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Nitroglycerine/N-acetylcysteine in the management of unstable angina pectoris

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N-acetylcysteine (NAC) has been shown to potentiate the haemodynamic and antiplatelet effects of nitroglycerine (NTG) in man, and to limit the development of haemodynamic tolerance to NTG. These effects may be mediated by the formation of S-nitroso-NAC, which induces vasodilation and strongly inhibits platelet aggregation. In a randomized double-blind study in 46 patients with severe unstable angina pectoris unresponsive to standard treatment (including cutaneous nitrates and calcium antagonists in 45 patients) we compared the effects of intravenous (IV) NTG with those of IV NTG combined with IV NAC (5 g 6 hourly).

Treatment with NTG/NAC (24 patients) was associated with a similar frequency of episodes of chest pain as treatment with NTG alone (22 patients), but somewhat fewer increments in infusion rate for pain control (10 vs 17; P NS). The NTG/NAC group had a significantly lower incidence of acute myocardial infarction than the NTG/placebo group (3 vs 10 patients; P = 0·013).

Symptomatic hypotension occurred frequently in the NTG/NAC group (7 vs 0 patients; P = 0·006). It is concluded that combined administration of NTG and NAC in patients with unstable angina pectoris may augment the clinical efficacy of NTG, largely by reducing the incidence of acute myocardial infarction. However, the high incidence of severe hypotension with NTG/NAC suggests that this regimen should be used with some caution.

Introduction

Intravenously infused nitroglycerine (NTG) has been shown to be useful in the prophylaxis of myocardial ischaemia in patients with unstable angina pectoris unresponsive to other treatment measures[1–4]. However, some patients continue to experience episodes of ischaemic pain at rest despite intravenous infusion of NTG. Therefore NTG infusion rates may require to be increased considerably, resulting in an increased risk of NTG-induced adverse effects[5–7]; this problem may be partially associated with the development of haemodynamic tolerance to NTG[8–9].

Recent *in vitro* studies have demonstrated that the vasodilator effects of NTG are mediated via activation of soluble guanylate cyclase[10–12], a process which probably involves a number of sulphydryl (SH)-dependent steps, including denitration of NTG, formation of S-nitrosothiols as active intermediates, and possibly stabilization of the activated guanylate cyclase[13–15]. Thus both activation of guanylate cyclase by NTG and NTG-induced vasodilator responses may be modified by changes in SH availability[15–19]. The SH donor N-acetylcysteine (NAC) has been shown to potentiate the systemic[20] and coronary haemodynamic[21,22] effects of NTG in man, and to markedly potentiate the anti-platelet effects of NTG, via production of S-nitroso-NAC[23].

The currently reported studies were performed to test the hypothesis that the combined administration of NTG and NAC might be useful in patients with unstable angina pectoris, both by potentiating vasodilator effects of NTG, and by inhibiting the formation of intracoronary thrombi with resultant acute myocardial infarction.

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Methods

PATIENTS

Patients admitted to the Coronary Care Unit of the Austin or Brigham and Women's Hospitals with a diagnosis of unstable angina pectoris were eligible for trial entry only if frequent episodes of ischaemic pain persisted at rest, with associated reversible S–T segment changes on ECG, despite the use of conventional anti-anginal drugs, including nitrates. Criteria for exclusion were: 75 years of age or greater, Q-wave myocardial infarction within the preceding 3 months or non-Q-wave myocardial infarction in the preceding seven days, severe hypotension (mean BP less than 70 mmHg), concomitant therapy with drugs known to affect SH availability (such as captopril, penicillamine or ethacrynic acid), severe (Killip Class III or IV) left ventricular failure, clinically significant valvular heart disease, or severe renal or hepatic disease. No patient could be treated with isosorbide dinitrate or mononitrate in the six hours immediately prior to trial entry.

The investigational protocol was approved by the Ethics Committees of both participating hospitals and informed consent was obtained prior to trial entry.

PROTOCOL

The study was a double-blind, placebo-controlled comparative trial over the first 24 hours of intravenous NTG infusion. Patients entering the study were stratified according to age and presence or absence of prior Q-wave myocardial infarction in order to minimize the possibility of major differences between groups.

Each patient received intravenous NTG, delivered via non-absorbent polyethylene tubing utilizing an IMED pump at an initial delivery rate of 5 μg min^{-1}. Cutaneous NTG preparations were removed at the time of initiation of intravenous NTG infusion, but all other anti-anginal medications were continued unchanged throughout the study.

