Glyceryl Trinitrate (Nitroglycerin) and the Organic Nitrates
Choosing the Method of Administration

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Summary

Nitrate usage worldwide is on the increase as the indications for therapy expand. Present indications for nitrate therapy include chronic stable angina pectoris, unstable angina pectoris, complications of acute myocardial infarction, and ‘unloading’ therapy for acute and chronic congestive heart failure. Nitrates are also being used in the operating suite by anaesthesiologists to control systolic blood pressure during various surgical procedures. New nitrate delivery systems have recently become available which provide considerable dosing flexibility, further increasing the interest in this group of compounds.

The dominant action of nitrates is a direct effect on vascular smooth muscle, producing vasodilatation of the veins and arteries. These drugs decrease myocardial work by lowering systolic blood pressure, systemic vascular resistance, and reducing intracardiac dimensions. In addition, nitrates have a potent effect on cardiac preload as a result of systemic venodilatation. There is also some evidence that nitrates exert direct effects on the coronary circulation (vasodilatation of coronary arteries and coronary collateral vessels, and direct atherosclerotic stenosis dilatation). These actions may play a role in relieving myocardial ischaemia.

Adverse sequelae of nitrate therapy are well known and serious adverse reactions are uncommon. Headache and dizziness are the most frequent side effects. Nitrate tolerance is a definite problem – present evidence indicates that long acting formulations, high doses,
or frequent dosing regimens are particularly likely to induce vascular tolerance to nitrates. Consequently, provision of a nitrate-free interval has taken on increasing significance as a strategy to avoid tolerance.

Nitrate delivery systems are numerous. Although availability varies from country to country, in most countries there are a wide variety of formulations of glyceryl trinitrate (nitroglycerin) available, including sublingual and oral tablets, oral spray, topical ointment as well as discs or patches for transdermal administration, a transmucosal tablet and an intravenous formulation. Similar formulations of isosorbide dinitrate, except buccal tablets, are available in some countries. Isosorbide 5-mononitrate, a potent metabolite of isosorbide dinitrate, is achieving increasing popularity as an antianginal drug.

Optimum nitrate therapy requires a good understanding of the properties of the various formulations, particularly onset and duration of action and propensity to induce tolerance. Patient preference is also an important factor in making a final choice of a formulation, particularly for angina prophylaxis where several preparations show approximately equivalent efficacy.

Glyceryl trinitrate (nitroglycerin) and various organic nitrate esters remain a mainstay of treatment for ischaemic heart disease. The increasing utilisation of vasodilator therapy for congestive heart failure provides an important additional role for nitrate therapy. These drugs are potent venodilators and also have arteriolar vasodilating capacity, actions which are beneficial in patients with congestive heart failure, producing a reduction in left ventricular filling pressure. Pulmonary artery and right atrial pressures decrease after nitrate administration, which may be quite beneficial in patients with biventricular failure. Nitrate effects on the pulmonary arterial circulation have been used experimentally in treating pulmonary hypertension. The arterial-arteriolar dilating effects of these drugs cause a reduction in left ventricular afterload; cardiac output is maintained and may be even modestly increased through the ‘unloading’ effects of these drugs. This is in contradistinction to effects in subjects with normal circulation, where nitrate administration results in a modest fall in stroke volume and cardiac output which may be partially prevented by reflex tachycardia.

Recently, there has been increasing utilisation of intravenous glyceryl trinitrate in acute myocardial infarction and for blood pressure control in acute cardiovascular emergencies or during various surgical procedures.

The recent resurgence of interest in nitrate therapy has been in part related to the proliferation of delivery systems for organic nitrates (see section 4). It is of historic interest that the first use of glyceryl trinitrate in angina pectoris was reported in 1879, but that until the early 1970s only sublingual administration of glyceryl trinitrate or isosorbide dinitrate were considered to be beneficial modes of delivery. Oral nitrates, available for many years, were believed by many experts to be of no usefulness in clinical practice. Glyceryl trinitrate ointment did not become widely utilised until the mid-1970s, and only recently has intravenous glyceryl trinitrate become commercially available. Current dosing flexibility is related to the wide variety of available nitrate formulations. At the same time, clinicians have an increased understanding of how best to use oral nitrates to obtain optimal results.

For the purposes of this article, only glyceryl trinitrate and isosorbide dinitrate are discussed. Penterythritol tetranitrate and erythrityl tetranitrate represent two ‘old fashioned’ oral agents which are not widely used, and for which available clinical data documenting efficacy are so limited as to preclude meaningful discussion. On the other hand, there are a large number of published reports on the use of glyceryl trinitrate and isosorbide dinitrate.

1. Problems with Nitrate Therapy

Nitrates cause definite adverse effects in many patients, and some individuals cannot continue ni-