Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris

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ABSTRACT

The vasodilator effects of nitroglycerin (NTG) are mediated via activation of guanylate cyclase; this process is believed to require the availability of free sulfhydryl groups. Previous studies in man have shown that the sulfhydryl donor N-acetylcysteine (NAC) potentiates the systemic and coronary vasodilator effects of NTG. Furthermore, interaction of NTG and NAC may lead to the formation of S-nitroso-NAC, which strongly inhibits platelet aggregation. The effects of intravenous NTG combined with intravenous NAC (5 g 6 hourly) were compared with those of intravenous NTG alone in a double-blind trial in 46 patients with severe unstable angina pectoris unresponsive to conventional treatment, which included calcium antagonists and cutaneous nitrates in all but one patient. Treatment with NTG/NAC (24 patients) and that with NTG alone (22 patients) was associated with a similar frequency of episodes of chest pain and of increments in NTG 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 (three vs 10 patients; p = .013). Symptomatic hypotension occurred frequently in the NTG/NAC group (seven vs 0 patients; p = .006). Lactate-pyruvate ratios and venous NTG concentrations were not significantly affected by NAC. Subsequently, another 20 consecutive patients were treated with intravenous NTG and continuously infused NAC (10 g/day). Seven remained pain free during the first 24 hr of NTG infusion; 11 required increments in NTG infusion rate for pain control. Acute myocardial infarction occurred in one patient, while none developed symptomatic hypotension. It is concluded that combined administration of NTG and NAC may augment the clinical efficacy of NTG, particularly by preventing acute myocardial infarction. However, the risk of development of hypotension with combined NTG/NAC is increased when NAC is administered by rapid intravenous infusion.


INTRAVENTOUSLY INFUSED nitroglycerin (NTG) has been shown to be useful in the management of patients with severe unstable angina pectoris unresponsive to other treatment measures.1–5 While many patients experience marked symptomatic improvement with intravenous NTG, a significant proportion continue to experience episodes of angina pectoris at rest. In some patients, infusion rates of NTG must be increased repeatedly to achieve control of symptoms, resulting in increased risk of adverse effects.6–9 While the basis for variable patient responsiveness to NTG may partially reflect the underlying disease state, a further factor involved may be the onset of tolerance to the hemodynamic effects of NTG.10, 11

A number of studies in vitro have demonstrated that the vasodilator effects of NTG are mediated via activation of soluble guanylate cyclase.12–14 This process probably involves initial sulfhydryl (SH)-dependent denitration of NTG,15 with formation of S-nitrosothiols as a possible intermediate step.16–18 Previous studies in vitro have shown that activation of guanylate cyclase by NTG and associated vasodilator responses may be modified by SH availability.17, 19–25 In patients with ischemic heart disease, the SH donor N-acetylcysteine (NAC) has been shown to potentiate the systemic and coronary26 hemodynamic effects of NTG. Furthermore, while neither NTG nor NAC alone exert significant effects on platelet aggregation in concentrations likely to occur during normal therapy, their
combination results in the formation of S-nitroso-
NAC, which is a potent inhibitor of platelet aggregation.\textsuperscript{28}

These findings raise the possibility that NAC coad-
ministration may be useful in patients receiving long-
term NTG, both as a result of augmentation of the
vasodilator responses to NTG and inhibition of intra-
coronary thrombus formation. The currently reported
studies were performed to test this hypothesis in a group
of patients with severe unstable angina pectoris.

Methods

Patients. The study population consisted of 46 patients
admitted to the Coronary Care Unit of the Austin or Brigham
and Women’s Hospitals with a diagnosis of unstable angina
pectoris. Unstable angina pectoris was diagnosed on the basis
of typical ischemic chest pain occurring at rest and associated
with reversible ST segment depression. Patients were eligible for
the trial only if frequent ischemic symptoms persisted at rest
despite the use of conventional antianginal measures, including
nitrates, and normal clinical practice would involve the com-
 mencement of intravenous NTG infusion. Characteristics result-
ing in exclusion were: age 75 years or greater, Q wave myo-
cardial infarction within the preceding 3 months or non-Q wave
myocardial infarction in the preceding 7 days, severe hypoten-
sion (mean BP less than 70 mm Hg) before initiation of intrain-
avenous NTG therapy, previous adverse effects of NTG or NAC,
concomitant therapy with drugs known to affect SH availability
(such as captoril, penicillamine, and ethacrylic acid), severe
(Killip class III or IV) left ventricular failure, clinically signif-
cicant valvular heart disease, or severe renal or hepatic disease.
No patient could be treated with isosorbide dinitrate or mono-
nitrate in the 6 hr immediately before trial entry.

