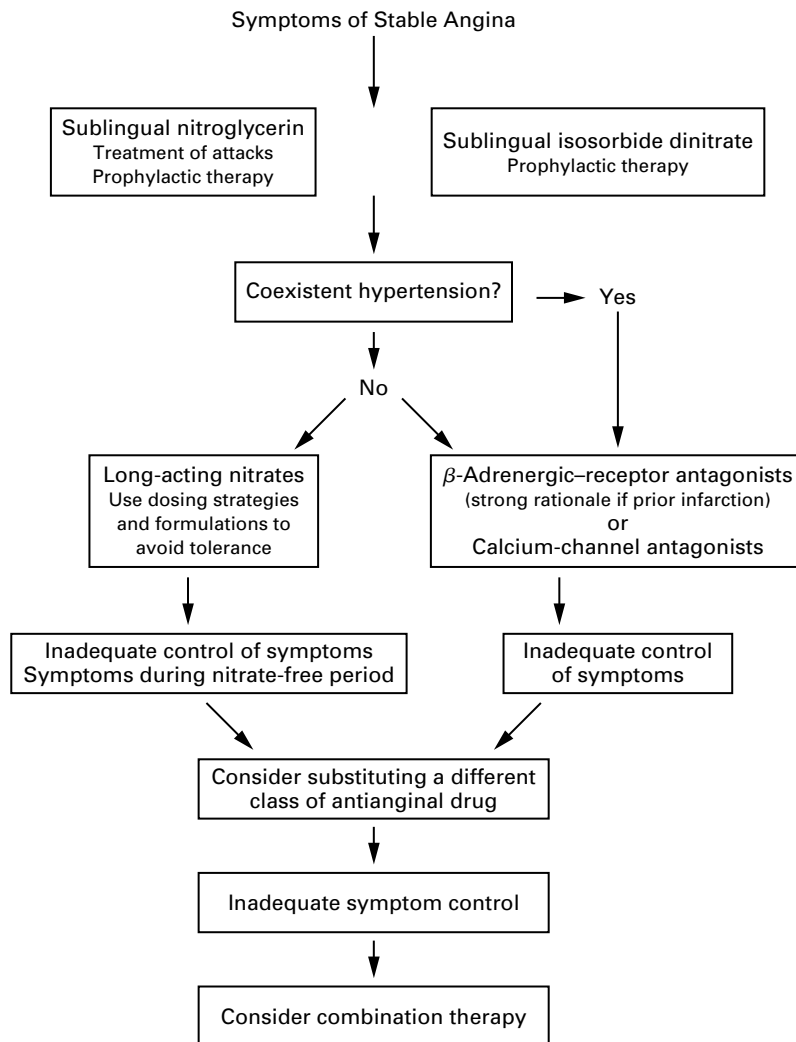


Figure 3. Diagram of the Treatment of Stable Angina with Antianginal Drugs. This scheme assumes that management decisions concerning possible revascularization have been made by using standard clinical approaches.

because they can prevent intermittent coronary constriction. Nitrates are also a good choice in patients with left ventricular dysfunction or mitral insufficiency, because they can reduce filling pressures and mitral regurgitation. In contrast, in patients with concomitant hypertension or myocardial infarction, nitrates should not be used initially, because they are not effective in the treatment of hypertension or for secondary prevention after myocardial infarction. Although there are no data to suggest that nitrates are superior to β -adrenergic antagonists or calcium-channel antagonists, we believe that nitrates are appropriate initial therapy for many patients with angina pectoris.

Of the available nitrate preparations, only a limited number have been demonstrated to have antianginal efficacy for up to 12 hours each day. They include transdermal nitroglycerin patches, standard-formulation isosorbide mononitrate given eccentrically, and controlled-release isosorbide mononitrate given once daily (Table 1). Although sustained-release preparations of isosorbide dinitrate provide antiischemic effects for 12 hours each day, there are no studies supporting the use of the long-acting preparation marketed in the United States. There are also no studies suggesting the superiority of a particular nitrate preparation. Since their side-effect profiles are similar, the choice of nitrate preparation should be made on the basis of convenience, compliance, and cost, and a once-daily regimen should be used whenever possible.

