COMMENTARY

Aminoethyl nitrate – the novel super nitrate?

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Long-term use of most organic nitrates is limited by development of tolerance, induction of oxidative stress and endothelial dysfunction. In this issue of the *BJP*, Schuhmacher et al. characterized a novel class of organic nitrates with amino moieties (aminoalkyl nitrates). Aminoethyl nitrate was identified as a novel organic mononitrate with high potency but devoid of induction of mitochondrial oxidative stress. Cross-tolerance to nitroglycerin or the endothelium-dependent agonist acetylcholine after in vivo treatment was not observed. Like all nitrates, aminoethyl nitrate-induced vasorelaxation by activation of soluble guanylate cyclase. Thus, in contrast to the prevailing view, high potency in an organic nitrate is not necessarily accompanied by induction of oxidative stress or endothelial dysfunction. This work from Daiber’s group is an important step forward in the understanding of nitrate bioactivation, tolerance phenomena and towards the development of better organic nitrates for clinical use.


This is a Commentary on the Research Paper in this issue by Schuhmacher *et al.* (pp. 510–520). To view this article visit http://www3.interscience.wiley.com/journal/121548564/issueyear?year=2009

**Keywords:** endothelium; nitric oxide; organic nitrates; mitochondrial aldehyde dehydrogenase; oxidative stress; vascular function

**Abbreviations:** ALDH, aldehyde dehydrogenase; cGMP, cyclic guanosine monophosphate; GTN, glycerol trinitrate (nitroglycerin); PETN, pentaerythritol tetranitrate; PTIO, 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide; sGC, soluble guanylate cyclase

Organic nitrates are still an important part of the therapeutic armamentarium in symptomatic patients with coronary artery disease. Mechanistically, by liberation of nitric oxide (NO) or a related molecule, nitrates stimulate soluble guanylate cyclase (sGC) in smooth muscle cells, leading to enhanced formation of cyclic guanosine monophosphate (cGMP) and relaxation, thus replacing the diminished endogenous vasodilator capacity. Although there is no data to show prognostic improvement by use of organic nitrates in coronary artery disease, the symptomatic effectiveness during an acute episode of angina pectoris is well proven and seen by physicians on a daily basis. More problematic is the long-term use of organic nitrates, which is limited by side effects, such as headache, as well as by development of tolerance associated with impaired efficiency to prevent episodes of angina. Furthermore, the induction of oxidative stress and endothelial dysfunction demonstrated during long-term treatment with organic nitrates with the suspicion of potential aggravation of atherosclerosis has led to some reluctance to use these compounds (Munzel *et al.*, 2007). While considerable efforts have been made to find novel compounds stimulating the NO/sGC/cGMP axis, such as enhancers of endogenous endothelial NO synthase, activators of sGC or inhibitors of phosphodiesterases (Schafer *et al.*, 2006; Fraccarollo *et al.*, 2008), so far, none of these drugs have been proven useful to replace nitrates in treatment of patients with symptomatic coronary artery disease.

However, research efforts during the last years revealed that there are considerable differences among organic nitrates with regard to development of tolerance, as well as induction of endothelial dysfunction. Münzel’s group, as well as that of Parker, have published seminal papers demonstrating in mice and man that the induction of vascular tolerance and oxidative stress during long-term exposure to nitrates such as nitroglycerin and isosorbide-5-mononitrate is not shared by other nitrates, such as pentaerythritol tetranitrate (PETN) (Münzel *et al.*, 1996; Thomas *et al.*, 2007; Thum *et al.*, 2007). In addition to the considerable importance for the clinical application of organic nitrates, these research efforts also generated novel concepts in terms of nitrate bioactivation and the development of tolerance (Sydow *et al.*, 2004).

In this issue of the *British Journal of Pharmacology*, Schuhmacher *et al.* (2009) describe the characterization of a novel class of organic nitrates with amino moieties (aminoalkyl nitrates) (see Figure 1). Their results challenge traditional concepts regarding nitrate bioactivation and tolerance development. Aminoethyl nitrate was characterized as a novel...
organic mononitrate with high potency but devoid of induction of mitochondrial oxidative stress and cross-tolerance to nitroglycerin or the endothelium-dependent agonist acetylcholine after \textit{in vivo} treatment. Although the intermediate role of NO for nitroglycerin-induced vasorelaxation has been questioned (Kleschyov \textit{et al.}, 2003), aminoethyl nitrate, like most nitrates, elicited vasorelaxation by the liberation of NO (proven by use of the NO scavenger 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide) and sGC stimulation (proven by use of the selective sGC inhibitor NS2028, Figure 1).

As the nitrates were delivered by osmotic minipumps, important questions of enteral uptake and the bioavailability after oral application remain to be settled. Furthermore, the bioactivation pathway is not unequivocally defined, but does not appear to involve aldehyde dehydrogenase or cytochrome P450 enzymes. Aminoethyl nitrate did not cause tolerance to any of the other vasodilators tested, but did induce \textit{in vivo} tolerance to itself, implying that aminoethyl nitrate has its own bioactivation system. However, the metabolism of aminoethyl nitrate was apparently not inactivated by other nitrates or oxidative stress, as nitroglycerin therapy \textit{in vivo} did not induce cross-tolerance to aminoethyl nitrate. This work from Daiber’s group is an important advance in our fuller understanding of nitrate bioactivation, of tolerance phenomena, and, from the view of drug discovery, an important step towards the development of better organic nitrates for clinical application.

\textbf{Conflict of interest}

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\textbf{References}


