Effects of nitrates on mortality in acute myocardial infarction and in heart failure

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- 1 Seven randomized controlled trials of intravenous nitroglycerin in a total of about 850 patients have been reported. Overall, there were 51 deaths (12.5%) in the nitroglycerin group and 87 (20%) in the control group. This indicates a 48% reduction in the odds of death ($P < 0.001$, 95% confidence limits (25% to 64%)).
- 2 There are five randomized trials of oral nitrates after acute myocardial infarction. In these trials, 11.8% of the patients in the nitrate group compared with 13.3% in the control group died. This indicates a nonsignificant 12% reduction in the odds of death but the 95% confidence interval overlaps widely with the i.v. trials. If all trials of i.v. or oral nitrates are considered the reduction in the odds of death is 32% ($P < 0.01$).
- 3 Nitrates have a beneficial effect on haemodynamics in heart failure but the data on mortality effects are sparse. In combination with hydralazine, however, long-term mortality was reduced in the V-HEFT trial of chronic heart failure.

Keywords nitrates acute myocardial infarction heart failure mortality

Introduction

Nitrates have, since the first description of their clinical effects (Brunton, 1867), been used for over a century for the treatment of angina pectoris. The indications for their use have expanded to include unstable angina, acute myocardial infarction, and as vasodilator therapy for acute and chronic congestive heart failure (Abrams, 1985).

The primary action of nitrates is to produce vascular smooth muscle relaxation that results in dilatation of veins, arteries, and arterioles. Maximum venodilation occurs at very low plasma concentration ($<0.2 \text{ ng ml}^{-1}$) of nitroglycerin (Imhof *et al.*, 1980). Venodilation results in pooling of blood in the capacitance vessels, leading to reduced venous return to the right side of the heart. Consequently, there is a decrease in intracardiac pressures and volumes and a reduction in left ventricular preload. This is potentially beneficial in acute myocardial infarction and in patients with heart failure but may cause a decrease in stroke volume and cardiac output if left ventricular filling pressure is low.

Arteriolar vasodilatation occurs with large doses of nitrates, resulting in a drop in blood pressure through a reduction in systemic vascular resistance (Imhof *et al.*, 1980). Reflex tachycardia can occur, particularly when left ventricular filling pressure is normal, which may obviate the beneficial effects of the agent on myocardial oxygen demand. A drop in blood pressure may also decrease the myocardial perfusion pressure. In con-

gestive heart failure, however, a reduction in afterload because of arteriolar vasodilatation and a decrease in preload caused by venodilatation may improve cardiac output without increasing myocardial oxygen demand. In these patients, the drop in blood pressure appears less prominent, and sympathetic-mediated reflex tachycardia is less marked than in those with normal left ventricular function (Abrams, 1985).

The described haemodynamic effects may theoretically be of benefit both in acutely ischaemic conditions such as unstable angina and acute myocardial infarction and in acute and chronic heart failure. Indeed, in animal experiments nitrates have been shown to decrease infarct size and improve ventricular function. The ratio of the subendocardial-subepicardial blood flow in the ischaemic myocardium is improved after nitrate administration (McGregor, 1983). The main mechanism by which nitrates relieve angina and myocardial ischaemia is probably a decreased myocardial oxygen demand secondary to decreased blood pressure, reduced left ventricular diastolic and systolic volumes, and a fall in intraventricular filling pressures.

To be able to demonstrate clinical benefit in terms of mortality and major morbidity, randomised controlled clinical trials are needed. Unfortunately, only a limited number of such studies are available in acute myocardial infarction and in heart failure. Since most trials are small and the results hence somewhat unreliable, the data are

presented both for each trial individually and with all information pooled by the Mantel-Haenszel method (Yusuf *et al.*, 1985).

Available trial results

Acute myocardial infarction

A recent overview has summarised the results in the seven available randomised trials of intravenous nitrates in acute myocardial infarction (Yusuf *et al.*, 1988). In addition five trials of oral nitrates have been published (Fitzgerald & Bennet, 1990; Mellen *et al.*, 1967; Newell & clinical collaborators, 1970; Oscharoff, 1964; Ryan & Schnee, 1965).