Combination Therapy

The nitrates are commonly prescribed in combination with other antianginal drugs if exertional angina is poorly controlled or if it occurs during a nitrate-free interval. There is little evidence that combination therapy is of greater benefit than monotherapy in the treatment of exertional symptoms. The results of small studies designed to determine the efficacy of combined therapy with nitrate and β -adrenergic antagonists have been contradictory.⁴⁶⁻⁴⁹ Several recent large clinical trials of the efficacy of oral and transdermal nitrates permitted concurrent therapy with a β -adrenergic antagonist. In these studies, in which approximately 50 percent of the patients were receiving combined therapy, the long-acting nitrate provided clear benefit.^{34,36,44,45} No attempt was made in these trials to optimize concurrent β -adrenergic-antagonist therapy. Therefore, it remains unclear whether such combination therapy is more effective than optimal nitrate or β -adrenergic-antagonist therapy alone. Even less information is available concerning the role of combination therapy with a nitrate and a calcium-channel antagonist.

Only a small number of studies of triple-antianginal-drug therapy have been reported. Most of these

studies involved the addition of a calcium-channel antagonist to therapy with a nitrate and a β -adrenergic antagonist. Although positive results were reported, the nitrate regimen used either was known to be associated with tolerance⁵⁰ or was unspecified.⁵¹

Given the limited data supporting combination therapy, it seems best to maximize monotherapy before instituting combination therapy. Furthermore, consideration should be given to substituting another antianginal drug in patients with persistent symptoms rather than routinely prescribing combination therapy. If combination therapy is necessary, it would seem logical to combine a nitrate with a drug that has a negative chronotropic effect (a β -adrenergic antagonist or nondihydropyridine calcium-channel antagonist).

NITRATE TOLERANCE

A major limitation of the use of nitrates is the development of tolerance, defined as the loss of hemodynamic and antianginal effects during sustained therapy. Although the cause of nitrate tolerance is unclear, it is not due to altered pharmacokinetics, because with continued nitrate therapy plasma drug concentrations are similar to or higher than those during initial therapy.¹⁰ Initially, it was thought that tolerance was due to loss of the vascular effects of the nitrate, a conclusion based largely on the results of *in vitro* studies demonstrating rapid loss of the vasodilating effects during exposure to nitrates.^{16,52-54} Although there can be no doubt that loss of hemodynamic effects does occur, it is now clear that some vascular effects of nitrates persist during continued therapy. Plasma volume remains expanded during continued nitroglycerin therapy, despite the presence of tolerance as defined by loss of the initial hypotensive effect.⁵⁵⁻⁵⁸ Similarly, withdrawal of nitroglycerin is associated with a decrease in exercise performance, despite the presence of tolerance before withdrawal, a finding suggesting that the nitrate continues to be active despite loss of effects on exercise performance.^{34,59} The mechanism of nitrate tolerance has been the subject of intense debate⁶⁰⁻⁶³ but remains poorly understood. The four most important hypotheses are summarized below, and a number of other hypotheses are presented in Table 3.

Sulfhydryl-Depletion Hypothesis

The most extensively studied hypothesis concerning the mechanism of nitrate tolerance is the sulfhydryl-depletion hypothesis.⁶⁹ According to this hypothesis, the loss of efficacy of nitrates during continued treatment is due to the depletion of reduced sulfhydryl groups necessary for the biotransformation of nitrate to nitric oxide.

The exact role of thiol groups in the biotransformation of organic nitrates is controversial. *In vitro*,

TABLE 3. PROPOSED MECHANISMS OF NITRATE TOLERANCE.

