Nitrate therapy for ischaemic heart disease

C. R. CONTI

University of Florida, College of Medicine, Division of Cardiology, Gainesville, FL 32610, U.S.A.

KEY WORDS: Nitrates, ischaemic heart disease.

The beneficial effects on nitrates are related to a combination of coronary and non-coronary effects of the drugs. Patients with different forms of ischaemic heart disease may respond differently. For instance, in a patient with rest angina due to coronary artery spasm, nitrates will reverse or prevent coronary artery spasm. In contrast, the patient with severe coronary artery stenosis and reproducible angina during exercise, may obtain relief because nitrates decrease venous return, left ventricular size and left ventricular pressure, thus decreasing myocardial oxygen demands.

Nitrates can be used to treat patients with chronic angina, unstable angina and myocardial infarction. In patients with chronic angina, oral nitrate preparations with sustained-release action have been shown to decrease the indices of myocardial oxygen demand for up to 12 h. In patients with unstable angina, intravenous nitrates usually relieve symptoms in patients refractory to oral therapy. In patients with acute myocardial infarction, early administration with intravenous nitrates may benefit patients as suggested by randomized prospective trials.

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Although nitrates are effective drugs, it is naive to think that they will be used alone to manage the complex problems associated with ischaemic heart disease. Other than hypotension and adverse effects of the drug, there seems to be no contraindication to the combination of nitrates with calcium antagonists or beta blockers.

Introduction

The commonest indication for the use of nitrates is to treat and prevent myocardial ischaemia in patients with exertional angina or rest angina. Recently, nitrates have been used early in the course of evolving myocardial infarction with the hope of diminishing periinfarction ischaemic zones and perhaps limiting infarction size. In this group of patients with myocardial infarction, nitrates may provide relief of pulmonary congestion by lowering ventricular end diastolic pressure and thus, diminishing pulmonary venous pressure. The purpose of this review is to summarize pertinent data on nitrate therapy for patients with chronic angina, unstable angina and acute myocardial infarction.

Physiologic effect of nitrates

The direct coronary artery effects of nitrates include dilatation of large coronary arteries, small intramural coronary arteries and conduit vessels that carry collateral flow to several narrowed or totally narrowed blood vessels (Table 1). The diameter of many coronary artery stenoses also increases. Measurements of coronary blood flow in patients with severe coronary artery diseases have shown potential for coronary blood flow to increase in some regions perfused by either collateral flow or by severely stenosed arteries after nitrates (2).

The non coronary effects of nitroglycerine are those of systemic arterial and venous dilation. Dilation of the systemic venous system will lower right atrial pressure and left ventricular pressure and volume. Systemic arterial dilation usually occurs to a lesser extent but arterial pressure usually also decreases. These effects should
Table I  Physiologic effects of nitrates

<table>
<thead>
<tr>
<th>Direct coronary effects</th>
<th>Dilution of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) large coronary arteries</td>
<td></td>
</tr>
<tr>
<td>(b) small intramural coronary arteries</td>
<td></td>
</tr>
<tr>
<td>(c) collaterals</td>
<td></td>
</tr>
<tr>
<td>(d) coronary arteries stenoses</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non coronary effects</th>
<th>Dilution of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) systemic veins</td>
<td></td>
</tr>
<tr>
<td>(b) systemic arteres</td>
<td></td>
</tr>
</tbody>
</table>

decrease left ventricular oxygen demand. The decreased left ventricular volume and diastolic pressure could favour endocardial perfusion.

