Short and Long-Acting Oral Nitrates for Stable Angina Pectoris

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Summary. Nitroglycerin (NTG) spray and sublingual tablets rapidly relieve an established attack of angina, and their infrequent use is not associated with the development of tolerance. Although, following a suitable nitrate-free interval, the first dose of oral, long-acting nitrates produces significant hemodynamic effects, increases angina free walking, and decreases exercise-induced ischemia, during continued long-term therapy tolerance limits their usefulness. Appropriate dosing regimens of controlled-release formulations of isosorbide dinitrate (ISDN) and controlled-release NTG during long-term therapy have not been established. Use of immediate-release formulation of 15–120 mg of ISDN in a qid regimen lead to a marked reduction in the size and duration of antianginal effects compared to the initial dose. Asymmetric tid therapy with 30 mg of ISDN (7 a.m., 1 p.m., and 5 p.m.) is also associated with the development of partial tolerance and appears to provide antianginal prophylaxis for only a period of 6 hours each day. Asymmetric bid therapy with ISDN at 7 a.m. and noon may give sustained effect but is supported by only a single, small study that did not examine effectiveness after the noon dose in long-term use. Isosorbide-5-mononitrate (IS-5-MN) has been the subject of more recent studies than other nitrates because of attempts to bring a number of products into the U.S. market. IS-5-MN in qid, tid, and standard bid (8 a.m. and 8 p.m.) dosage regimens produce tolerance. Asymmetric regimens of immediate-release IS-5-MN (10 and 20 mg) given bid (once in the morning and again 7 hours later) decrease the development of tolerance compared to symmetric regimens and produce an increased exercise duration after each dose of the agent; the 20 mg bid dosing is more effective. Similarly, once-daily 120 and 240 mg controlled-release IS-5-MN does not produce tolerance and gives a sustained increase in daytime exercise duration. Both asymmetric bid immediate-release and once-daily controlled-release IS-5-MN preparations do not produce deterioration in exercise performance prior to the administration of the medication in the morning (i.e., no zero-hour effect). Further studies are needed to establish useful dosing regimens for ISDN, for controlled-release ISDN, and for controlled-release nitroglycerin. None of the dosing regimens of any oral, long-acting nitrate (including IS-5-MN) provide 24 hour antianginal and antiischemic effects. Although it is intuitively attractive to add an agent (beta-blocker or calcium channel blocker) that exerts 24 hour antianginal and antiischemic effects, which appear to depend on mechanisms different from those of nitrates, there are no studies that allow an evaluation of the usefulness of adding beta-blockers or calcium channel blockers to nitrate therapy (or vice versa).

Key Words. stable angina pectoris, isosorbide dinitrate, exercise, isosorbide-5-mononitrate, oral nitroglycerin, buccal nitroglycerin, pentaerythritol tetranitrate, combination treatment

Nitroglycerin (NTG) and other oral nitrates are extensively used for the treatment of patients with stable angina pectoris [1–3]. Since the first use of NTG in 1879 by Murrell [4], short and rapidly acting nitrates have become established as the treatment of choice to shorten the duration of pain of an established attack of angina or to prevent an anticipated attack by administering the agent just prior to physical activity or emotional stress [5–8]. The role of longer acting nitrates is much less well defined. When oral, long-acting nitrate therapy is first initiated or is withheld for a day or longer after chronic use, it can be shown [9–15] to increase angina free walking time and to prolong the time to exercise-induced myocardial ischemia, but continued use is associated with rapid development of tolerance [16–22]. Although knowledge of the appropriate doses or dosing intervals for many long-acting oral nitrates is only rudimentary, it is clear that the development of tolerance can be lessened [3] by choosing appropriate interdosing intervals, specifically by providing one “long nitrate” low or free interval determined by dose, the elimination half-life of the active agent(s), and the release characteristics of the formulation. Use of an interdosing interval during a single 24-hour period does not provide

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continuous 24-hour antianginal effects from any oral nitrate formulation.