MECHANISM	COMMENTS
Biotransformation hypothesis Sulfhydryl depletion	Role of sulfhydryl groups in biotransformation of organic nitrates is controversial; exogenous thiols (e.g., acetylcysteine) augment nitrate responses even in the nitrate-free state; in vivo evidence does not support the hypothesis that nitrate administration leads to tissue thiol depletion; recent studies do not report a decrease in nitric oxide production during sustained therapy
Neurohormonal hypothesis Systemic responses	Although sympathetic activation and other neurohormonal responses have been documented during nitrate administration, there is no convincing evidence that they contribute to tolerance
Local vascular responses	Vascular production of endothelin-1 may be increased during therapy with nitroglycerin, and this may represent a local, counterregulatory response
Plasma-volume-expansion hypothesis	Response to therapy with nitrates is consistent, but there is no clear causal relation to tolerance
Free-radical hypothesis	Experiments in animals show that nitroglycerin therapy causes increased production of superoxide anion by the endothelium, which enhances nitric oxide degradation
Other hypotheses	
Decreased cellular uptake of nitrates	Vascular uptake of nitrates in tolerant animals is decreased ^{64,65} ; contradictory findings have been reported ⁶⁶ ; no human data are available
Decreased sensitivity to guanylyl cyclase	There are limited data from in vitro studies ⁶⁷ ; no human data are available
Increased phosphodiesterase activity	There are limited data from in vitro studies ⁶⁸ ; no human data are available

sulfhydryl groups do not prevent tolerance,^{53,70} and recent in vivo studies have failed to confirm that nitrate therapy is associated with the depletion of sulfhydryl groups in the tissues.⁷¹ Although sulfhydryl donors can restore responsiveness to nitrates in patients made tolerant to nitroglycerin,^{72,73} sulfhydryl-containing drugs such as acetylcysteine can potentiate the vascular effects of nitroglycerin in the absence of tolerance.^{74,75} The ability of sulfhydryl-containing drugs to augment vascular responses to nitrates has been interpreted as evidence of reversal of tolerance, but the augmentation of vascular responses may occur by a mechanism independent of nitrate tolerance.⁵⁴ Therefore, depletion of tissue sulfhydryl groups is probably not the cause of tolerance.

Neurohormonal Hypothesis

The neurohormonal hypothesis states that nitrate administration is associated with reflex release of several vasoconstrictor hormones that reduce the vasodilating effect of the nitrate. The administration of nitroglycerin may be associated with increases in the plasma concentrations of catecholamines, renin, and other vasoactive hormones.⁷⁶ This has not been a consistent observation, since other studies have not documented neurohormonal activation.^{58,77} Some attempts to prevent tolerance by the concurrent administration of angiotensin-converting-enzyme inhibitors were successful, but others were not.^{58,77,78} Recent evidence suggests that counter-regulatory responses may occur at the level of the vascular tissues. Studies have shown that nitrate administration is associated with increased vascular production of super-

oxide anion and the vasopressor hormone endothelin.^{79,80} Such local biochemical responses may have an important role in the loss of nitrate responses and the clinical phenomenon of tolerance.

Plasma-Volume-Expansion Hypothesis

Expansion of plasma volume is a consistent response to therapy with nitroglycerin.^{55,57,58,76} The plasma-volume-expansion hypothesis states that nitrate-induced expansion of plasma volume reverses the effects of nitrates on ventricular preload. The cause of the expansion of plasma volume is uncertain, but it does not appear to be due to sodium retention.^{55,58} The expansion persists for several days of sustained nitroglycerin therapy, which suggests continued nitrate effects despite hemodynamic tolerance (Fig. 4).⁵⁸ As with the neurohormonal responses, the role of plasma volume expansion in the development of tolerance is not clear. Attempts to prevent the development of tolerance with diuretic therapy have been carried out, with conflicting results.^{57,81-83} We recently reported that hydrochlorothiazide had no effect on the development of tolerance to the antianginal effects of transdermal nitroglycerin in a double-blind, randomized trial.⁸³

Free-Radical Hypothesis

In animals, the development of tolerance during the administration of nitroglycerin was associated with increased production of superoxide anion and could be reversed by the introduction of an antioxidant into tolerant vascular tissue.⁷⁹ These observations led to the suggestion that nitrate tolerance was