If the various physiologic effects of the nitrates are matched with the different groups of patients presenting with ischaemic heart disease one can formulate an explanation of how the nitrates potentially relieve myocardial ischaemia in each group. For instance in a patient with rest angina due to coronary artery spasm, nitrates will reverse or prevent coronary artery spasm. Thus, coronary artery dilation is the primary physiologic event responsible for the relief of myocardial ischaemia in this patient. In contrast, the patient with severe coronary artery stenosis and reproducible effort angina may find relief by a different mechanism. In this patient, nitroglycerine reduces venous return, left ventricular size and aortic pressure and thus, decreases myocardial oxygen demand. In this type of patient, the peripheral systemic effects of nitrates are the principle mechanism by which myocardial ischaemia is relieved. Thus, in the individual patients, the coronary or the non coronary effects of the nitrates may be of principle importance with variable contribution from the other effects of nitrates. In addition, the ability of nitrates to redistribute blood flow and to dilate certain coronary artery stenoses may be important in some individuals. In a few instances, patients with exercise induced angina have been shown to have coronary spasm during exercise associated with either ST segment depression or elevation.

Nitrate tolerance

It is probably true that chronic exposure to nitrates by munitions workers can result in tolerance since many workers report disappearance of headaches after several days of work. What is not clear, however, is whether this type of exposure to nitrates has any relevance to the use of nitrates in clinical practice.

Experienced clinicians treating large numbers of patients with ischaemic heart disease rarely if ever, note patients who develop tolerance or a decreased effectiveness of the nitrates they have currently administered. Perhaps the clinician perceives nitrate tolerance as an unusual phenomenon because of the method of dosing the patient. Until recently nitrates have been administered on a 4 to 8 h basis and in many instances are not administered throughout the night during sleep. Thus, it would be unusual for these patients to develop constant blood levels of nitrates. It is more likely that a pulse dose of the drug is being administered. This would allow for the recovery from the initial dose. The next administration of the drug would either begin with a low or absent blood level of nitrates.

Patients with chronic angina treated with nitrates may develop increasing frequency or duration of angina attacks despite continuance of the same dose of nitrates. These patients are considered to have unstable ischaemic syndromes. Since the pathophysiology of unstable angina is not clear, one hypothesis to explain this phenomenon is that nitrate tolerance developed in these patients. Unfortunately, this hypothesis has neither been confirmed nor refuted.

At the present time, the evidence for clinically important nitrate tolerance in patients with ischaemic heart disease is not strong. However, there are no data testing the long-term effects in patients receiving newer transdermal preparations in which blood levels are maintained for a 24 h period. In all previous studies constant levels of nitrates probably have not been maintained.

Despite this lack of evidence for clinically important nitrate tolerance it seems prudent to be cautious about the rapid and precipitous withdrawal of nitrate preparations. When nitrates are discontinued, levels decline rapidly and pharmacologic effect parallels this. It is possible that under these conditions, there may be a rebound increase in coronary tone, increase in venous return, and increase in systemic blood pressure.

Clinical usefulness of nitrates

CHRONIC ANGINA

Patients with chronic angina the beneficial effects are due to (1) reduction of systemic blood

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Table 2  Action of nitrates in chronic angina

| 1 | ↓ Systemic pressure |
| 2 | ↓ Left ventricular diastolic pressure |
| 3 | ↓ Left ventricular volume |
| 4 | Dilation of epicardial arteries |
| 5 | Dilation of collaterals |

pressure, (2) reduction of left ventricular diastolic pressure, (3) reduction of left ventricular volume and (4) dilation of epicardial coronary arteries and coronary collaterals (Table 2). The above effects combined to decreased myocardial oxygen consumption and diminish any effect of coronary vasoconstriction on coronary blood flow. These effects occur in patients regardless of the type of nitrate preparation used or route of administration with the exception of intracoronary route. Fig. 1 summarizes the routes of administration of nitrates.

**Symptom relief**

In the typical patient with stable angina pectoris sublingual nitrates are commonly used to abort an attack of angina. In addition these same nitrates can be used to prevent angina in patients who can recognize situations which invariably provoke angina. In the experience of many, sublingual nitrate doses of 0.4 mg or less are effective treatment for most attacks of angina in patients with chronic symptoms.