The investigational protocol was approved by the Ethics
Committees of the Austin and Brigham and Women’s Hospitals.
Informed consent was obtained before trial entry.

Protocol. The study was a double-blind, placebo-controlled
comparative trial over the first 24 hr of intravenous NTG infu-
sion.

To minimize the possibility of major differences between
patients receiving the two treatment regimens, patients were
stratified at the time of trial entry on the basis of age (less than
or >60 years) and the presence or absence of prior Q wave
myocardial infarction. Random assignment of patients to NAC
or placebo was carried out separately according to stratification
of patients. The randomization code was held in the Pharmacy
Department and a member of the Pharmacy Department
assigned a code number to each patient and made up the trial
medication at the time of patient entry to the study.

Each patient received intravenous NTG, delivered via nonad-
sorbent polyethylene tubing, by use of an IMED pump at an
initial delivery rate of 5 \(\mu\)g/min. Pilot experiments demonstrated
that NTG losses of less than 5\% occurred within the NTG
infusion apparatus over 24 hr. Cutaneous NTG preparations were
removed at the time of initiation of intravenous NTG infusion.
Therapy with all other antianginal medications was continued
unchanged throughout the study period.

Fifteen minutes after initiation of the NTG infusion, a blinded
supplement consisting of either NAC (5 g in 200 ml 5\% dextrose)
or placebo (5\% dextrose only) was infused intravenously over
15 min. The NAC dosage regimen was selected on the basis of
previous hemodynamic and pharmacokinetic studies, as well as
the results of pilot studies in seven patients. A supplement
infusion was repeated every 6 hr for the 24 hr of the study.
Indications for adjustment in the NTG infusion rate during the
study period were: (1) continued severe episodes of ischemic
chest pain and/or persistent systolic blood pressure greater than
140 mm Hg (leading to increases in NTG infusion rate), and (2)
development of symptomatic hypotension (leading to decreases
in rate or cessation of NTG infusion).

In the event of development of prolonged chest pain with
electrocardiographic changes suggestive of acute infarction,
further doses of blinded supplement were withheld.

Clinical observations made throughout the trial period in-
cluded those of heart rate and arterial blood pressure. After pilot
experiments in which NAC was administered to seven patients
with unstable angina, it was believed that there might be a
significant risk of hypotension in the 60 min after NAC admin-
istration, or after NTG infusion rates had been increased. For this
reason, blood pressure was measured at least every 15 min under
such circumstances.

All episodes of chest pain reported by the patients during the
24 hr study period were recorded. Episodes of pain could be
treated by administration of sublingual NTG and/or increases in
NTG infusion rate. To facilitate data analysis, all increments in
NTG infusion rates involved doubling of the preceding rate.
Venous blood samples were drawn for estimation of plasma
creatine kinase (CK) levels at the time of trial entry and at 12
hourly intervals thereafter. Additionally, in all patients treated
at the Austin Hospital, venous nitroglycerin concentrations and
plasma lactate-pyruvate ratios were determined at the time of
trial entry, during intravenous NTG infusion alone, and 1, 6, and
24 hr after initial administration of NAC or placebo.

Indications for withdrawal from the study were persisting
severe ischemia occurring despite increased NTG infusion rates
and thought to require initiation of intra-aortic balloon coun-
terpulsation, emergency coronary artery bypass grafting or coro-
ary angioplasty, or the occurrence of severe adverse reactions
to NTG or NAC. The prospectively defined primary end point
of the study was control of symptomatic ischemia, determined by:
(1) total number of episodes of chest pain, and (2) number of
increments of NTG infusion rate for pain control.

The secondary end points of the study were: (1) incidence of
acute myocardial infarction since it was anticipated that ele-
vation of plasma CK levels would occur in 25\% to 35\% of the
patients studied,\textsuperscript{29-33} and (2) adverse effects, particularly hypo-
tension.

