Haemodynamic Aspects of Nitrate Tolerance

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Summary

Development of tolerance to the haemodynamic effects of nitrates is influenced by the degree of left ventricular dysfunction and a number of other factors related to the circulatory system. Patients with angina pectoris and normal cardiac function at rest differ in response compared with patients with chronic congestive heart failure. Several studies have shown that haemodynamic tolerance to nitrates will develop in patients with angina pectoris. Slow-release oral nitrates and transdermal nitrates, as well as higher dosages, are more likely to induce tolerance. Patients with congestive heart failure will usually not develop tolerance after oral nitrate therapy. With transdermal therapy, however, tolerance frequently develops even in these patients. The individual response of patients to the effects of nitrates and the development of tolerance is variable, regardless of clinical status. Future studies on the development of tolerance must consider the complexity of the effects of nitrates and the various factors that may affect the haemodynamic changes.

The problem of nitrate tolerance has been discussed extensively, but there seems to be no consensus on its clinical relevance (Flaherty 1986). Tolerance may develop to the antianginal, haemodynamic and side effects of nitrates. The haemodynamic effects and possible development of tolerance depend on a number of factors, which are reviewed in this paper.

1. Effects of Nitrates on the Cardiovascular System

The primary effects of nitrates are simple to describe in theory but difficult to understand in practice. The principle basic effect of nitrates is to relax vascular smooth muscle cells. Different vascular systems, however, react differently. Not only do veins and arteries react differently but responsiveness to nitrates also varies within these systems (Abrams 1985).

Veins in the limbs dilate more than hepatic and renal veins (Leier et al. 1981). Splanchnic veins are particularly important, together with veins of the arms and legs, for the venous pooling effect of nitrates (Loos et al. 1983; Strohm et al. 1983). The effects of venous pooling, however, differ between patients with congestive heart failure and healthy people (Loos et al. 1983), and patients with left ventricular failure differ from those with combined left and right ventricular failure. Zelis (1974) studied venous tone in patients with congestive heart failure and proposed that both an increase
in sympathetic tone and local factors led to venoconstriction. However, blood volume is also important, and patients with angina pectoris have been shown to have a decreased blood volume of about 20% compared with controls (Åström et al. 1979). Furthermore, concomitant drug therapy, e.g. β-blockers, may affect venous tone and lead to changes of venous compliance, depending on the type of β-blocker used (Maarek et al. 1986). Pulmonary artery pressure will usually decrease significantly after nitrate administration (Sorkin et al. 1984). However, in pulmonary vasoconstriction due to hypoxia, nitrates will not always give rise to pulmonary vasodilation (Naeije et al. 1982).

In dose response studies of nitrates it has been found that higher doses are required to change arterial compared with venous tone (Gwilt et al. 1983). The influence on the windkessel function may be mediated not by the aorta itself but by large muscular-type branches such as the mesenteric and hepatic arteries (Strohm et al. 1983).

The effect on arterioles and peripheral resistance is seen only after high dosages. Nitrates have a different effect at higher dosages in patients with an increased peripheral resistance compared with those with normal peripheral resistance. Increases in cardiac output are seen in patients with severe congestive heart failure and attenuated reflexes (Packer 1985). Such reflex mechanisms may also be influenced by therapy itself (Daly et al. 1986; Levine et al. 1986).

The presence of oedema decreases the preload-reducing effects of nitrates, which are restored after treatment with diuretics (Magrini & Niarchos 1980, 1983). Furthermore, all nitrates may not have the same effects on vascular systems, as indicated in the study of Rezakovic et al. (1983), who proposed that glyceryl trinitrate (nitroglycerin) is a more potent venous dilator than isosorbide dinitrate, which is a mixed vasodilator.

Apart from their direct vascular effects, it has also been proposed that nitrates influence left ventricular diastolic properties. This beneficial effect, however, is more related to changes of external constraint (Amende et al. 1983; Kingma et al. 1986). Direct effects of nitrates on left ventricular contractility have also been proposed but are probably secondary to anti-ischaemic properties (Harris et al. 1983).

In summary, the effects of nitrates on various vascular systems are very complex and depend on a number of factors (fig. 1). It is therefore not surprising that studies addressing the question of nitrate tolerance have shown conflicting results.

2. Nitrate Tolerance and Haemodynamics

Development of haemodynamic tolerance to nitrates has been studied both in patients with angina pectoris and those with congestive heart failure. Indicators of haemodynamic response have been pulse and blood pressure reactions, changes of pulmonary artery pressures, and exercise tolerance. Patients with angina pectoris, usually with normal left ventricular function at rest, cannot be compared with patients who have left ventricular dysfunction with or without activation of various hormonal and reflex systems. Also, in patients with congestive heart failure the activation of, for example, the sympathetic nervous system and the renin angiotensin system may not be uniform (Levine et al. 1986).

Because of the complicated action of nitrates, both the haemodynamic effects and the tendency to develop tolerance differ between patients with and without left ventricular dysfunction at rest. Therefore, the haemodynamic aspects of tolerance to nitrate therapy in patients with angina pectoris will be discussed separately from those in patients with manifest congestive heart failure.

2.1 Haemodynamic Tolerance in Angina Pectoris

Development of tolerance has been studied with all types of nitrates (glyceryl trinitrate, isosorbide dinitrate, isosorbide 5-mononitrate) as well as with various administration formulations. As early as 1977, Danahy and Aronow (1977) described partial tolerance to the haemodynamic effects measured by pulse and blood pressure changes, which were