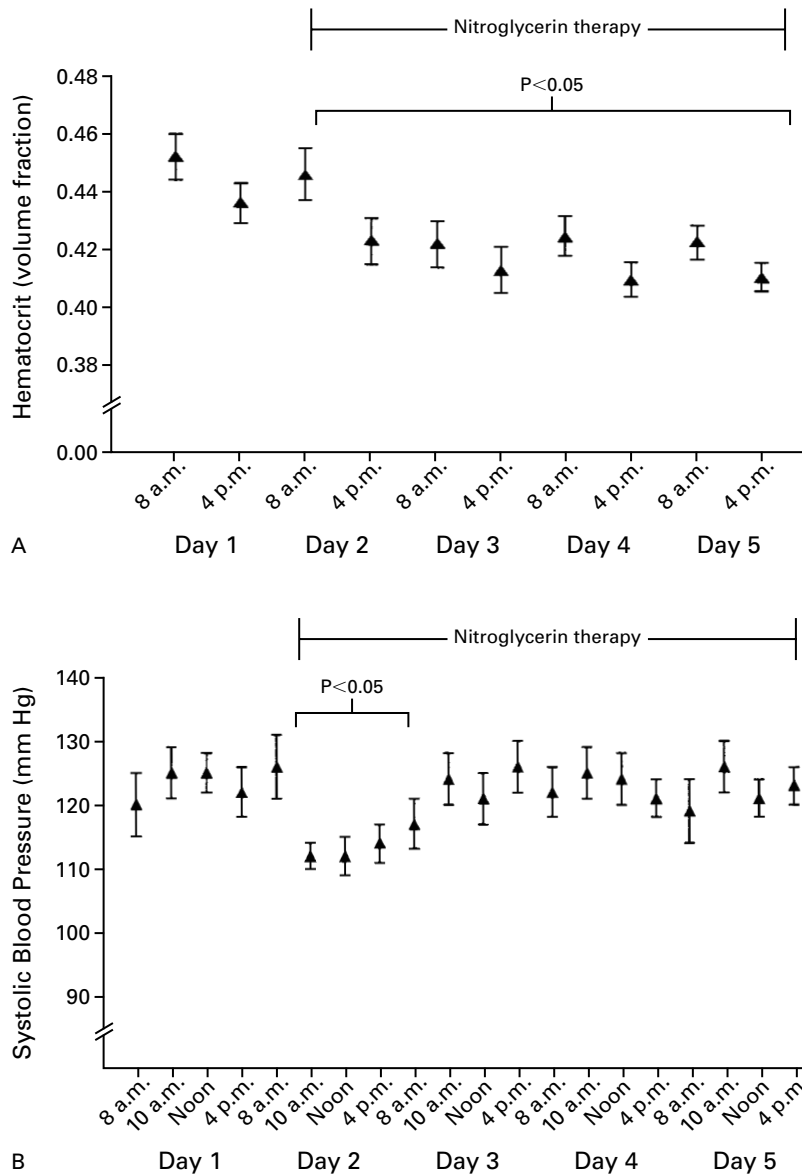


Figure 4. Effects of Transdermal Nitroglycerin Therapy. Panel A shows evidence of expansion of plasma volume, manifested by a decrease in hematocrit, in 11 normal subjects receiving continuous transdermal nitroglycerin for four days. Panel B shows systolic blood pressure responses in the same subjects during the same period. In both panels, the P value is for the comparison with day 1. Modified from Parker and Parker.⁵⁸

caused by an increase in free-radical production by the endothelium during nitroglycerin therapy. This oxidative hypothesis is supported by an earlier report of the prevention of nitrate tolerance with antioxidant compounds in rabbit aortic tissue.⁸⁴ Furthermore, a recent study reported that the administration of vitamin E prevented the development of tolerance to the arterial vascular effects of nitroglycerin.⁸⁵ The mechanism by which nitrates lead to an

increase in the production of superoxide anion is unclear, but recent evidence suggests a specific role for angiotensin II.⁸⁶ Furthermore, hydralazine can inhibit membrane-bound oxidases that may be responsible for the nitrate-induced increase in the production of superoxide anion.⁸⁷ This is of particular interest because hydralazine, when given in combination with isosorbide dinitrate in patients with heart failure, had a beneficial effect on mortality de-