**Symptom prevention**

Long acting nitrate preparations should not be used to treat individual attacks but are effective to prevent subsequent episodes of myocardial ischaemia. Most of the 'longer acting preparations' have shown alterations of blood pressure, end diastolic pressure, heart rate, ventricular volume, and exercise tolerance lasting several hours. Udhoji and Heng recently tested the haemodynamic effects of 40 or 80 mg oral isosorbide dinitrate (sustained action) in 10 patients with chronic angina\cite{3}. They demonstrated significant reduction in mean arterial pressure, cardiac index, pulmonary artery wedge pressure, mean pulmonary artery pressure, double product, stroke volume index, and stroke work index in the first hours after administration of the drug which persisted for 12 h.

Miner and Conti demonstrated the prolonged action of nitro paste in 10 patients with chronic angina pectoris\cite{4}. Systolic and diastolic pressure, heart rate, and end diastolic dimension (M-mode echo) was measured over a 240 min study in patients in a semi-recumbent position. In general the haemodynamic effects of nitro paste which began within 15 min, were sustained for 240 min.

In contrast, Crean and colleagues tested a nitroglycerine skin patch (25 mg — 10 cm$^2$) in 10 patients with stable angina\cite{5}. This was a randomized double blind double cross over trial of 4, 1-week periods. Efficacy of therapy was tested by angina diary, exercise testing, and 96 h of ambulatory ST segment recording. These investigators could not detect any significant difference in objective or subjective evidence of ischaemia in patients with frequent stable angina treated with transdermal nitroglycerine compared with placebo.

Topical nitrate preparations can be used in the same manner as the oral long acting nitrates. The ointment form of the drug probably has a physiologic effect lasting 3 to 4 h. Some of the newer transdermal preparations may last 24 h or more (as determined by plasma levels of nitrates). Reichek and his colleagues have reported an increase in exercise capacity of patients for periods of up to 3 h after nitroglycerine ointment treatment\cite{6}. This would correspond to the data of Miner and Conti\cite{4}.
Prognosis of patients with chronic angina treated with nitrates

There are no modern studies comparing nitrate monotherapy to any form of therapy. The drug is rarely used alone in patients with chronic angina pectoris and is most often combined with either a beta-blocker or calcium antagonists.

Safety and adverse effects of nitrate administration in patients with chronic angina

Despite widespread use of nitrates, no long-term studies in animals been performed to evaluate their carcinogenic potential. It is not known whether nitrates can cause fetal harm or if it can effect reproduction capacity nor is it known whether nitrates are excreted from human milk. Nitrates should be used with caution in patients receiving pentobarbital anaesthesia since they will prolong pentobarbital sleep time. Nitrates also potentiate the hypotensive and anticholinergic effects of tricyclic antidepressants. Nitrates also have an additive effect of many other hypotensive agents and may precipitate severe hypotension in patients receiving antihypertensive therapy. The commonest side-effects of chronic administration of nitrates include headache, mild increase in heart rate and hypotension. These problems can be controlled easily by either dose reduction or other appropriate measures, e.g. in some instances patients who develop severe hypotension or severe headache after administration of the drug can be given smaller doses and these reactions avoided. Topical preparations, especially the ointment form of the drug, have produced skin irritations in some patients requiring discontinuance of this therapy.

UNSTABLE ANGINA PECTORIS

In this group of patients loosely defined as those with angina severe enough to require prompt admission to the Coronary Care Unit for treatment, nitrates in all forms have been used. Until recently, the mainstay of therapy has been sublingual nitroglycerine to treat individual attacks and long-acting nitroglycerine preparations to prevent subsequent attacks.

Symptom relief

In general, patients presenting this way may require more than one type of therapy. However, nitrates still form the basis for that therapy. There are no published data to support the exclusive use of one group of drugs over another in this condition.

Distante et al. performed a double cross over study in the Coronary Care Unit in patients with frequent transient ischaemic episodes at rest[7]. Intravenous isosorbide dinitrate (1.25 to 5.0 mg h⁻¹) was infused and compared with saline. The total number of transient ischaemic attacks was reduced from 104 and 91 in the two placebo periods, to 13 and 20 during the treatment periods. Two patients complained of headache during the initial hour of the infusion. A rebound in the number of ischaemic episodes was observed in a preliminary pilot study after sudden interruption of the infusion. There was a slight increase in heart rate and decrease in blood pressure during infusion. The investigators conclude that continuous intravenous infusion of isosorbide dinitrate appears to be an effective treatment, with negligible side-effects, for the management of patients with recurrent episodes of transient myocardial ischaemia at rest.