In all intravenous trials, treatment was started within 24 h of onset of symptoms. Typically, exclusion criteria were age above 75 years, presence of pulmonary oedema, cardiogenic shock, systolic blood pressure below 90 or 100 mm Hg or above 200 mm Hg, chronic obstructive pulmonary disease, or any non-cardiac life-threatening disease. The infusion usually started with a small dose (5 to 15 $\mu\text{g min}^{-1}$) and was titrated upward to reduce systolic blood pressure by 10 to 15% or to reach 100 or 90 mm Hg. Duration of the infusion was for 24 to 48 h.

The seven intravenous nitroglycerin trials varied in size from 28 patients to 310 patients. Two of these reported statistically significant reductions in mortality. The largest trial reported a mortality of 24/154 (16%) in patients allocated to nitroglycerin and 44/156 (28%) in

control patients ($P < 0.01$) at 3 months (Jugdutt & Warnica, 1988). The other trial followed 60 patients for 18 months and reported a 4/31 (13%) mortality in actively treated patients and 12/29 (41%) in control patients ($P < 0.02$) (Bussmann *et al.*, 1981). The pooled mortality rate in the seven intravenous trials was 12.0% (51/426) for patients randomly assigned to nitroglycerin and 20.5% (87/425) for those to control (Table 1; $P < 0.001$) (Yusuf *et al.*, 1988).

Early and late mortality by allocated treatment in the trials were also analysed separately (Yusuf *et al.*, 1988). During the early period (7 day or in-hospital), the mortality was 21/426 (4.9%) for those allocated to active treatment and 57/425 (13.4%) for controls. After this initial period, the mortality rate in the active treatment group was 30/291 (10.3%) and 30/262 (11.5%) in the control group. Overall, these data suggest that the beneficial effect of nitrates occurs chiefly during the early period but that there may be some later benefit.

In the five oral treatment trials (Table 2) nitrates or placebo were started as soon as a provisional diagnosis of acute myocardial infarction was made. Nitrates were given for some days to weeks and in one trial for 6 months (range, 5 days to 6 months). Four trials used pentaerythritol tetranitrate (Mellen *et al.*, 1967; Newell and clinical collaborators, 1970; Oscharoff, 1964; Ryan & Schnee, 1965) and one isosorbide-5-mononitrate (Fitzgerald & Bennet, 1990). In two trials, patients who were subsequently found not to have acute myocardial infarction were excluded from analysis (Mellen *et al.*, 1967; Newell and clinical collaborators, 1970). In three trials, in-hospital mortality was reported (Mellen *et al.*,

Table 1 Mortality in trials of intravenous nitroglycerin

Study (follow-up period)	Deaths		Statistics		
	Treated	Control	O-E	V	2P
Chile (Hospital)	3/50 (6%)	8/45 (18%)	-2.8	2.5	NS
Bussman <i>et al.</i> (1981) (18 months)	4/31 (13%)	12/29 (41%)	-4.3	3.0	<0.02
Flaherty <i>et al.</i> (1983) (3 months)	11/56 (20%)	11/48 (23%)	-0.8	4.4	NS
Nelson (Hospital)	0/14 (0%)	0/14 (0%)	0	0	NS
Jaffe <i>et al.</i> (1983) (Hospital)	4/57 (7%)	2/57 (4%)	-1.0	1.4	NS
Lis (4 months)	5/64 (8%)	10/76 (13%)	-1.9	3.3	NS
Jugdutt <i>et al.</i> (1983) (3 months)	24/154 (16%)	44/156 (28%)	-9.8	13.3	<0.01
Overall	51/426 (12%)	87/425 (20.5%)	-18.5	27.9	<0.001

Overall Odds Ratio = 0.52 (95% confidence interval 0.36–0.75; $P < 0.001$)

Modified from Yusuf *et al.* (1988) with permission.