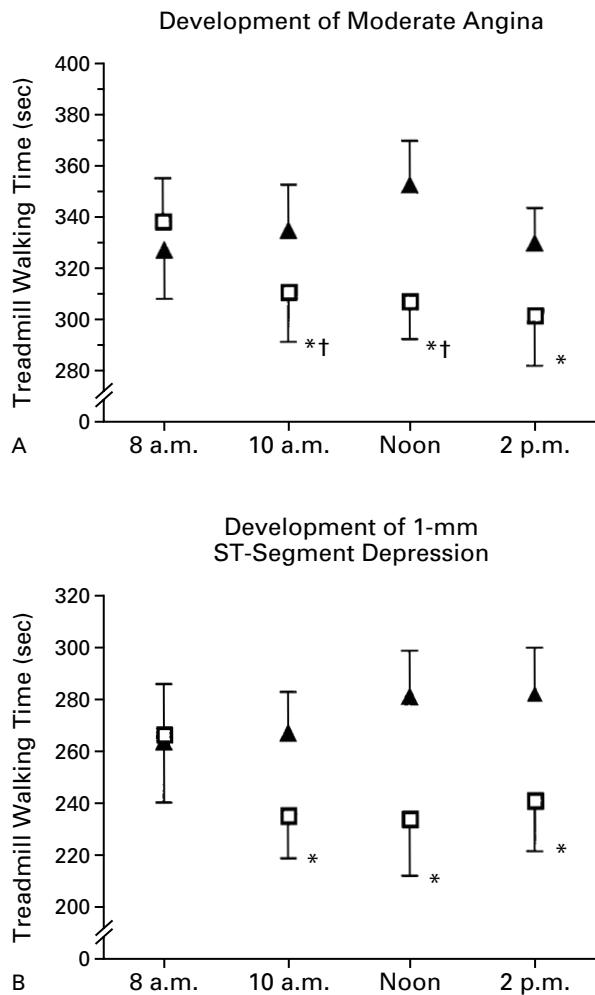


Figure 5. Treadmill Walking Time until the Onset of Moderate Angina (Panel A) and 1 mm of ST-Segment Depression (Panel B) before and after Withdrawal of Transdermal Nitroglycerin (Squares) or Placebo (Triangles) in 12 Patients with Angina Pectoris.

The withdrawal of nitroglycerin caused a significant decrease in treadmill walking time as compared with the change during the placebo period. Asterisks indicate $P < 0.05$ for the comparison with 8 a.m. The daggers indicate $P < 0.05$ for the comparison between transdermal nitroglycerin and placebo. Modified from Parker et al.⁵⁹

spite a nitrate-dosing regimen known to induce tolerance.⁸⁸ Furthermore, hydralazine has been reported to prevent the development of tolerance to the hemodynamic effects of nitroglycerin in both animals⁸⁹ and humans,⁹⁰ although in a recent study we did not confirm this.⁹¹

If these findings are correct, a new construct of nitrate tolerance can be developed, whereby the generation of reactive oxygen species with inactivation of nitric oxide has a role in the loss of responsiveness to nitrates. Such an effect could be a local, counter-regulatory response, in which the stimulating effects

of nitrate on nitric oxide production are diminished because of local degradation. This possibility would provide another explanation for the observation that acetylcysteine potentiates responsiveness to nitrates. Acetylcysteine can act as a free-radical scavenger, and it may be this characteristic, rather than its ability to act as a thiol donor, that modifies the effects of nitrates.¹⁵ At present, the mechanism of increased production of superoxide anion in response to nitrate therapy is not known. As mentioned, angiotensin II may have a role through its regulation of membrane-bound oxidases,⁸⁶ but it is not known how this might be triggered by nitrate therapy. The importance of clarifying this mechanism is emphasized by the fact that angiotensin II may also have a role in increasing endothelin production in response to nitrate therapy.⁸⁰

