Secondary preventive potential of nitrates in ischaemic heart disease

U. Thadani

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Nitrates exert their anti-anginal activity by a number of mechanisms. By reducing venous return and left ventricular end-diastolic pressure they lower myocardial oxygen demand and at the same time enhance blood flow to the sub-endocardium. They also directly increase myocardial oxygen supply by dilating the coronary artery stenoses and increasing collateral blood flow. These pharmacodynamic attributes are clinically efficacious in all the ischaemic myocardial syndromes. In stable angina pectoris, nitrates reduce myocardial ischaemia and ischaemic pain and increase exercise tolerance. In unstable angina, nitrates similarly reduce electrocardiographic evidence of myocardial ischaemia and relieve anginal pain. Following acute myocardial infarction, nitrates reduce ventricular dilatation and by so doing reduce pulmonary congestion and mitral regurgitation. The weak anti-aggregatory effect of nitrates on platelets may also play an adjuvant role in their anti-ischaemic activity. Early small-scale studies with both intravenous and oral nitrates demonstrated a trend to reduced mortality and reinfarction in survivors of acute myocardial infarction. However, the later and larger ISIS-4 and GISSI-3 trials have not confirmed this trend possibly due to the smaller doses of nitrates used and the diluting effect of the widespread use of open-label nitrates in the placebo group. In patients with congestive heart failure, including those of ischaemic aetiology, nitrates together with hydralazine have clearly demonstrated a significant reduction in the medium term mortality risk.

Nitrates have the undoubted ability, probably greater than any other single anti-anginal drug, to rapidly and often completely relieve the pain and breathlessness associated with myocardial ischaemia. They are haemodynamically efficacious in reducing dilatation of the ischaemic left ventricle and enhancing coronary blood flow to ischaemic areas. Although their preventative impact in survivors of acute myocardial infarction awaits clarification, they have been shown in combination with hydralazine to extend survival in patients with congestive heart failure, including those of ischaemic origin.

(Key Words: Ischaemic heart disease, angina, myocardial infarction, heart failure, nitrates.)

Introduction

Nitrates are widely recognised as clinically efficacious for the treatment of acute and chronic myocardial ischaemic syndromes. Their potent dilatation of the systemic resistance vessels and venous capacitance system reduces dilatation of the ischaemic ventricle and enhances blood flow to ischaemic sub-endocardial regions. Nitrates also directly dilate epicardial coronary arteries and particularly those with eccentric stenoses. However, it is still controversial whether these drugs reduce the morbidity and mortality risks of patients with stable or unstable angina pectoris or of survivors of acute myocardial infarction. Nitrates are, however, amongst the safest of drugs currently used in the treatment of ischaemic myocardial syndromes.

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Nitrates in angina pectoris

(a) In stable angina

Nitrates improve exercise performance and reduce exercise-induced myocardial ischaemia[43,44]. Despite reports of the diminished efficacy of nitrates due to the development of tolerance[45-47], when used appropriately, nitrates can be minimized or avoided[48-51]. In this regard, mononitrate has an advantage over other agents as it has a rapid onset of action and intermittent twice-a-day treatment is not associated with a rebound increase in nocturnal or early morning angina[49,50]. However, it is unknown if long-term use of nitrates reduces morbidity and mortality risk in patients with stable angina pectoris.

(b) In unstable angina

Intravenous nitroglycerin relieves myocardial ischaemia and chest pain in many patients with unstable angina[52,53]. During this acute phase of ischaemic heart disease, nitrates have a high safety record but it is unknown whether they reduce subsequent morbidity or mortality risk[53]. Tolerance to intravenous nitroglycerin frequently develops but can be overcome by dose escalation and clinical benefit maintained for at least 48-72 h[53-55].

Nitrates in acute myocardial infarction

Nitrates are efficacious in relieving acute pulmonary congestion and pulmonary oedema following acute myocardial infarction[56]. Both in animals and in patients, intravenous nitroglycerin has been shown to reduce infarct size and ischaemic mitral regurgitation[38-41, 57-59]. This has been attributed to the prevention of ventricular remodelling[29,30]. Nitrates rapidly relieve anginal pain in the post-infarct period and reduce electrocardiographic evidence of myocardial ischaemia[60]. It remains to be determined whether nitrates prevent reinfarction, reduce the risk of development of congestive heart failure and lower increased mortality risk following myocardial infarction[9,16,61].

