Nitrates as Adjunct Hypertensive Treatment
A Possible Answer to Resistant Systolic Hypertension

Shawna D. Nesbitt

Systolic hypertension occurs most commonly in the elderly and it significantly increases cardiovascular and cerebrovascular risk. Furthermore, although once thought inadvisable, treatment with various drug choices has been clearly shown to be beneficial.\(^1\)-\(^3\) Despite concerted efforts to reach blood pressure goal in these studies, none of them has achieved blood pressures of \(<140/90\) mm Hg. Furthermore, based on National Health and Nutrition Examination Survey, the elderly have the poorest rates of achieving blood pressure control.\(^4\) This raises the query of whether the lack of success is a matter of compliance versus a physiological aberration, which conventional therapy does not completely address. The article “Long-Term Effectiveness of Extended-Release Nitrate for the Treatment of Systolic Hypertension” by Stokes et al in this issue addresses the utility of an old agent, “nitrates,” to improve blood pressure control in resistant systolic hypertension.\(^5\)

An interesting facet of this treatment approach is the synchronization of the mechanism of action of the drug with an individualized underlying pathophysiology of disease. This is a concept that has been discussed in hypertension but is quite difficult to implement without easily accessible methods to assess pathophysiology. In the case of systolic hypertension, newer noninvasive techniques of measuring compliance may represent a helpful tool in defining the most specific antihypertensive regimen. The current study makes use of the Sphygmocor device to assess arterial compliance and distensibility. Although this device and others like it have some inherent inaccuracies because of the assumptions made in the calculations, there are studies to suggest that they bear a reasonably sound correlation to invasive measures of vascular compliance.\(^6\)

In this trial, the pulse wave reflection effect of nitrates is supported because the augmentation index decreases after dosing whether given at 8:05 AM in sequence A or 12:05 PM in sequence B. The design of the study cleverly isolates the dosing times of the concurrent therapy from the nitrate dosing. Yet it is still possible that concurrent therapies could have some effect on the aortic compliance measurement.\(^7\)

The primary use of nitrates has been in the treatment of angina. They have potent vasodilatory effects on coronary vessels. Although nitrates are helpful in acute management of severe hypertension and aortic dissection, these drugs have received less attention in the chronic treatment of hypertension because of the phenomenon of tachyphylaxis. The mechanism of nitrate tolerance is thought to be caused by the increase in peroxynitrite that overrides the vasodilatory effects initiated by nitric oxide donors. In the treatment of angina, the tachyphylaxis effects are overcome by intermittent dosing.\(^7\) This study evaluates whether the blood pressure effects of nitrates are maintained after long-term exposure using similar intermittent dosing. Although others have shown that long-term nitrates reduce blood pressure acutely, it has not been demonstrated that nitrate tolerance to blood pressure effects may be overcome with 12-hour dosing of nitrates.

The clinical implication that intermittent dosing of long-acting nitrates may represent a new tool to improve blood pressure control in the most difficult to treat population is timely and important. In particular, the subjects in this trial were on maximized concurrent therapy; thus, the observed effects represent additional benefit. Furthermore the benefits are clearly maintained after a mean of 2 years of treatment in most of the patients in the study. Whereas nitrates may be a viable option as adjunct therapy in the treatment of systolic hypertension, the need for intermittent dosing limits them as initial monotherapy. However, the concurrent drugs used in these patients may affect the large artery compliance and nitrate tolerance because drugs such as angiotensin-converting enzyme/angiotensin receptor blockers and aldosterone antagonist may increase the availability of nitric oxide, and others such as hydralazine may quench peroxynitrite with the donation of a sulfhydryl group.\(^8\) Characterizing these interactions further will have important implications on the use of nitrates in the long-term treatment of systolic hypertension.

The major limitation to this data is the selection of patients in the trial. The majority of these subjects were selected initially because they had a robust blood pressure response to nitrate therapy. Thus, although it is impressive to see this effect maintained over time, it does not address the overall response rates for systolic hypertensive subjects. Furthermore, there is the problem of nitrate-induced side effects such as headache for the larger population. Additional studies of blood pressure response to nitrates in a broader selection of patients with systolic hypertension are needed. Given that there is no reduction in diastolic blood pressure, the focus of these studies should be on systolic hypertensive subjects.

This trial is a well-done follow-up to an earlier study in this population. In this demonstration of long-lasting antihyper-
tensive effects of nitrates, beyond background therapy in this small group of elderly individuals with systolic hypertension, the sustained effects of nitrates implies that nitrates have the potential to augment hypertension control rates in the elderly. This “old” therapy may represent a new answer to an “old problem.” Further studies are needed to establish response rates and to delineate the ideal patients for whom nitrates are indicated for adjunct hypertensive treatment.

References


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