15. EXPERIMENTAL EVALUATION AND CLINICAL RELEVANCE OF TOLERANCE TO NITRATES

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Summary

The organic nitrates are clearly the most effective agents for the treatment of acute ischemic episodes. However, due to the rapid development of tolerance to their hemodynamic and clinical effects, these agents cannot provide continuous antiischemic protection. A clear demonstration of tolerance development has been obtained with all forms of nitrate administration—intravenous, oral, ointment, or patch—and is dose dependent. Hemodynamic tolerance has been shown both in the pulmonary and systemic circulation, and implies a shorter duration of action and loss of a dose-response relationship. Those formulations that provide continuous nitrate exposure (such as nitroglycerin patches) have been shown to produce only a short period of antiischemic effect, as can be demonstrated by exercise testing. Since tolerance develops within a few hours of nitrate administration and is rapidly reversed following their withdrawal, clinical studies to show the development and reversal of tolerance need not be long in duration.

The mechanism of the development of tolerance remains poorly understood. Three separate theories have been suggested to explain this phenomenon. The sulphhydryl depletion hypothesis has not yet been uniformly confirmed by studies with sulphhydryl donors such as N-acetylcysteine and methionine. The neurohormonal activation hypothesis suggests reflex sympathetic and renin-angiotensin system activation; however, studies with ACE inhibitors have not shown any protection against nitrate tolerance. The plasma volume expansion hypothesis suggests that an increase in intravascular volume may partly counteract the nitrate effect; however, studies with diuretics to prevent volume expansion have not supported this hypothesis.

The present clinical strategy for overcoming the development of tolerance is the use of intermittent nitrate therapy, with a nitrate free period each day: Well-controlled clinical trials have shown that although partial tolerance develops acutely, a significant antiischemic effect can be maintained during intermittent nitrate therapy.

The organic nitrates have been employed in the management of angina pectoris for more than a century. Despite the availability of beta-adrenergic receptor blockers, calcium channel blockers, and other newer therapeutic agents, the nitrates continue to be the most widely utilized drugs in the management of myocardial ischemia. The nitrates are clearly the most effective agents for the treatment of acute ischemic episodes, and they also are useful in angina prophylaxis. Although monotherapy with the nitrates is appropriate in many patients with stable angina pectoris, these agents cannot provide continuous antiischemic effects because of the problem of nitrate tolerance. In some clinical situations, monotherapy with nitrates is inadequate, and other agents should be employed in combination therapy or replace the nitrates.

Evaluation of Nitrate Therapy

CLINICAL ASSESSMENT

The effect of nitrate therapy in patients with angina pectoris was initially studied employing subjective
parameters. Thus, the frequency of angina and nitroglycerin (GTN) consumption were utilized to assess clinical efficacy. It is now recognized that these endpoints are of limited value in documenting drug effects because of variability in activity levels, changing climatic conditions, and the fact that patients with stable angina pectoris modify their activity level to prevent ischemic episodes. This has been shown in clinical studies where patients with marked limitation of exercise capacity, as assessed by exercise testing, commonly have infrequent episodes of angina pectoris during a study period. This was clearly demonstrated in the transdermal GTN cooperative study (1). In that study patients were enrolled if they developed moderate angina pectoris during a study period. This was documented in clinical studies where patients with stable angina pectoris modify their activity level to prevent ischemic episodes. This was clearly demonstrated in the transdermal GTN cooperative study (1). In that study patients were enrolled if they developed moderate angina pectoris during 2.5 and 7.5 minutes on the Bruce protocol. There were 562 patients who completed this study, and despite documentation of major limitation in exercise capacity, only 25% of patients experienced more than seven episodes of angina per week. This discrepancy between the objective evidence of limitation of exercise performance during treadmill testing and the frequency of angina pectoris during daily activities documents the difficulty of defining antianginal efficacy by measurements of anginal frequency and GTN consumption.

**Exercise Performance.** Exercise testing is considered to be the best method of assessing the efficacy of therapeutic agents in patients with angina pectoris. In North America, treadmill exercise testing is most frequently employed, but bicycle exercise is more commonly employed in Europe. Treadmill exercise is a more physiological method as it more closely represents daily physical activity. Bicycle exercise testing may be employed in either the upright, semirecumbent, or supine position. The upright position is best suited for assessing the therapeutic effects of the nitrates, since preload reduction plays such an important role in their efficacy in angina pectoris. In considering the clinical efficacy of a particular agent, the commonly used endpoints are the duration of exercise to the onset of angina pectoris (P₁) and to the development of angina of moderate severity (P₂). Moderate severity is usually defined as angina of an intensity that the patient would normally stop activity and take sublingual GTN for relief. While anginal symptoms are considered to be objective in nature, it is clear that these exercise endpoints are somewhat subjective, and this may interfere with proper assessment of the efficacy of a particular agent. However, in well-controlled clinical studies in patients with angina, reproducibility of exercise testing to these anginal endpoints is generally quite satisfactory (1-4).

The value of exercise testing in assessing drug interventions is questioned by many investigators because of the variability in the anginal or ischemic threshold. This may be related to changes in neuro-hormonal influences that modify coronary vasomotor tone throughout the day and between days. Thus patients who are enrolled in antianginal trials, where reproducibility of exercise times to ischemic endpoints is required, may not represent the angina population at large, where substantial variability in the anginal threshold is common (5).

**Electrocardiographic Evidence of Ischemia.** Because of the subjective nature of angina pectoris, electrocardiographic indices of myocardial ischemia are commonly employed to document antiischemic changes during drug therapy. The development of myocardial ischemia is traditionally said to be present when ST-segment depression develops during exercise testing or during ambulatory electrocardiographic monitoring. The most widely accepted criteria for ischemia is ST-segment depression of $>0.1 \text{mV}$ that is horizontal or downsloping when measured 80 msec after the J point (6). Some investigators consider ST-segment depression to be ischemic when it is upsloping, but where the ST segment is depressed $>0.15$ is 80 msec after the J point (6).

Some investigators assess only ST-segment depression during exercise testing and consider this to be a more important indicator of myocardial ischemia than the development of angina pectoris. In most studies, investigators compare the time to 1 mm of ST-segment depression before and after a therapeutic intervention and use this change in exercise performance as an indicator of clinical benefit. Some investigators have patients exercise and determine the time to the development of electrocardiographic evidence of ischemia. Exercise testing is then carried out following an intervention, and the extent of ST-segment depression is determined at the same workload that was associated with ischemia during the control test (7). The magnitude of ST-segment depression following drug administration is compared with that before therapy. This is commonly expressed as a percentage change, suggesting that this is an index of improvement in myocardial ischemia. This approach implies a degree of accuracy in quantitating myocardial ischemia that may not be possible by this technique.

While ST-segment depression is considered by some to be a much more objective and meaningful