Intravenous nitrates seem to be the ideal way to treat patients with unstable ischaemic syndromes. Table 3 indicates the current use of intravenous nitroglycerine. Intravenous nitroglycerine can provide rapid and controlled alteration of the systemic haemodynamics and favourably alter the myocardial oxygen supply equation. Several groups have reported a marked reduction in frequency of angina episodes of patients who were considered 'refractory to maximum standard medical therapy'. Page and his colleagues reported 67 patients treated with the intravenous preparation[8]. Therapy was begun during the first days of hospitalization and the dose was increased from 10 to 30 min intervals. Systolic arterial pressure was maintained greater than 90 mmHg with a dose varying from 36 to 108 mcg. Using this

<table>
<thead>
<tr>
<th>Table 3 Uses of intravenous nitroglycerine</th>
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</thead>
<tbody>
<tr>
<td>1. Unstable angina</td>
</tr>
<tr>
<td>2. Acute myocardial infarction</td>
</tr>
<tr>
<td>3. Post infarction angina</td>
</tr>
<tr>
<td>4. Hypertension post CABG</td>
</tr>
<tr>
<td>5. Prevention or treatment of coronary spasm</td>
</tr>
<tr>
<td>6. Treatment of heart failure</td>
</tr>
</tbody>
</table>
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Table 4  Unstable angina pectoris. Treatment with intravenous glycerol trinitrate

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dose (μg min⁻¹)</th>
<th>Pain relief (%)</th>
<th>Duration of treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>Brodsky et al. [10]</td>
<td>14</td>
<td>30–350</td>
<td>0</td>
</tr>
<tr>
<td>Dauwe et al. [11]</td>
<td>14</td>
<td>9–180</td>
<td>significant decrease</td>
</tr>
<tr>
<td>Depace et al. [12]</td>
<td>20</td>
<td>15–226</td>
<td>70</td>
</tr>
<tr>
<td>Kaplan et al. [13]</td>
<td>27</td>
<td>152 (AVG)</td>
<td>81</td>
</tr>
<tr>
<td>Mikoliche et al. [14]</td>
<td>45</td>
<td>5–267</td>
<td>0</td>
</tr>
<tr>
<td>Page et al. [15]</td>
<td>67</td>
<td>12–5–50</td>
<td>63</td>
</tr>
<tr>
<td>Roubin et al. [16]</td>
<td>16</td>
<td>85–1020</td>
<td>38</td>
</tr>
<tr>
<td>Squire et al. [17]</td>
<td>42</td>
<td>227–393</td>
<td>45</td>
</tr>
</tbody>
</table>

therapy there was a decrease in the mean number of anginal attacks from 9·8 ± 7·6 (previous 7 days) to 1·2 ± 2·4. Most of the patients were treated for greater than 2 days (mean 7·4 days ± 4·2). Sixty-four of the 67 patients had a decrease in anginal symptoms during treatment and 42 became asymptomatic. Bradycardia and hypotension occurred in two patients. These symptoms were easily reversed by reducing the nitrate infusion. Headaches occurred in three patients requiring a lowering of the nitrate dose. During the nitrate infusion a myocardial infarction evolved in one patient. There were no deaths during the initial hospitalization.

Kaplan and colleagues recently reported 35 patients with angina at rest that was unresponsive to standard oral or topical nitrates and beta blocking drugs[9]. These patients were treated with continuous infusion of intravenous nitroglycerine. The average IV nitroglycerine infusion rate was 140 ± 15 μg min⁻¹. On this therapy the number of angina episodes decreased from 3·5 ± 0·4 to 0·3 ± 0·1 and morphine sulfate administration decreased from 5·5 ± 1·3 to 0·4 ± 0·2 mg day⁻¹ (P < 0·001). Of the 35 patients, 25 eventually became pain free, 8 had > 50% decrease in the number of angina episodes per day and 2 failed to respond. The investigators admit that the mechanism whereby the addition of intravenous nitroglycerine was successful in controlling rest angina that has not responded to high doses of oral and topical nitrates was not entirely clear. However, they conclude that the use of intravenous nitroglycerine appears to be effective therapy for angina at rest, refractory to standard oral and topical medication.

