Organic Nitrates: Unusual Problems in Pharmacokinetics and Drug Therapy

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)rganic nitrates, such as nitroglycerin (NTG) and isosorbide dinitrate, are important odilators indicated for a variety of cardiovascular diseases. However, their effectness has been hampered because of rapid elimination and extensive first-pass hepatic abolism. Transdermal delivery is used currently in an attempt to provide sustained ion. Until recently, the primary criterion for evaluating the success of this delivery le was whether sustained plasma drug concentration could be maintained over the posed dosing period. This criterion assumes that (i) nitrate pharmacokinetics are e-independent, (ii) plasma drug is in rapid equilibrium with the pharmacologically ive moiety at the site of action, and (iii) the relationship between plasma concention and therapeutic effect is not affected by the duration of therapy.

Evidence has now appeared which questioned the validity of these assumptions. rate pharmacokinetics have been found to depend on *in vivo* hemodynamic status l duration of dosing. Systemic NTG clearance in rats is shown to be related cardiac output; this physiological dependence may, in part, be responsible for the stantial variations in plasma NTG concentration observed during presumed "steadyte" periods. An arterial-venous concentration gradient for NTG also exists; this dient diminishes during chronic dosing, probably due to a decrease in systemic NTG arance in the venous circulation.

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We have also shown that plasma NTG is not in instantaneous equilibrium with drug in large blood vessels. Accumulating evidence suggests that nitrate action may be mediated by active intermediates (viz: nitrosothiols) formed within the smooth muscle cells. Thus, other rate-determining steps may be present besides the availability of drug in plasma. Indeed, during chronic therapy, plasma nitrate concentration increases but the vascular effects are attenuated. This apparently paradoxical relationship can be attributed to a generalized reduction in *in vivo* metabolism of these drugs upon repeated dosing. Thus, reduced systemic metabolism leads to increased plasma concentration while depressed metabolic activation in the vasculature leads to a diminition in pharmacologic effect. Recent results show, however, that incorporation of nitrate-free intervals in the regimen may avoid the development of tolerance in man.

In this presentation, these findings will be discussed, along with their implications on possible strategies that may be adopted for effective sustained nitrate therapy. These concepts may also be applicable to other drugs which exhibit pharmacological tolerance during chronic dosing.