On the basis of the primary end point, it was intended that 70
patients should be enrolled in the study. Furthermore, we
planned to review the study when two-thirds of this sample size
had been completed. At the time of this review (after 46 patients
had been studied), a striking effect on both secondary end points
was observed, and so a decision was made to interrupt and report
the study at this stage.

Plasma NTG concentrations were measured after extraction
into hexane; the threshold sensitivity of the assay was 0.1
ng/ml.\textsuperscript{34} Lactate-pyruvate ratios were determined by an enzy-
matic-colorimetric method (Sigma Pharmaceuticals, St. Louis)
by use of absorption at 340 nm.

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
after NAC or placebo were compared by analysis of variance,
as were fluctuations in venous NTG concentration and lactate-
pyruvate ratios during the study period. Significance of varia-
tions between groups with respect to episodes of chest pain and
increments in NTG infusion rate was assessed with the Wilcoxon
rank-sum test, while Fisher’s exact test was used to assess effects
of NAC on incidence of acute myocardial infarction and symp-
tomatic hypotension. Results are expressed throughout as the
mean ± SEM. All analyses were performed on an "intention to treat" basis. A p value of <.05 was used to reject the null hypothesis that no difference existed between NAC and placebo groups.

**Drugs.** NTG was made up as a 37.5 µg/ml solution in glass bottles containing 5% dextrose by dilution from ampules (Tridil; American Critical Care). NAC for intravenous infusion (Parvolex; Glaxo Laboratories, Sydney) was diluted in 5% dextrose solution.

**Results**

**Patients.** Clinical features of the 46 patients admitted to the study are summarized in table 1. Twenty-four patients (15 men; nine women) received NAC while 22 (17 men; five women) received placebo. There was no significant difference in ages of the patients in the two groups; six patients in the NAC and four in the placebo group had sustained prior Q wave myocardial infarction.

All but one patient had received cutaneous (44 patients) or slow-release transdermal NTG (one patient) in the period immediately before commencing intravenous NTG. The remaining patient (No. 24, NAC group) had received frequent doses of sublingual NTG.

Concomitantly prescribed antianginal medications included a calcium-channel blocker (usually verapamil) in 45 of the 46 patients, a β-adrenoceptor antagonist in nine patients and perhexiline maleate in 12 patients. No patient had developed adverse effects attributable to any of these medications or their combination before the study period; in no case was the dose regimen of these drugs changed during the study period. No patients received aspirin and two (one in each group) received heparin during the study period.

Coronary arteriography was performed during the admission associated with the study in 32 of the 46 patients (18 in the NAC group and 14 in the placebo group). The majority of patients studied had extensive coronary artery disease; all patients had fixed stenoses greater than 70% in at least one major coronary artery (Table 1).

**Effect of NAC.** No patient developed symptomatic hypotension during the period between trial entry and initial administration of NAC or placebo. However, one patient (number 17; NAC group) developed severe ischemic pain unresponsive to sublingual NTG with marked anterior ST segment depression on the electrocardiogram ECG. It was believed that these changes represented evolving acute myocardial infarction and the patient therefore did not receive NAC. All other patients received at least the initial dose of NAC or placebo medication. No patient was withdrawn from the study during the 24 hr observation period.

**TABLE 1**

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<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
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<td>NP</td>
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Placebo group

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<td>V</td>
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</table>

CAD = coronary artery disease (>70% occlusion); LAD = left anterior descending artery; Circ = circumflex artery; RCA = right coronary artery; NP = coronary angiography not performed during current admission; β = β-adrenoceptor antagonist; D = diltiazem; N = nifedipine; P = perhexiline maleate; V = verapamil; Cut = cutaneous NTG; TD = transdermal NTG.
On intravenous NTG alone, systolic blood pressure was 124 ± 3 mm Hg in the NAC group and 129 ± 3 mm Hg in the placebo group (p = NS). The administration of NAC induced no significant changes in systolic blood pressure relative to those in the control group throughout the trial period (figure 1). A minor fall in systolic blood pressure occurred in the placebo group between 1 and 6 hr after trial entry, perhaps reflecting in part the effects of increases in NTG infusion rate and/or the onset of acute myocardial infarction in some patients within this group.

