Leading Article

In support of nitrate ointment for patients with acute myocardial infarction

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Introduction

Glyceryl trinitrate (GTN) is a potent vasodilator. It causes venodilatation which reduces venous return to the heart and thus reduces preload and also causes arterial vasodilatation which reduces left ventricular afterload. In angina pectoris these effects reduce myocardial wall tension and thereby reduce myocardial oxygen consumption and arterial vasodilatation increases myocardial oxygen delivery. In heart failure left ventricular filling pressures are high causing pulmonary venous congestion and pulmonary oedema and preload reduction improves these. Afterload reduction also improves forward flow and cardiac output. Thus, nitrates have important haemodynamic effects in the context of ischaemic heart disease.

Acute myocardial infarction

In acute myocardial infarctions involving the left ventricle, filling pressures are invariably raised. Drug treatment that lowers filling pressures without any effect on systemic blood pressure is haemodynamically desirable.¹ In an acute myocardial infarction, there is some evidence to suggest that excessive hypotension caused by arterial vasodilatation with early administration of enalapril² or nifedipine³ could be harmful and may increase mortality. An overview⁴ of trials of intravenous nitrates on mortality in acute myocardial infarction showed a substantial and important reduction in mortality of the order of 35%. This effect was larger than that produced by arterial vasodilatation alone in other trials with the use of intravenous nitroprusside. All these trials were conducted in the era before the routine use of thrombolysis was established and it is not certain that nitrates would confer an additional benefit now.

Nitrate preparations

There are many different preparations of nitrates which are designed to produce different onsets of action and effective blood nitrate levels. It is important to recognize that there are dose-related differences in the haemodynamic effects of nitrates. In low dosage nitrates act principally by venodilatation while at higher infusion rates a balanced venous and arterial dilating effect is seen.⁵ In patients with left ventricular failure it has been shown, using invasive haemodynamic monitoring, that sublingual GTN has a rapid onset of action with a peak effect within 5 minutes, causing a reduction in pulmonary capillary wedge pressure and mean pulmonary artery pressure.⁶ However by 30 minutes the pulmonary pressures had returned to baseline. In comparison topical GTN ointment (2%) had a peak effect at 30 minutes which was sustained for 3–6 hours. Armstrong *et al.*⁷ also showed GTN ointment to be effective in reducing pulmonary capillary wedge pressure and right atrial pressure without an effect on systemic pressures. Measurements of blood nitrate levels in this study showed that GTN ointment produced levels equivalent to those produced by intravenous infusion in the same patients and showed the same dose–response curve with a correlation coefficient of 0.96. There is evidence to show that the ointment can be applied to thigh, arm or chest wall with the same haemodynamic effect.⁸ High dose transdermal GTN (20 mg) formulated as patches produced similar effects but low-dose transdermal GTN delivery systems (e.g. Transiderm nitro) produce such low levels of nitrates^{9,10} as to have virtually no haemodynamic effect.¹¹

Higher doses of nitrates also cause systemic hypotension. Buccal GTN and intravenous isosorbide dinitrate have been compared in a randomized study using haemodynamic monitoring in patients with heart failure following acute myocardial infarction. Both caused falls in systemic and pulmonary pressures.¹² Buccal GTN caused a very

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early rapid fall in systolic blood pressure which was greater and quicker than that induced by intravenous isosorbide dinitrate. Oral isosorbide mononitrate (40 mg) and isosorbide dinitrate (40 mg) given to patients with left ventricular failure both caused reductions in pulmonary capillary wedge pressure, and pulmonary artery pressure which were maximal at 60–120 minutes after dosing. The effects of the mononitrate formulation persisted for 4 hours, although those of the dinitrate were shorter. In this study neither preparation had any significant effect on cardiac output or arterial pressure.¹³ However, sometimes oral nitrates in doses necessary to reduce filling pressures cause marked hypotension.¹⁴

Conclusions

So in acute myocardial infarction, which nitrate preparation is best? The mortality data³ were

derived using intravenous nitrates but intravenous nitrate therapy requires careful monitoring to avoid excessive systemic hypotension and is expensive. Oral therapy on the other hand, may be associated with variable and inconsistent absorption in patients who are seriously ill and bed bound, as has been shown with other drugs,¹⁵ and has variable effects on systemic blood pressure. Oral isosorbide mononitrate is currently being tested in this context in the ISIS IV trial. By comparison, high dose GTN given as ointment is rapidly absorbed, has a duration of action equivalent to oral treatment, produces blood levels equivalent to intravenous nitrates⁷ and rarely affects systemic blood pressure to any important degree whilst lowering filling pressures. GTN ointment is my favoured preparation for patients with acute myocardial infarction.

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