Several open trials of intravenous nitroglycerine infusion have been reported[8–16]. These are summarized in Table 4. Sorkin in his comprehensive review of the pharmacologic properties and therapeutic efficacy of intravenous glycerol trinitrate, also noted in all studies reported the infusion rate needs to be adjusted to individual requirements[17]. Either pain relief, drop in systolic blood pressure, or dose limiting side effects were the end points in most of the studies reported. Dose ranges for the intravenous preparation vary widely as did the duration of treatment.

Heinsimer et al. studied 32 patients with unstable angina treated with either intravenous nitroglycerine (mean dose 82 μg min⁻¹ or a combination of oral isosorbide dinitrate 187 mg day⁻¹ and 2% glycerol trinitrate ointment (142 mm day⁻¹)[18]. Both therapies proved efficacious. The IV preparation decreased ischaemic episodes per day by 70% and the other therapy decreased ischaemic episodes by 55%.

Symptom prevention in patients with unstable angina

Chronic administration of nitrates to these patients seems to be efficacious, but there are no long-term clinical trials that refer to that point.

Prognosis of patients with unstable angina treated with nitrates

There are no long-term studies to document the efficacy of nitrate therapy used alone in patients with unstable angina. However, Hill et al. reported a beneficial effect of isosorbide dinitrate compared with previous therapy in a group of patients with coronary artery spasm treated for 5 weeks[19].
The dose of isosorbide dinitrate ranged from 40–120 mg day\(^{-1}\). Fifteen of 21 patients (71\%) had a greater than 50% decrease in angina frequency compared with previous therapy.

**Safety/adverse effect of nitrates in treating patients with unstable angina**

All of the hazards and side-effects of nitrate therapy reported in patients with chronic angina occur in patients with unstable angina. Intravenous nitroglycerine may precipitate bradycardia in occasional patients. Since it is a potent hypotensive agent, rate of infusion must be monitored frequently. Hill et al., noted the following adverse effects in 21 patients with coronary spasm, treated with isosorbide dinitrate for a period of 5 weeks: death (1), mild headache (9), severe headache (1), dizziness (4), hypotension (2), and fatigue (2). One patient with hypotension and one with severe headache had to have the drug discontinued.

**THERAPY OF MYOCARDIAL INFARCTION WITH NITRATES**

Until recently it was recommended that nitrates be avoided in patients with acute myocardial infarction. The rationale was that nitrate-induced hypotension reduced coronary perfusion pressure and perhaps extended the infarction. Perhaps the lack of haemodynamic monitoring in the past contributed to this concern. In those patients who become hypotensive, haemodynamic monitoring might have shown a normal systemic blood pressure and a low or normal left ventricular filling pressure. Many patients who responded in this manner may have been hypovolemic. Fig. 2 illustrates the varying effect on cardiac output in patients with acute myocardial infarction. The difference is related to the left ventricular filling pressure.

**Symptom relief**

The use of nitrates in patients with acute myocardial infarction can be grouped into three major headings. Firstly, treatment of symptoms of myocardial ischaemia during the initial presentation, secondly, treatment of pulmonary congestion and, thirdly, treatment of recurrent ischaemic cardiac pain.

When nitrates are used to treat the symptom of cardiac pain in the early stages of acute myocardial infarction, many patients will obtain relief or at least have their morphine requirements diminished. If the decision to use nitrates is made, the intravenous form of the drug should be used.