Prevention of Nitrate Tolerance

Although the mechanisms of nitrate tolerance remain unknown, several approaches to its prevention have been studied. A number of pharmacologic interventions have been tested, such as angiotensin-converting-enzyme inhibitors, diuretics, and sulfhydryl-containing drugs, but none have proved effective. The only widely accepted method of preventing tolerance is the use of a dosing strategy that provides an interval of low nitrate exposure during each 24-hour period. The rationale for such dosing regimens is based on the observation that although tolerance to nitrates develops rapidly, it is rapidly reversed during the nitrate-free interval.⁹²

PROBLEMS WITH INTERMITTENT NITRATE THERAPY

An increased frequency of acute myocardial infarction has been described among workers in the munitions industry after withdrawal from occupational exposure to nitrates.^{93,94} Although intermittent nitrate therapy has proved superior to continuous therapy, intermittent therapy may be associated with rebound myocardial ischemia during the nitrate-free period. Patients receiving intermittent nitroglycerin therapy may therefore have an increase in angina at rest or suffer a fatal myocardial infarction.^{34,35,95} Although these reports are a cause of concern, no such effects were reported in a recent large trial of intermittent transdermal nitroglycerin therapy.³⁶ In the light of these results, no firm conclusions can be drawn concerning the risk of acute ischemic events during intermittent nitrate therapy. Despite this uncertainty, patients and their physicians should be aware of the fact that the nitrate-free period during intermittent dosing regimens may be associated with increased angina.

Intermittent transdermal nitroglycerin therapy also has adverse effects on performance on treadmill exercise tests during the period of withdrawal from ni-

trates. In a study of 215 patients given nitroglycerin or placebo patches, the time spent walking on the treadmill in the morning increased before application of the patch in the placebo group but not in the nitroglycerin group, suggesting that withdrawal of nitroglycerin had an adverse effect on exercise performance.³⁴ This finding, termed the "zero-hour effect," was confirmed in another large study of transdermal nitroglycerin therapy.³⁶ Recently, we confirmed that withdrawal of transdermal nitroglycerin has an adverse effect on exercise tolerance (Fig. 5).⁵⁹ Adverse effects on exercise tolerance have not been reported in studies of other long-acting nitrates given once daily or in eccentric dosing regimens.^{43,96}

The mechanism of adverse responses during the nitrate-free interval of intermittent transdermal nitroglycerin therapy is unclear, but they may be due to a heightened sensitivity to vasoconstrictors. Vascular responses to vasoconstrictor substances are increased during nitrate therapy, perhaps due to local production of endothelin.⁸⁰ In animals, withdrawal of nitrate therapy was associated with a decrease in the diameter of epicardial coronary arteries, which was prevented by the concurrent administration of high doses of enalapril.⁹⁷ Whether these responses are related to clinical events that occur after nitrate withdrawal is unclear. No information is available concerning such adverse effects during eccentric dosing with isosorbide dinitrate. Isosorbide mononitrate has not been reported to cause either rebound ischemia or adverse effects on exercise performance.⁴³⁻⁴⁵

CONCLUSIONS

The organic nitrates are important drugs for the treatment of patients with angina, but important questions remain about their efficacy. Sublingual preparations of nitroglycerin and isosorbide dinitrate are effective in the treatment of acute episodes of angina. Sublingual preparations are also effective when used prophylactically before activity that causes angina. Long-acting nitrate preparations are effective, but the development of tolerance during sustained therapy continues to be an important clinical problem. Long-acting nitrates can provide protection against the development of angina for up to 12 hours each day if an appropriate dosing regimen or formulation is used. Regimens with proved effectiveness include intermittent transdermal nitroglycerin, standard-formulation isosorbide mononitrate given eccentrically, and sustained-release isosorbide mononitrate given once daily, but there is some concern that nitrate-free periods may have adverse effects in some patients. Although the mechanism of nitrate tolerance has remained elusive, studies in animals suggest that nitrate therapy causes specific biochemical responses in the vasculature that limit the vasodilator effects of nitrates. These new data may

allow us to understand the mechanism of tolerance and thus develop strategies for its prevention.

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