Table 1 Effects of nitrates on haemodynamics

<table>
<thead>
<tr>
<th>MVO₂ reduction</th>
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<tr>
<td><strong>Preload</strong></td>
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<tr>
<td><strong>Venous return</strong></td>
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<tr>
<td><strong>LV and RV size</strong></td>
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<tr>
<td><strong>LV and RV pressure</strong></td>
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<td><strong>Wall stress</strong></td>
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<td><strong>Afterload</strong></td>
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<tr>
<td><strong>Systolic pressure</strong></td>
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<tr>
<td><strong>Aortic compliance and conductance</strong></td>
</tr>
<tr>
<td><strong>Systolic wall stress</strong></td>
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Table 2 Effects of nitrates on coronary blood flow

<table>
<thead>
<tr>
<th>Increased flow to ischaemic areas</th>
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<tr>
<td>Dilatation of epicardial vessels</td>
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<tr>
<td>Dilatation of atherosclerotic eccentric stenoses</td>
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<tr>
<td>Vasodilatation despite endothelial dysfunction</td>
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<tr>
<td>Decrease LV end-diastolic pressure</td>
</tr>
<tr>
<td>Collateral flow increase</td>
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<tr>
<td>Prevention of coronary artery spasm</td>
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Table 3 Effects of nitrates on platelet function

<table>
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<th>Anti-aggregatory</th>
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<tbody>
<tr>
<td>Anti-adhesion</td>
</tr>
<tr>
<td>Decreased thrombus formation</td>
</tr>
<tr>
<td>Decreased platelet thrombus induced vasoconstriction</td>
</tr>
</tbody>
</table>

collateral blood flow[17,18,21], dilate coronary eccentric stenoses[6], and reduce left ventricular end-diastolic pressure at rest and during exercise[19], these agents preferentially increase blood flow to the vulnerable subendocardial regions.

Recent studies suggest that nitrates may possess further preventative qualities (Table 3). Both in vitro and in vivo they have been shown to reduce platelet aggregation, deposition, and adhesion to injured endothelium and thus have the potential to decrease thrombus formation[22-26]. However, it is unknown if these anti-platelet effects of nitrates summate with those of aspirin, another potent platelet anti-aggregating agent frequently used in ischaemic syndromes. In theory at least, the potential of added beneficial effects of nitrates in patients receiving aspirin remains a distinct possibility as nitrates exert their effects on platelets via the production of nitric oxide[27] while aspirin inhibits cyclooxygenase[28].

(b) Effects of nitrates on remodelling and left ventricular dilation following an acute myocardial infarction

Left ventricular hypertrophy and chamber dilation commonly follow acute myocardial infarction and adversely affect prognosis[29-34]. Similar to angiotensin converting enzyme inhibitors[35,36] nitrates may prevent or retard remodelling of the dilated infarcted ventricle[37-42]. In animal studies early post-infarct treatment with intravenous nitrates has been shown to reduce infarct size and maintain left ventricular geometry and function by preventing remodelling[41]. In patients with anterior myocardial infarction, intravenous nitroglycerin has also been shown to improve haemodynamics, prevent left ventricular dilation and reduce ventricular arrhythmias[40,42].

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Early studies in a small number of patients showed that intravenous nitroglycerin reduced infarct size and infarct-related complications, particularly when administered within 10 h of onset of chest pain\(^\text{56,58,62,63}\). In one study there was a marked reduction in infarct-related complications in patients treated with intravenous nitroglycerin compared to placebo\(^\text{64}\), an improvement that was greatest in those with large anterior infarctions\(^\text{60}\). In contrast, another study failed to show any significant influence of nitrates on infarct size, reperfusion and ventricular remodelling\(^\text{66}\).

