Nitrate Therapy and the Development of Tolerance

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The efficacy of organic nitrates in the treatment of acute episodes of angina pectoris is unquestioned. However, long-term use of these agents is associated with the development of tolerance or of reduced efficacy over time when given in doses or formulations that maintain therapeutic blood levels for 24-hour periods. Thus, the role of long-term use of nitrates in prophylactic treatment of stable angina has been questioned. The purpose of this brief review is to evaluate nitrate tolerance, a key issue in the prophylactic use of nitrates, as well as to review what is known about clinical rebound. These issues are discussed, and ways of preventing tolerance development are explored. Intermittent therapy involving a dose-free interval during each 24-hour period helps prevent tolerance. *(Arch Fam Med. 1993;2:880-885)*

The efficacy of the nitrates in the treatment of acute anginal episodes is unquestioned.[1-3] Considerable evidence suggests, however, that the long-term use of these agents is associated with the development of tolerance or of reduced efficacy over time when administered in doses or formulations that maintain therapeutic blood levels for 24-hour periods.[4-8] Nitrate tolerance may be associated with a progressive decline in antianginal efficacy.[4-7] In this brief review, the clinical significance of nitrate tolerance will be discussed, the phenomenon of clinical rebound will be examined, and ways of preventing the development of tolerance will be explored.

ISSUES IN NITRATE TOLERANCE

Considerable controversy has arisen in recent years over the clinical significance of nitrate tolerance.[3] This tolerance is often observed during long-term administration of nitrates.[4-10] However, clinical studies assessing the effects of long-term nitrate therapy on antianginal efficacy have yielded conflicting results.[4,7,8,11-18]

How can the opposing findings best be interpreted? It should be noted that testing the efficacy of long-term nitrate treatment is not a straightforward task. Tolerance to many nitrate preparations has been noted, with durations of action longer than those of a sublingual or intravenous bolus of nitroglycerin.[19] Evidence suggests that tolerance may develop rapidly—within 1 to 2 days[10]—and may be partly or completely reversed by withholding treatment for 12 hours or longer.[2,5,13,14] Thus, the timing of testing may be crucial to the assessment of the development of tolerance.[2,13,20]

In addition, patient adherence to therapy, which is rarely evaluated, may be critical, because failure to take even one dose of medication may lead to the restoration of nitrate responsiveness at the next test.[1,8] Individual variability in response to nitrates and to nitrate tolerance may also underlie some conflicting findings.[8,13-16] It has been pointed out that the detection of tolerance may depend on the measurement of efficacy within a few hours after administration of the test dose and on compar-

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ison between measurements obtained after long-term therapy and after the first dose.[19]

Recent studies have suggested that intervals between doses during long-term nitrate therapy may be key to the development or prevention of tolerance. In general, frequent[4-6,13,14,21] or continuous treatment[7,14,22] is accompanied by the development of tolerance, while an extended dose-free interval[5,23-27] results in better antianginal efficacy during long-term therapy. Differences between various nitrate preparations and factors affecting the development of tolerance are discussed more extensively below.

NITRATE TOLERANCE: MECHANISMS

Before discussing the clinical effects of nitrate tolerance, it is useful to review briefly the mechanisms by which tolerance develops. These mechanisms are not completely understood but are thought to be related to the actions of these agents on sulfhydryl groups in vascular muscle cells[28] and, possibly, to the activation of certain counterregulatory mechanisms.[29-32]

At the cellular level, the organic nitrates are prodrugs that enter vascular smooth muscle cells and become activated at the plasma membrane, a process that involves the production of nitric oxide from the prodrug.[33] Nitric oxide formation requires reduced sulfhydryl groups in the form of cysteine or glutathione. Nitrate metabolism also produces S-nitrosothiols which, along with nitric oxide, initiate smooth-muscle relaxation through a metabolic pathway that decreases the levels of free intracellular calcium.[3]

Nitrate tolerance may be related to a decrease in availability of the reduced sulfhydryl groups required for the formation of nitric oxide and S-nitrosothiols.[28-31] The partial reversal of nitrate tolerance in patients with heart failure[30] and complete reversal of venous tolerance in patients with ischemic heart disease[34] obtained by providing patients with sulfhydryl groups via *N*-acetylcysteine[30,34] lend support to this hypothesis.

It should be noted that when blood vessels become tolerant to nitrates, vascular metabolic activity of these agents decreases.[35] It is possible that nitrate uptake by veins and arteries in the tolerant state is diminished as a result of interactions with nitrate metabolites.[20]

Counterregulatory activity, such as activation of the renin-angiotensin-aldosterone system,[31,32] may also play a role in the development of nitrate tolerance. Such mechanisms may increase plasma volume and vasoconstriction, thus offsetting the vasodilatory effects of nitrate therapy.