Table 2 Mortality in trials of oral nitrates

Study (follow-up period)	Deaths		Statistics		
	Treated	Control	O-E	V	2P
Oscharoff (1964) (Hospital)*	2/50	11/50	-4.5	2.9	<0.02
Mellen <i>et al.</i> (1967) (Hospital)*	11/108	10/89	-0.5	4.7	NS
Ryan & Schnee (1965) (Hospital)*	9/53	12/54	-1.4	4.3	NS
Newell <i>et al.</i> (1970) (21 days)*	25/181	24/165	-0.6	10.5	NS
Fitzgerald & Bennet (1990) (6 months)**	21/184	14/176	+3.1	7.9	NS
Overall	68/576 (11.8%)	71/534 (13.3%)	-3.9	30.3	

Odds Ratio = 0.88 (95% confidence interval -0.53 to +1.88; NS)

* = pentaerythritol tetranitrate

** = isosorbide-5-mononitrate.

Table 3 Exercise capacity in randomised trials of nitrates in heart failure

<i>Trial (follow-up period)</i>	<i>Number patients</i>	<i>NYHA Class</i>	<i>Exercise capacity</i>	<i>Statistics</i>
Franciosa <i>et al.</i> (1978) (2 × 2 months)	14	III–IV	improved	NS
Franciosa <i>et al.</i> (1980) (3 months)	16	II–IV	improved*	$P < 0.02$
Leier <i>et al.</i> (1983) (3 months)	30	III–IV	improved**	$P < 0.05$

All trials compared ISDN with placebo treatment

* = Maximal oxygen consumption

** = Exercise duration.

Figure 1 Effects of intravenous and oral nitrates on mortality in patients with acute myocardial infarction. An odds ratio to the left of the vertical continuous line indicates a decreased risk of death in the nitrate group compared with the placebo group.

1967; Oscharoff, 1964; Ryan & Schnee, 1965), in one, the 21-day mortality was available (Newell and clinical collaborators, 1970) and in the fifth trial, 6 months' mortality was reported. One of the five trials reported a conventionally significant reduction in mortality in the actively treated patients (Oscharoff, 1964). The overall mortality during the first few weeks after myocardial infarction was 68/576 (11.8%) for the treatment group and 71/534 (13.3%) for the control group ($P = \text{NS}$).

The confidence intervals for the intravenous and oral trials overlap substantially. When the data from the oral trials are combined with those from the intravenous studies, nitrate therapy is associated with a 32% reduction in mortality (95% confidence interval from 12 to 47%, $P < 0.001$) (Figure 1).

Myocardial infarct size, estimated from creatine kinase (CK) enzyme profiles, was significantly reduced by about one third in patients with nitrates compared with controls in three of the intravenous trials that provided such data (Bussmann *et al.*, 1981; Jaffe *et al.*, 1983; Jugdutt & Warnica, 1988). One other trial compared peak CK enzyme levels of treated and control patients but did not find any difference between the groups (Flaherty *et al.*, 1983). Intravenous nitroglycerin has also been shown to decrease infarct expansion (Jugdutt

& Warnica, 1988) and improve regional and global left ventricular function (Bussmann *et al.*, 1981; Jugdutt *et al.*, 1983).

Heart failure

The data on the effects of nitrates in heart failure are sparse. During short-term therapy nitrates improve haemodynamics. Left ventricular filling pressures can be reduced and cardiac output increases. Only a few small trials have compared the effect of nitrates with control treatment in heart failure (Franciosa *et al.*, 1978, 1980; Leier *et al.*, 1983). All reported improved exercise capacity after 3–4 months of treatment (Table 3). The interpretation of the results has, however, to be careful because of small sample sizes and a high drop out rate (Franciosa *et al.*, 1978; Leier *et al.*, 1983). Due to the limited number of patients enrolled, no reliable data on mortality effects are available. In the V-HeFT trial (Cohn *et al.*, 1986), however, the combination of hydralazine and ISDN was associated with a 34% decrease in 2 year mortality, compared with placebo. This promising difference was marginally statistically significant and indicates that nitrates may be able to reduce mortality in congestive heart failure.

Summary and future directions

The collective evidence from the intravenous and oral trials of nitrates in acute myocardial infarction do indicate that infarct size may be limited and that mortality is reduced by treatment. All trials were, however, individually small and confirmation of these effects in larger trials of broad patient populations is desirable. Indeed, two mortality trials are presently being planned. In ISIS-four nitrates, captopril and magnesium will be compared with placebo in a factorial design. In the Italian GISSI-three trial nitrates and lisinopril will be tested in a similar way. The results of nitrates in the few available exercise trials in heart failure are encouraging while the effect on mortality is not clear. The combination of ISDN with hydralazine seems to lower mortality but confirmation of these results in a larger trial would be important.

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