Fifteen minutes after initiation of intravenous NTG infusion, a blinded supplement consisting of either NAC (5 g in 200 mls 5% dextrose) or placebo (5% dextrose only) was infused intravenously over 15 minutes. This procedure was repeated every six hours. NTG infusion rates were adjusted if patients experienced ongoing severe ischaemic pain and/or persistent systolic BP >140 mmHg, or symptomatic hypotension. All increments of infusion rates were in multiples of two, in order to facilitate data analysis. In the event of development of prolonged chest pain with ECG changes suggestive of acute myocardial infarction, further doses of blinded supplement were withheld.

Blood pressure was measured frequently throughout the study period, with recordings made every 15 minutes for 1 hour after administration of supplement. All episodes of chest pain reported by patients were recorded. At the Austin Hospital, venous blood samples were drawn at entry and 1, 6 and 24 hours thereafter for determination of plasma NTG concentrations[24] and lactate–pyruvate ratios.

The prospectively defined major end-points of the study were:

(1) control of symptomatic ischaemia, as assessed by total numbers of episodes of chest pain and number of increments of NTG infusion rate for pain control;
(2) incidence of acute myocardial infarction—it was estimated that elevation of plasma creatine kinase (CK) levels would occur in 25–35% of the patients studied[25–27]; and
(3) incidence of adverse effects, particularly hypotension.

ANALYSIS OF RESULTS

Differences in baseline characteristics of the two groups of patients were assessed by the two-tailed unpaired Student's *t*-test. Changes in systolic blood pressure following NAC or placebo administration were compared utilizing analysis of variance. Significance of variations between groups in episodes of chest pain and increments in NTG infusion rate was assessed utilizing the Wilcoxon rank sum test. The Fisher's exact test was used to assess effects of NAC on incidence of acute myocardial infarction and symptomatic hypotension. All analysis was performed on an 'intention to treat' basis. Results are expressed throughout as mean ± SEM.

DRUGS

NTG (Tridil; American Critical Care) was made up as a 37·5 ug/ml solution in glass bottles containing 5% dextrose. NAC for intravenous infusion (Parvolex; Glaxo Laboratories, Sydney) was diluted in 5% dextrose solution.

Results

Forty-six patients were admitted to the study: their clinical features are summarized in Table 1. Twenty-four received NTG/NAC while 22 received NTG/placebo. As was intended by the stratification

Table 1 Clinical data

Group	NTG/NAC (N = 24)	NTG/placebo (N = 22)
Age (years)	57·9 ± 1·6	56·5 ± 2·1
Sex (M:F)	15:9	17:5
Previous Q-wave infarction	6	4
Prior treatment:		
(a) Cutaneous nitrates	23	22
(b) Calcium antagonists	23	22
(c) Beta-adrenoceptor antagonists	5	4
(d) Perhexiline maleate	7	5

Table 2 Occurrence of major end-points

Group	NTG/NAC (N = 24)	NTG/placebo (N = 22)
Episodes of chest pain	48(19)	52(20)
Increases in NTG infusion rate for pain control	10(8)	17(11)
Acute myocardial infarction	3	10*
Symptomatic hypotension	7	0†

Figures in brackets are patient numbers. All figures given are on 'intention to treat' basis.
* P = 0·013 † P = 0·006.

method used, the two groups were well matched for age; six patients in the NTG/NAC and four in the placebo group had sustained prior Q-wave myocardial infarction. Prior therapy had included cutaneous nitrates and calcium antagonists (usually verapamil) in almost all patients. No patient received aspirin and two (one in each treatment group) received heparin during the study period. Coronary arteriography, performed during the index admission in 32 of the 46 patients, revealed extensive coronary artery disease in most patients; all had fixed stenoses of greater than 70% in at least 1 major coronary artery.

No patient developed symptomatic hypotension prior to initial administration of NAC or placebo. However, one patient (number 17; NAC group) developed severe chest pain with ECG changes consistent with evolving acute myocardial infarction and therefore did not receive NAC. All other patients received at least the initial dose of NAC or placebo medication.

Patients in the NTG/NAC group experienced 48 episodes of chest pain, compared to 52 episodes in the NTG/placebo group (Table 2), 5 and 2 patients respectively remaining pain-free throughout (difference not significant). In the NTG/NAC group, 10 increases in NTG infusion rate for pain control occurred in 8 patients, compared with 17 increases in 11 patients in the NTG/placebo group (P = NS).

Acute myocardial infarction occurred in 3 patients assigned to NTG/NAC and 10 assigned to NTG/placebo (P = 0·013). Peak plasma CK concentrations ranged from 320 to 2223 IU^{-1} and there was no significant difference between groups. Additionally, one patient in the placebo group developed an extensive postero-inferior myocardial infarction two hours after trial entry, with rapid subsequent development of cardiogenic shock and death.