THE CLINICAL CONSEQUENCES OF NITRATE TOLERANCE

In clinical practice, nitrate tolerance often goes undetected but may be suspected when patients report an increased frequency of anginal episodes, angina produced at shorter walking distance, or increased use of sublingual nitroglycerin. Such symptoms may be attributed to disease progression rather than nitrate tolerance. The phenomenon of nitrate tolerance has been well documented, however, in clinical studies in which more objective measures of antianginal efficacy were made during the course of long-term therapy. These studies have been well reviewed elsewhere,[2,8,13,14,20] and a few representative studies are described here.

Antianginal Effects

Studies measuring the antianginal effects of long-term treatment with nitrates on exercise performance have noted certain changes in efficacy over time.[4] Reduced efficacy of nitrates, as seen in the development of angina at shorter walking times, has been observed in some studies using transdermal nitroglycerine patches,[7,23] oral isosorbide dinitrate,[4-6] and oral isosorbide mononitrate.[36]

For example, in a study comparing differences in exercise time to the onset of angina and to termination of exercise due to moderately severe angina caused by single oral doses of 15, 30, 60, and 120 mg of isosorbide dinitrate and the same doses given four times a day for 1 week, the first doses increased exercise times for up to 8 hours.[4] After 1 week of four-times-a-day therapy, the time to anginal pain and total exercise duration increased only at hours 1 and 2 and not at post-dose hours 4 and 8 for any given dose. This change in antianginal efficacy of the nitrate was attributed to the development of partial tolerance.[4] These findings were confirmed in another study in which 30 mg of isosorbide dinitrate, given four times daily, increased exercise time to angina for only 1 hour compared with the first dose, whose effects persisted for up to 5 hours.[5] Similarly, continuous therapy with varying sizes (10 to 105 cm^2) of transdermal patches releasing 5 to 52.5 mg of nitroglycerin every 24 hours, and thus delivering small, moderate, and large quantities of nitroglycerin per 24-hour period, led to a decrease in antianginal efficacy, as measured by duration of treadmill exercise until onset of anginal pain, after 8 weeks of treatment.[7]

Circulatory Effects

The development of tolerance to nitrates during long-term therapy has also been assessed by measuring changes in the circulatory effects of these agents over time. Nitrates, which are vasodilatory agents, may lower blood pressure; however, this effect is not usually of clinical significance. During long-term nitrate therapy, blood pressure tends to return to pretreatment values more quickly.[4-10] For example, oral administration of isosorbide dinitrate in a non-sustained-release form was reported to cause a dose-related drop in blood pressure after a single dose, but this effect was greatly diminished when administered four times a day for 1 week.[4] Similar results were obtained in a second study after 2 weeks' treat-

ment with a sustained-release formulation of isosorbide dinitrate given four times daily.[36] Corresponding results have been obtained for isosorbide mononitrate administered in sustained-release form in a daily dose of 60 mg.[37]

Cross-tolerance to the circulatory effects of long-term nitrate therapy has been described.[9,10] In two studies involving a challenge dose of sublingual nitroglycerin following long-term nitrate therapy with isosorbide dinitrate[9,10] or pentaerythritol tetranitrate,[9] systolic blood pressure reduction after nitroglycerin therapy was markedly attenuated compared with the initial effects of sublingual nitroglycerin before long-term therapy with isosorbide dinitrate or pentaerythritol tetranitrate.

FACTORS INFLUENCING THE DEVELOPMENT OF TOLERANCE

Tolerance, as measured by a decrease in the antianginal effects of long-term nitrate treatment, is not a universal finding.[8,11-20] An analysis of the factors influencing the development of tolerance is therefore useful.

Formulation

Many nitrate formulations are employed in long-term nitrate therapy (**Table**). Tolerance has been observed with many of these formulations (nitroglycerin patches, ointments, intravenous nitroglycerin) that produce constant blood levels.[7,22,38-42] Frequent administration of oral nitrates, which do not provide daily low-nitrate periods (or blood levels) at night, also produce tolerance as therapeutic levels are maintained throughout the 24-hour period.[4,5,43] Only short-acting nitrate preparations such as sublingual nitroglycerin, which are used infrequently, do not produce tolerance (Table).