Although it seems reasonable to expect that nitrates might limit infarction size, studies have not conclusively proved that hypothesis. In contrast, IV nitrates are effective treatment for pulmonary oedema secondary to acute myocardial infarction. Intravenous nitrates rapidly reduce left ventricular end diastolic pressure which in turn decreases pulmonary venous pressure and relieves pulmonary congestion. In addition, lowering left
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Table 5  Acute myocardial infarction. Treatment with intravenous glycerol trinitrate. Randomized prospective studies

<table>
<thead>
<tr>
<th>Randomized prospective studies</th>
<th>Patients</th>
<th>Dose (μg min⁻¹)</th>
<th>Outcome</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaherty et al.¹²⁰</td>
<td>104</td>
<td>90</td>
<td>EF ↑ 10% and thallium defect score ↓ 75% in 48% of early treated patients</td>
<td>48 h</td>
</tr>
<tr>
<td>Bussman et al.¹²¹</td>
<td>60</td>
<td>47</td>
<td>CK enzyme ↓ 23%</td>
<td>48 h</td>
</tr>
<tr>
<td>Jaffe et al.¹²²</td>
<td>85</td>
<td>54</td>
<td>CK enzyme ↓ 37% but only in inferior transmural infarction</td>
<td>24 h</td>
</tr>
<tr>
<td>Derrida et al.¹²³</td>
<td>74</td>
<td>51</td>
<td>Hospital mortality ↓ from 8/35 to 2/39</td>
<td>1-7 days</td>
</tr>
</tbody>
</table>

ventricular end diastolic pressure allows better perfusion of subendocardium, probably decreases peri-infarction ischaemic zones and may improve systolic function of the ventricle increasing cardiac output.

Four major prospective randomized studies have been reported in patients with acute myocardial infarction receiving intravenous nitroglycerine (see Table 5).

Flaherty et al. reported 104 patients randomly assigned to IV nitrate (56 patients) and placebo (48 patients) within 18 h of infarction¹²⁰. The infusion lasted 48 h. If IV nitrate was given within 10 h after infarction, ejection fraction increased and thallium defect score was less than in patients given placebo or who received nitrates later than 10 h after onset of infarction.

Bussman and colleagues compared 31 patients with acute myocardial infarction receiving intravenous nitroglycerine for 48 h with 29 patients not receiving nitroglycerine¹²¹. Only patients with pulmonary wedge pressures of > 12 were included in this study. There were two groups, i.e., those receiving early treatment (<8 h) and those receiving late treatment (>8 h) after the onset of chest pain. All patients had transmural myocardial infarction. Treatment was initiated 10-2 h (mean) after the onset of the myocardial infarction. The mean infusion rate of nitroglycerine was 47 μg min⁻¹. The study showed that mean creatine kinase was 23% lower in the nitroglycerine treated patients compared with control. There was no difference between early and late treatment when CK or CKMB enzymes were used as end points.

Jaffe and associates randomized 85 patients to nitroglycerine and placebo infusion for 24 h¹²². The infusion was initiated within 10 h after the acute infarction (mean 6 h). The goal of the infusion was to lower blood pressure by 10% or a maximum dose of 200 μg min⁻¹. In these patients creatine kinase was 37% lower with nitroglycerine treatment but only in the subgroup of patients with inferior transmural myocardial infarction (P<0.5).

In another prospective trial Derrida and colleagues randomized 74 patients with acute myocardial infarction to either nitroglycerine or control¹²³. They noted a significant reduction of hospital mortality from 23% to 5% in those receiving nitroglycerine. In this study blood pressure was lowered by 20 mmHg and the infusion was maintained for 1 to 7 days. Mean nitroglycerine dose was 51 μg min⁻¹. Patients received this dose 10 h (mean) after the onset of the infarction.

Use of nitrates to prevent reinfarction

In patients recovering from acute myocardial infarction, chest pain occasionally occurs during hospitalization. In some instances, this may be due to coronary artery spasm or extension of the myocardial infarction. In others it may occur as activity is increased secondary to limitation in coronary flow in regions distal to the recent infarction by coronary stenoses. Nitrates are useful in the group of patients. Flaherty reported that myocardial extension (as measured by serial creatine kinase) was less frequent in the early intervention group (8%) than in the late intervention group (26%) or in the placebo group (33%)¹²⁴.
Prognosis of patients with acute myocardial infarction treated with intravenous nitroglycerine

Flaherty et al. reported a 10 day mortality in 4% of patients treated with IV nitrates compared with 7% in patients treated with placebo.[20] Mortality increased to 15% in 3 months in the early treated nitrate group and 22 to 27% in the other subgroups, but these differences were not statistically significant.