Of the three patients assigned to NTG/NAC who developed acute myocardial infarction, one received no NAC, as the onset of infarction was recognised prior to supplement administration. In the remaining two patients, infarction followed the development of severe hypotension, and occurred approximately 60 minutes after NAC administration.

Systolic blood pressure did not vary significantly between the two treatment groups throughout the study. However, adverse effects, particularly symptomatic hypotension, were more common in the NTG/NAC group (Table 3). Symptomatic hypotension occurred in seven patients in this group, and none in the placebo group (P = 0·006). Minimum systolic blood pressure ranged between 50 and 100 mmHg, following acute falls of between 30 and 60 mmHg. In all cases, hypotension resolved after cessation of NTG infusion. Hypotension developed less than 60 minutes after NAC administration in five of

Table 3 Adverse effects

Group	NTG/NAC (N = 24)	NTG/placebo (N = 22)
Symptomatic hypotension	7*	0
Nausea	2	1
Headache	2	2

* In 2 patients, hypotension was followed by prolonged chest pain and development of acute myocardial infarction.

these patients; in three of these patients, sublingual NTG had been administered just prior to the hypotensive episode. Nausea and headaches occurred in a small number of patients in both treatment groups (Table 3).

There were no significant differences in venous NTG concentrations and lactate–pyruvate ratios between the two groups at any stage of the study.

Discussion

The results of this study suggest that the combined intravenous administration of NTG and NAC in patients with severe unstable angina pectoris lowers the incidence of acute myocardial infarction relative to that seen with NTG alone. Furthermore, patients treated with NTG/NAC required somewhat fewer increments in NTG infusion rate for pain control, although this trend did not reach statistical significance. However, NTG/NAC treatment was associated with a high incidence of symptomatic hypotension, which did not occur in the NTG/placebo group. These findings are consistent with the results of previous *in vitro* and clinical investigations of the NTG/NAC interaction.

Activation of guanylate cyclase by NTG is potentiated by SH-containing materials, but most markedly by cysteine[15]. The mechanism of this potentiation remains uncertain, as several steps in the biochemical 'cascade' of events in initiated by exposure of NTG to tissues are SH-dependent[28]. Of particular interest, however, is the formation of S-nitroso-NAC, which, apart from activating guanylate cyclase, markedly potentiates the antiplatelet effects of NTG[23]. NAC has also been shown to potentiate the systemic[20] and coronary[21,22] haemodynamic effects of NTG, and to limit the onset of haemodynamic tolerance to NTG in patients with congestive cardiac failure[29].

Analysis of the frequency of episodes of ischaemic pain revealed no difference between the NTG/NAC and NTG/placebo groups, while the trend towards fewer increments in NTG infusion rate in the NTG/NAC group fell short of statistical significance. This may represent type II error, or possibly in part a reduction in frequency of ischaemic episodes after development of acute myocardial infarction in 10 patients in the NTG/placebo group. The question of efficacy of NTG/NAC in relief of symptomatic ischaemia in these patients is therefore not answered at this stage.

The high short-term incidence of acute myocardial infarction in patients enrolled in this study was predictable on the basis of previous investigations, which have identified fluctuations in S–T segments during rest pain and lack of response to calcium antagonists and cutaneous NTG as markers of increased risk[25–27]. Acute myocardial infarction occurred in 10 patients in the NTG/placebo group and 3 patients randomized to NTG/NAC (P = 0·013). Of the latter patients, only 2 actually received NAC (see above): in both of these cases, infarction may have been precipitated by hypotensive responses to NTG/NAC. We postulate that the reduced incidence of acute myocardial infarction in this group of patients reflects the antiplatelet effects of NTG/NAC[23]. As no patient received aspirin during the study, it is uncertain whether such beneficial effects may be incremental over those of aspirin in such patients[30,31].

Hypotension was significantly more common in patients randomized to NTG/NAC, although overall systolic blood pressure was not lower in this group of patients. The temporal correlation between NAC administration and 5 of the 7 hypotensive episodes suggests that this adverse effect represented potentiation by NAC of the haemodynamic effects of NTG, but the factors responsible for development of hypotension require further elucidation.

In the current study, NAC was administered by intermittent, rapid intravenous infusion. Recent pharmacokinetic investigations suggest that NAC has a relatively short half-life[32,33]. It is therefore possible that continuous infusion of NAC together

with NTG might induce more constant effects and further augment the beneficial effects of combined NTG/NAC in this group of patients.

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