Dosage

Tolerance can develop with the use of nitrate treatment regimens that produce continuous therapeutic levels,

Nitrate Formulations, Tolerance, and Efficacy in Chronic Stable Angina*

Preparation	Route of Administration and Dose	Comments
Nitroglycerin	Sublingual tablets and oral spray (0.3-1.5 mg); 0.4 mg per spray as needed	Very short acting; tolerance not a problem during intermittent use
	Oral	Data inadequate for long-term therapy
	Buccal (2.5-6 mg)	Data inadequate for long-term therapy
	Ointment 2%	Inadequate data, not generally used
	Transdermal patches 5-52.5 mg every 24 h	Continuous therapy produces tolerance; with intermittent therapy tolerance can be avoided but dose titration may be needed for efficacy
Isosorbide dinitrate	Oral 15-120 mg	Three- and four-times-a-day dosage produces tolerance; data inadequate for twice-daily therapy
	Slow release 40-120 mg	Two- and three-times-a-day dosage produces tolerance; data inadequate for once-daily therapy
Isosorbide-5-mononitrate	Oral 20 mg	Two-, three-, and four-times-a-day dosage produces tolerance; eccentric two-times-a-day dosage at 8 AM and 3 PM prevents tolerance
Pentaerythritol tetranitrate	Oral 40 mg	Data inadequate

*Based on data from Thadani.[14]

within 24 hours of an initial single application of a nitroglycerin transdermal patch[42] or isosorbide dinitrate cream,[22] as well as within 12 hours of a single dose of a slow-release, 120-mg isosorbide dinitrate formulation.[40] Long-term therapy with isosorbide dinitrate, given four times daily, also produces tolerance, as measured by diminished antianginal efficacy.[4-6]

In recent years, some studies of long-term nitrate therapy have demonstrated that tolerance can be prevented or diminished by adjusting the dosage to include a low-nitrate period. In one study,[5] 30 mg of isosorbide dinitrate given four times a day (at 7 AM, noon, 5 PM, and 11 PM) was associated with diminished antianginal efficacy. The same dose given two (at 7 AM and noon) or three (at 7 AM, noon, and 5 PM) times a day was significantly more effective than placebo in increasing exercise time 1, 3, and 5 hours after drug administration for a week. However, the antianginal effect was not as great as that observed after the initial single dose at hours 3 and 5 (**Figure 1**).

Bassan[43] recently reported that 30 mg of isosorbide dinitrate given three times a day at 8 AM, 1 PM, and 6 PM significantly increased exercise time to angina at hours 1 and 2 after the 8-AM dose and at hours 1 and 2 after the 1-PM dose, and had little effect after the 6-PM dose. Thus, patients receiving this regimen had, at best, 6 hours of antianginal protection during each 24-hour cycle.

Similarly, intermittent treatment with nitroglycerin transdermal patches (with and without the patch for 12 hours each day) seemed to avoid or diminish the potential for a decrease in antianginal efficacy.[23,24] DeMots and Glasser,[24] for example, compared the antianginal efficacy of two nitroglycerin transdermal patches (10 to 20 cm^2 releasing 5 to 10 mg and 30 to 40 cm^2 releasing 15 to 20 mg every 24 hours) with that of placebo; duration of treadmill walking to anginal pain during

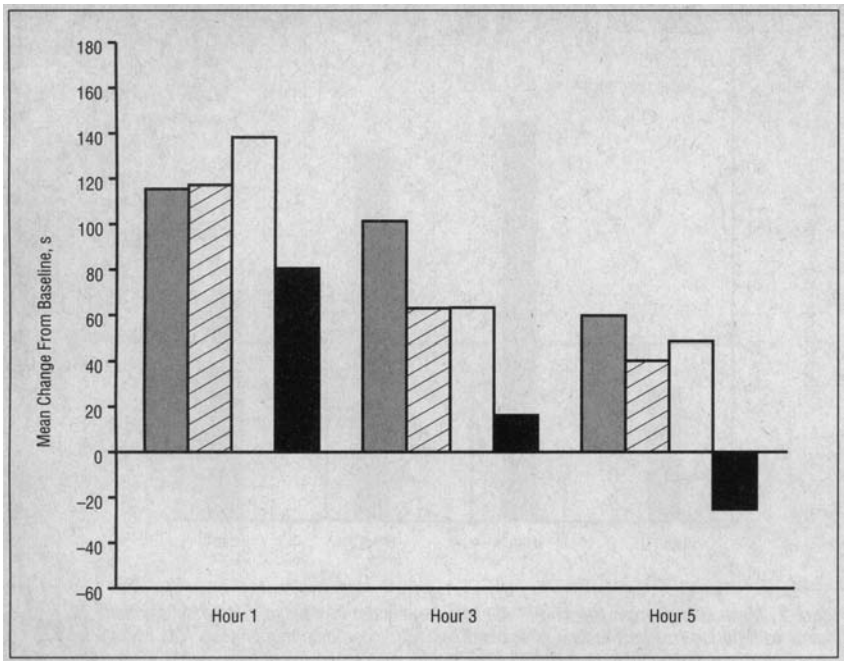

Figure 1. *Mean change from baseline in walking time to development of angina after the first dose and 1 week of long-term therapy. Reduced efficacy is seen at later time points with all dosages (data from Parker et al[5]). Shaded bars represent the first dose of isosorbide dinitrate; hatched bars, twice-a-day dosage; open bars, three times a day; and closed bars, four times a day.*

