EDITORIAL COMMENT

Long-Term Therapy With Organic Nitrates

The Pros and Cons of Nitric Oxide Replacement Therapy*

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Organic nitrates are among the oldest and most commonly used drugs for the treatment of cardiovascular disease. In the short term, nitrates have a rapid onset of action, lowering blood pressure and cardiac filling pressures, and they are used to treat episodes of angina for short-term control of blood pressure and in the treatment of pulmonary congestion. Despite the wide clinical use of these drugs and a large body of research in this field, it is interesting to note that 160 years after Ascanio Sobrero first synthesized nitroglycerin, we remain with three questions of fundamental importance: 1) How do nitrates work? 2) Why do nitrates stop working upon continuous administration? and 3) What are the long-term effects of nitrate therapy on clinical outcome? Interestingly, these questions appear to be closely interrelated.

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Ignarro et al. (1) apparently answered the first of these questions some 20 years ago when they hypothesized that nitric oxide (NO) release mediates the effects of nitrates. Within this conceptual construct, nitrates are believed to be prodrugs that undergo denitrification within the vascular wall. The enzymatic pathway involved in this denitrification process has remained uncertain, with a number of candidate enzymes suggested, although recent evidence points to an important role for mitochondrial aldehyde dehydrogenase (2). A differential capacity to biotransform nitrates to NO explains the selectivity for certain vascular beds and the relatively low effect on resistance arteries (3). Because they are considered to exert their vascular effect through the release of NO (or some NO adjunct), nitrates have been considered to be the prototypical endothelium-independent (NO-dependent) vasodilators. Of note, recent experimental evidence seems to challenge these earlier conclusions because: 1) 60% of the arterial vasodilatory effect of nitroglycerin is, at least in vitro, mediated by opening of potassium channels in endothelial cells (4); 2) recent observations suggest that nitroglycerin might not act through NO release (5); and 3) sustained exposure to nitrates causes a marked impairment of endothelium-dependent vasodilatation, an important parameter of vascular function with prognostic implications (6,7). This impairment in endothelium-dependent vasomotor responses appears to be associated with an increased bioavailability of free radical species, among which superoxide anion and peroxynitrite are the best characterized. These observations, taken together, suggest that nitrates have profound interactions with the endothelium, a finding that challenges the traditional conceptual framework.

An unbalanced redox equilibrium also has been advocated to explain the pathophysiology of nitrate tolerance. The past decades of research into this area have documented that tolerance is a multifactorial phenomenon based on exhaustion of cofactors, inactivation, and altered expression of several enzyme systems. Although the increased production of reactive oxygen and/or nitrogen species appears to represent the common trigger for these abnormalities, the phenomenon of tolerance seems to result from abnormalities developing at a number of levels, including reduced nitrate biotransformation, reduced NO signal transduction, as well as counterregulatory responses (8,9).

The increasing awareness that nitrates cause abnormalities in endothelial function and are associated with increased vascular production of radical species has prompted speculation concerning the effect of these agents on clinical outcome during sustained therapy. Traditionally, it has been suggested that NO has beneficial effects on vascular function, based on its antiproliferative, antioxidant, and antiatherogenic capacities. As such, it has been suggested that exogenous (nitrate-released) NO might have the same properties (10). Concurrently, evidence that sustained nitrate therapy is associated with an increase in the production of proatherogenic oxygen free radicals (11) would suggest that the safety of long-term nitrate therapy requires systematic review. Importantly, these hypotheses have never been tested in large-scale, long-term clinical trials. In this issue of the Journal, Müller et al. (12) demonstrate that large doses of isosorbide mononitrate (ISMN), administered using an eccentric schedule, have antioxidant and endothelial protective effects in an animal model of hypercholesterolemia. Their data strongly support the hypothesis that ISMN-derived NO can substitute for the lack of endogenous NO production and can also actually protect the endothelial NO production. Although this hypothesis is interesting, one limitation of this article is that all studies were conducted early (3 h) after the morning dose of ISMN, after a 17-h dose-free interval. As the authors discuss, if measures of superoxide (and endothelium-dependent vasomotor responses to acetylcholine) had been made at later time points after dosing, different results might have been observed because this early testing period may have occurred.
before the development of increased oxygen free radical species production.

Among the data presented in the paper (12), those regarding the effect of ISMN on morphologic evidence of atherosclerosis are the most striking. Although a high-cholesterol diet caused a fourfold increase in intima-media thickness, this effect was significantly attenuated (approximately threefold compared with normal chow) after eccentric ISMN administration. Collectively, the data presented support the concept that ISMN, administered in very high doses using an eccentric dosing schedule, has the potential to have protective vascular effects in the setting of hypercholesterolemia.

Although such results are of potential clinical importance, these observations, made in a small animal model, will not necessarily translate into clinically beneficial effects in humans. Importantly, the therapeutic regimen used in the present article, although allowing a 17-h nitrate-free daily interval, caused evidence of “moderate” nitrate tolerance, likely due to the high dose of ISMN. This evidence might limit the possibility of transferring the beneficial effects of ISMN to clinical practice because: 1) regimens resulting in the development of tolerance would not be beneficial in the relief of symptoms; and 2) human studies have demonstrated potential complications during intermittent nitrate regimens (13).

In summary, the data presented by Müller et al. (12) are interesting and reserve confirmation in humans. Until recently, few studies addressed the effect of nitrate therapy on clinical outcome in patients with stable coronary artery disease (CAD). Large-scale trials in the postinfarction setting failed to demonstrate a significant effect of nitrates on clinical outcome. Unfortunately, both of these studies had short-term follow-up periods and suffered from a high percentage of open-label therapy in the control group (14,15). The shortcomings of these previous trials emphasize the need for long-term outcome studies examining the effect of nitrate therapy in patients with stable CAD. Evidence of a beneficial effect from angiotensin-converting enzyme inhibition (16) has been provided recently, and data on the effect of long-acting nifedipine are soon to be reported (17). Nicorandil also has been demonstrated to reduce mortality, but the relative importance of its NO donor properties versus the direct effect on potassium channel currents remains to be clarified (18). The existence of these large-scale studies examining clinical outcome in patients with stable CAD confirms their feasibility. It also emphasizes that the organic nitrates remain the only class of anti-ischemic/antianginal agents that have never been tested in long-term, large-scale clinical outcome studies. The time has come for the planning and completion of appropriately designed clinical trials of this type. Interestingly, these studies will also have to investigate whether treatment effects may be variable depending on the specific nitrate administered (19). The need is clear; the challenge is to find the funding and scientific leadership to conduct such studies.

The data presented in this issue of the Journal are relevant because they place new hope on the treatment of angina and the prevention of atherosclerosis. However, two aspects of nitrate therapy have to be considered when interpreting these data: on one side, the antiatherosclerotic effects of NO (donors), and on the other, the observation that, after continuous treatment, nitrates may actually cause endothelial dysfunction and sympathetic activation (6,7,20), both with potential negative prognostic influence. Future research is needed to investigate the mechanisms underlying this dichotomy. As well, the evidence of potential risks associated with tolerance-inducing regimens emphasizes the importance of following published recommendations for nitrate use (21). Furthermore, because nitrates are among the most commonly prescribed agents for patients with stable angina pectoris, a century after their introduction in clinical practice, it is definitely time for a large-scale, randomized, prospective human trial investigating their long-term effects, as advocated by the authors. However, turning their question around, the first reassurance that has to come from this trial, before investigating whether long-term therapy with organic nitrates has antiatherogenic effects, is whether or not it is actually safe in patients with chronic CAD.

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REFERENCES