Bussmann and Halber reported that sudden death and reinfarction was reduced at 18 months in those treated with nitrates (11%) compared with the control group (39%).[21]

Safety/adverse effects of nitrates in patients with acute myocardial infarction

Although it is clear that intravenous nitrates can have beneficial effect in many patients with myocardial infarction, adverse effects such as hypotension and Bradycardia can occur. Thus, the intravenous drug should be given only to patients continually monitored in a Coronary Care Unit.

Nitrates should not be given to patients who are obviously hypotensive for unknown reasons or who have uncorrected hypovolemia. The problem of hypovolemia is best illustrated in the patient with a recent myocardial infarction who has been sweating profusely for a prolonged period of time prior to admission to hospital. In this type of patient pooling of blood in the periphery after nitroglycerine administration may have disastrous results. However, it can be corrected by raising the legs and infusing intravenous fluids.

Summary

Nitrates are available in many preparations. These include parenteral, sublingual, buccal, oral and transdermal. The most common route of administration is sublingually, but the intravenous preparation is being used more frequently especially in the acute situation, i.e. patients with unstable angina and acute myocardial infarction.

The commonest indication for the use of nitrates is for the treatment and prevention of myocardial ischaemia.

Nitrates have a direct effect on the coronary arteries as well as noncoronary or systemic effects. Coronary effects include dilation of epicardial coronary arteries and decrease in some patients of coronary vascular resistance. Systemic effects are primarily due to peripheral venous dilation which results in decreased venous return, decreased filling pressure and decreased diastolic volume of the ventricles.

The beneficial effects of nitrates probably are related to a combination of coronary and non-coronary effects of the drug. However, patients with different forms of ischaemic heart disease may respond differently. For instance, in a patient with rest angina due to coronary artery spasm, nitrates will reverse or prevent coronary artery spasm. In contrast, the patient with severe coronary artery stenosis and reproducible angina during exercise may obtain relief because nitrates decrease venous return, left ventricular size and left ventricular pressure, thus decreasing myocardial oxygen demands.

Nitrates have been shown to be clinically useful in patients with chronic angina, unstable angina and myocardial infarction. In patients with chronic angina, oral nitrate preparations, e.g., sustained action isosorbide dinitrate, provides significant decreases of indices of myocardial oxygen demand for up to 12 h. In patients with unstable angina, intravenous nitrates are effective therapy to relieve symptoms in patients refractory to standard oral therapy. In patients with acute myocardial infarction, randomized prospective trials suggest that patients benefit from the early administration of intravenous nitrates.

Although nitrates are commonly used during the early phases of acute myocardial infarction, they should be avoided in the patient who is volume-depleted even though the blood pressure is in the normal range.

Idiosyncratic reactions to nitrates are rare but if they occur, administration of the drug should not be repeated. Unwanted side-effects such as hypotension or severe headache can sometimes be controlled by administering smaller doses of the drug. If this fails, the concomitant use of mild analgesics can sometimes allow continued use of nitrates in appropriate patients.

The problem of nitrate tolerance and nitrate dependence does not seem to be an important one in the clinical practice of cardiology. Perhaps this is in part related to the intermittent administration of the drug. Despite the lack of evidence for clinically important nitrate tolerance, it seems prudent to be cautious about rapid and precipitous withdrawal of nitrate preparations, particularly in patients treated with high doses.

When used in appropriate patients, in appropriate doses, nitrates can be effective therapy of myo-
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cardial ischaemia. However, in clinical practice it is highly likely that nitrates, calcium antagonists, and beta-blockers will be used in combination rather than separately.

References