An overview of early randomized trials showed a 24% reduction in morbidity and mortality but this has not been confirmed by later trials\(^\text{9}\). In the ISIS-4 study, the 35 day mortality in 29 032 patients who received placebo was 7.45% compared to 7.34% in the 29 018 patients who received once daily 60 mg of oral long-acting mononitrate\(^\text{151}\). This difference was not statistically significant (Fig. 1). Long-term follow-up of patients treated with mononitrate demonstrated a saving of life at 6 months of 2.9/1000 patients treated and at 12 months a saving of 1.8/1000 patients treated, but significantly less than the saving of 4.9/1000 patients treated with captopril (Fig. 2). The small effect seen in the patients receiving slow release mononitrate may have been the result of the dose and the formulation of the medication used. In the ISIS Study, a 60 mg daily dose of slow release mononitrate was used\(^\text{153}\), but in a recent study in patients with stable angina pectoris this dose was no different from placebo\(^\text{51}\).

In the GISSI-3 trial, patients were treated with either a nitrate preparation (nitroglycerin patch or mononitrate), placebo, lisinopril, or a combination of lisinopril plus nitrates\(^\text{144}\). Patients received intravenous nitroglycerin during the first 24 h followed by treatment with long-acting nitrates. There was a small but statistically non-significant reduction in mortality in the nitrates group compared to placebo group (Fig. 3). In the patients given nitrates in addition to lisinopril, there was a significant reduction in mortality which was greater than that observed in the lisinopril or nitrates groups alone.

In both the ISIS and GISSI trials, more than 50% of patients in the placebo group received open-label nitrates which may have diluted the beneficial effect of nitrates in both studies. Molsidomine, a nitric oxide donor has also been shown to have no beneficial effects in this situation\(^\text{67}\).

**Clinical efficacy of nitrates in congestive heart failure**

Isosorbide dinitrate often improves symptoms particularly breathlessness in patients with congestive heart failure\(^\text{68}\). In combination with hydralazine, it has been shown to improve the central haemodynamics and significantly reduce the mortality risk in patients with mild to moderately severe heart failure\(^\text{69,50}\). These benefits
Preventative potential of nitrates in IHD

(a) CAPTOPRIL comparison

<table>
<thead>
<tr>
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<th>Month 6</th>
<th>Month 12</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>90.13%</td>
<td>88.01%</td>
</tr>
<tr>
<td>Captopril</td>
<td>89.47%</td>
<td>87.47%</td>
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BENEFIT per 1000: 6.6 (SD 2.6) 5.4 (SD 2.8)

(b) MONONITRATE comparison

<table>
<thead>
<tr>
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<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>89.95%</td>
<td>87.83%</td>
</tr>
<tr>
<td>Captopril</td>
<td>89.65%</td>
<td>87.65%</td>
</tr>
</tbody>
</table>

BENEFIT per 1000: 2.9 (SD 2.6) 1.8 (SD 2.8)

Figure 2  Cumulative late mortality in ISIS-4 trial. (Reproduced with permission\textsuperscript{153}.)

\[ p \text{ (log-rank) } = 0.03 \]

Figure 3  Early (6 week) survival in the GISSI-3 trial for the nitrate and ACE inhibitor groups (Reproduced with permission\textsuperscript{141}.)

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were seen in both ischaemic and non-ischaemic heart failure.

**Recommendations for the use of nitrates in the syndromes of ischaemic heart disease**

Nitrates play an important role in the management of patients with acute and chronic ischaemic syndromes. They are effective in relieving anginal pain and electrocardiographic evidence of myocardial ischaemia both in patients with unstable angina and those with chronic stable angina. In post-infarction survivors, nitrates are associated with a small reduction in mortality risk (Fig. 4). Thus, it is prudent to use nitrates selectively in patients with acute myocardial infarction who are at maximum risk, i.e. those with large anterior infarction, those with acute pulmonary oedema or signs of pulmonary congestion, those with elevated blood pressure and those with post-infarct angina. Nitrates should not be used in patients with right ventricular infarction or those who are volume depleted or hypotensive, in whom their deleterious effects potentially outweigh their benefits.

The question remains — do nitrates have a role in secondary prevention? Their unique mechanisms of pharmacodynamic activity, their ability to reduce remodelling of the ischaemic left ventricle and perhaps even their antiplatelet activity, suggest a role for their potential in this respect. Whether further trials will be mounted to address this important issue is problematic. Fortunately, from the clinical standpoint, the nitrates as a group are symptomatically efficacious and above all safe when used to treat patients with ischaemic heart disease from angina through myocardial infarction to heart failure.

**References**