In this review, the pathophysiology of stable angina pectoris and the mechanism of action of nitrates is briefly discussed, and published data related to efficacy of various short and long-acting nitrate formulations are described. Conclusions are principally drawn from parallel-group, concurrent, placebo-controlled, exercise tolerance trials. This reflects our belief that baseline-controlled (i.e., lacking a concurrent placebo group) and, with some exceptions, crossover trials are difficult to interpret and can be misleading. Deficiencies in information are highlighted, and comments with respect to the appropriate use of various nitrate formulations are derived from evaluable data.

Role of Nitrates in Stable Angina Pectoris

There are no controlled clinical trials that have been designed to evaluate whether, compared to placebo, the use of long-acting oral nitrates has an effect on morbidity and/or mortality when used as a treatment of patients who have chronic stable angina pectoris. Oral nitrates are intended only to provide symptomatic relief (decreased angina frequency and prolongation of walking distance prior to development of angina, or relief of established angina despite continuing exercise). Their antiischemic properties (i.e., increase in walking distance to the development of significant ECG ischemia or wall motion abnormalities) are considered to be of value, although this seems less certain. This may be a moot point, however, as for nitrates the antianginal and antiischemic effects appear inseparable. When antianginal effects are discernable in studies, so are the antiischemic effects. When tolerance to the antianginal effects occur, so does tolerance to the antiischemic effects.

Pathophysiology of Stable Angina

The culprit lesion responsible for myocardial ischemia and angina pectoris is often the severe atherosclerotic eccentric lesion of one or more coronary arteries. This lesion limits segmental coronary blood flow during exercise or emotionally induced stress. The increase in myocardial oxygen requirement during stress cannot be met by a corresponding increase in segmental coronary blood flow, and this produces an imbalance between myocardial oxygen supply and demand, and leads to myocardial ischemia and angina pectoris. The endothelium of atherosclerotic vessels is dysfunctional [23–25] and stimuli that normally produce vasodilation, paradoxically produce vasoconstriction [23,24] due to deficiency of the endothelial derived relaxing factor [25–27]. The majority of patients with stable angina have reproducible exertion or excitement-induced angina. Many patients, however, also experience occasional episodes of angina at rest, probably due to a spontaneous increase in coronary vascular tone [28]. Only a minority of patients with stable angina do not have atherosclerotic heart disease, and in these patients reduction of coronary blood flow reserve probably plays a major role in the production of myocardial ischemia [3].

Mechanisms of Action of Nitrates in Stable Angina

Nitrates are effective smooth muscle relaxants and at low concentrations produce venodilation and changes in arterial compliance [29–32]. Arterial and arteriolar dilation occurs at higher concentrations [32]. Following nitrate administration, venous beds of the abdominal vasculature, arms, and legs become more compliant, blood volume in these regions is increased [30], and less blood returns to the heart and lungs. This results in a decrease in ventricular volume and pressure both at rest and during exercise [31]. Left ventricular wall stress is reduced with a resultant decrease in myocardial oxygen demand. A modest decrease in arterial pressure also reduces oxygen demand, but this is offset in part by a reflex increase in heart rate.

Nitrates produce dilation of coronary arteries when endothelium is denuded [26–33] or is dysfunctional [23,24,26]. Nitrates also dilate coronary stenosis [33] and increase collateral flow and improve subendocardial perfusion in the ischemic regions [1]. Nitrates relieve coronary spasm and prevent exercise-induced coronary constriction at the epicardial stenosis site [24]. Nitrates also reduce platelet aggregability and adhesions and thus may play a role in preventing coronary narrowing [38].

The current cellular model for these vascular effects is that after entering the smooth muscle cell, nitrates are converted to nitric oxide (NO) [27,33–36]. This process requires sulfhydryl groups [34]; NO or nitrosothiols stimulate soluble guanylate cyclase to produce cyclic guanosine monophosphate [37]. The cyclic nucleotide thus formed causes vasodilation as myocyte intracellular calcium is decreased, either by inhibition of calcium ion entry or by production of calcium exit [37]. Since nitrates are an exogenous source of NO, these agents are currently considered to replace the deficient NO in the vessels involved with atherosclerosis.

Short-Acting Nitrates and Single Doses of Long-Acting Nitrates

Nitroglycerin (NTG) administered as sublingual tablets or as an oral spray is rapidly absorbed and exerts its peak effect within 2–5 minutes [6–8,39]. These formulations of NTG are the mainstay for the rapid relief