treadmill testing was the end point. Treadmill walking time increased more after the first application of low- and medium-dose nitroglycerin patch than after placebo treatment. However, after 4 weeks of daily patch application, the improvement in exercise tolerance was lost during low-dose patch therapy and was discernible for only 8 hours during medium-dose patch therapy.[24] Therefore, it appears that individual dose titration may be required when using the patch intermittently.

The results of a study with isosorbide mononitrate suggested that the development of tolerance, as measured by a decrease in its antianginal effects, may be avoided if the agent is given on arising and 7 hours later (with a 17-hour dose-free interval) during each 24-hour period.[25] In this placebo-controlled, parallel, double-blind study, 20 mg of isosorbide mononitrate (given at 8 AM and 3 PM) and a slow-release formulation of 40 mg of isosorbide dinitrate (given at 8 AM, 3 PM, and 10 PM, in accordance with the approved treatment regimen) were both compared with placebo; 129 patients were included in the data analysis (43 each in the placebo, isosorbide mononitrate, and slow-release isosorbide dinitrate groups). Efficacy was measured by assessing mean time to anginal pain on treadmill testing on day 14 of active treatment. Changes in mean time to anginal pain from those obtained during the pretherapy stress exercise test were used as the end point. Each active treatment was compared with placebo treatment at hours 0, 1, 4, and 7.

The mean time to the onset of anginal pain was significantly increased in the isosorbide mononitrate–treated group compared with the placebo-treated group at hours 1 and 4 ($P<.025$) and was increased at hour 7; however, the increase was not statistically significant. For the slow-release isosorbide dinitrate group, changes were statistically insignificant. The diminution of efficacy after multiple doses of slow-release isosorbide dinitrate is consistent with the development of tolerance (**Figure 2**).[25]

CLINICAL REBOUND

Intermittent nitrate therapy may predispose to anginal symptoms during the nitrate-free interval,[24,44,45] and this has been referred to as "clinical rebound," possibly due to counterregulatory mechanisms. This phenomenon was observed by DeMots and Glasser[24] who evaluated 206 patients for the effectiveness of intermittent transdermal nitroglycerin treatment for chronic stable angina. Nine patients, all of whom received the active medication, experienced an increase in nocturnal angina during the periods without the patch. There was no relation between the increase in nocturnal angina and the dose of transdermal nitroglycerin received. In addition, there was a paradoxical reduction in exercise duration in the active treatment group compared with the placebo-treated group just before the patch renewal during long-term therapy. The authors referred to this as the "hour-zero" effect and postulated it to be a manifestation of clinical rebound during intermittent patch therapy.[24]

No significant difference has been observed in the number of anginal episodes or the frequency of sublingual nitrate use between patients receiving placebo and isosorbide mononitrate.[25]

IDEAL LONG-TERM NITRATE REGIMEN

The ideal treatment regimen in the long-term use of nitrates in patients with stable angina is one that will not produce tolerance and clinical rebound, will improve exercise tolerance, and will reduce angina frequency during the active hours.

Available evidence suggests that continuous or frequently repeated administration of nitrates will rapidly produce tolerance, as measured by the antianginal effects of these medications.[19,46] The relationship between total daily dose and tolerance is less certain, but the results of dose-ranging studies suggest that higher daily doses do not necessarily improve clinical efficacy, and are more likely to produce tolerance with development of cross-tolerance to sublingual nitroglycerin.[10,7,39,47] Thus, a

prudent approach would be to select the lowest total dose that results in reliable clinical efficacy.[19]

The results of studies that have used intermittent treatment regimens imply that a daily dose-free period during long-term nitrate therapy may avoid the development of tolerance.[5,23-25,27,46,48] However, many suggested regimens have not been extensively studied in large-scale, well-controlled, clinical trials.[46]

One placebo-controlled, double-blind, crossover study with isosorbide dinitrate suggests, for example, that dose-free periods of 14 or 17 hours may improve the antianginal efficacy of isosorbide dinitrate during long-term therapy.[5] However, this trial, which enrolled only 12 patients, had an active treatment phase of 1 week and measured efficacy for only 5 hours after administration of the test dose. Efficacy was somewhat attenuated at the 5-hour test during long-term use for the two- and three-times-daily regimens compared with the acute testing phase (Figure 1). In other studies with isosorbide dinitrate, a dose-free period of 10 hours during four-times-a-day therapy[4] and of 14 hours during three-times-a-day therapy at 8 AM, 1 PM, and 6 PM failed to prevent development of tolerance.[43]

A treatment regimen of 12 hours each with and without the nitroglycerin transdermal patch may also decrease the likelihood of the development of tolerance[23,24] but may predispose to a clinical rebound with nocturnal angina during the period without the patch in some patients.[24]

A multicenter, placebo-controlled, double-blind randomized trial with isosorbide mononitrate has demonstrated that a twice-daily regimen, given on awakening and 7 hours later, prevents the development of tolerance and provides continued efficacy after each dose for a total of 12 hours after 14 days of therapy.[48] No evidence of clinical rebound was seen with this regimen.[25,48]

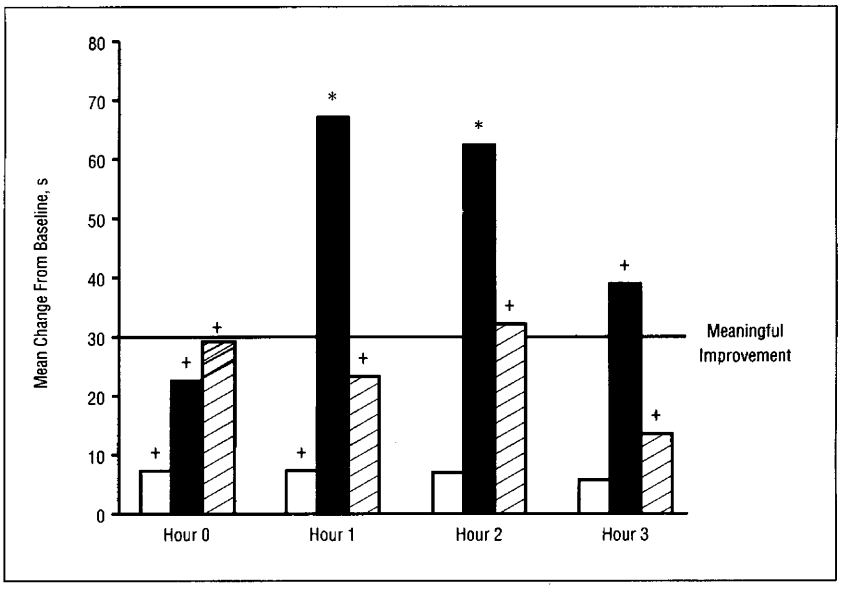

Figure 2. *Mean change from baseline (7 minutes 3 seconds) in walking time to development of anginal pain during treadmill testing after treatment with isosorbide mononitrate (closed bars; n=43), slow-release isosorbide dinitrate (hatched bars; n=45), or placebo (open bars; n=43) (data from Friedman and the ISMN Study Group[25]). Asterisk indicates P<.025; plus sign, differences not significant.*

SULFHYDRYL DONORS OR ANGIOTENSIN-CONVERTING ENZYME INHIBITORS FOR PREVENTING NITRATE TOLERANCE

Although partial reversal of tolerance to hemodynamic effects and complete reversal of venous tolerance[30,34] with *N*-acetylcysteine and angiotensin-converting enzyme inhibitors have been reported, a recent review[46] of all published data did not confirm usefulness of these agents in preventing nitrate tolerance in patients with congestive heart failure[31] or angina pectoris.[49]

CONCLUSION

The organic nitrates have been used for decades in the treatment of angina pectoris. The desire to treat this condition prophylactically has led to the long-term use of nitrates, which has become difficult by the potential for the development of nitrate tolerance. The use of intermittent treatment regimens involving a dose-free interval during each 24-hour period has been advocated as a means of circumventing the development of tolerance.

At present, the routine use of sulfhydryl donors or angiotensin-converting enzyme inhibitors for the prevention of nitrate tolerance cannot be supported by available data. The potential of possible adverse effects of concomitant therapy with these agents must also be considered.

To prevent tolerance, the proper dosage should be used. Intermittent therapy with nitroglycerin patches may prevent tolerance, but individual dose titration is warranted. Among oral nitrates, at present, only isosorbide mononitrate, in an approved dosage, has been demonstrated to prevent the development of tolerance. Further study will be necessary to identify appropriate dosages for other commonly used long-acting nitrate formulations.

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