Patients in the NAC group experienced 48 episodes of ischemic chest pain during the trial period, compared to 52 episodes in placebo group patients (table 2). Five patients in the NAC group and two in the placebo group remained pain free during the study period; this difference was not statistically significant. Four patients in the NAC group and eight in the placebo group required an injection of morphine for treatment of ischemic pain. The frequency distribution of episodes of chest pain within the trial period was similar for the two patient groups.

Increases in NTG infusion rate for control of chest pain were necessary in eight patients in the NAC group and 11 patients in the placebo group. A total of 10 increases occurred in the NAC group vs 17 in the placebo group (p = NS). Increases in NTG infusion rate were required in one other patient in each group for control of persistent hypertension.

### TABLE 2

<table>
<thead>
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<th>Occurrence of major end points</th>
<th>NAC (n = 24)</th>
<th>Placebo (n = 22)</th>
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<tbody>
<tr>
<td>Episodes of chest pain</td>
<td>48 (19)</td>
<td>52 (20)</td>
</tr>
<tr>
<td>Increases in NTG infusion rate for pain control</td>
<td>10 (8)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3</td>
<td>10*</td>
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<tr>
<td>Symptomatic hypotension</td>
<td>7</td>
<td>0*</td>
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Values in parentheses are numbers of patients. All figures given are on “intention to treat” basis.

*P = .013; **P = .006.

### TABLE 3

<table>
<thead>
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<th>Patient No.</th>
<th>Adverse effect(s)</th>
<th>Possible precipitating factor(s)</th>
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<td>NAC; S/L NTG</td>
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<td>Dizziness</td>
<td>NAC</td>
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<td>NAC; S/L NTG</td>
</tr>
<tr>
<td>10</td>
<td>Headache</td>
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<td>11</td>
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</table>

NAC is listed as possible precipitating factor for adverse effect only when adverse effect appeared 30 to 60 min after NAC infusion. S/L = sublingual.

Hypotension followed by prolonged chest pain and development of acute myocardial infarction.

Acute myocardial infarction occurred in three patients assigned to NAC and 10 assigned to placebo (p = .013). These included one patient withdrawn from the study before administration of NAC (see above). Peak plasma CK concentrations ranged from 800 to 2223 IU/liter in the NAC group and from 320 to 1426 IU/liter in the placebo group (p = NS). Additionally, one patient in the placebo group developed a posterior inferior transmural myocardial infarction with marked anterior ST segment depression 2 hr after entry into the trial. Cardiogenic shock developed rapidly and the patient died 2 hr later. Peak plasma CK was not yet elevated before death.

Two patients (Nos. 11 and 21) developed acute myocardial infarction after receiving NAC. In both cases, infarction followed the development of severe hypotension, and occurred approximately 60 min after initial administration of NAC. In both cases, no further NAC was administered throughout the 24 hr of the study.

**Adverse effects.** Adverse effects occurring during the study are summarized in table 3. Symptomatic hypotension occurred in seven patients in the NAC group and none in the placebo group (p = .006). Maximal changes in systolic blood pressure ranged from 30 to 60 mm Hg, while minimal systolic blood pressure was 50 to 100 mm Hg. In all cases, hypotension resolved after cessation of NTG infusion. In five patients, development of hypotension was associated with NAC infu-
sion in the preceding 30 to 60 min, sometimes together with administration of sublingual NTG (three patients). In the remaining two patients, no precipitating factor could be identified. One further patient (No. 8, NAC group) developed mild dizziness with only minimal hypotension after NAC. Nausea occurred in three patients in the NAC group and one in the placebo group; headaches were reported by one patient receiving NAC and two receiving placebo medication.

**Lactate-pyruvate ratios and venous plasma NTG concentrations.** Mean lactate-pyruvate ratios on NTG alone were 25.6 ± 2.0 in the NAC group and 25.0 ± 2.7 in the placebo group. After administration of supplement, ratios were 25.2 ± 2.8 and 22.2 ± 1.4, respectively. None of the differences were statistically significant.

Venous plasma NTG concentrations were compared in seven patients in the NAC group and 10 in the placebo group in whom sublingual NTG had not been administered in the preceding 20 min. Administration of NAC was associated with no significant changes in venous NTG concentrations.

**Discussion**

The results of this study suggest that the concomitant use of intravenous NTG and NAC in patients with severe unstable angina pectoris leads to a lower incidence of acute myocardial infarction. It is also possible that concomitant NAC treatment may reduce the number of changes in NTG infusion rate required for pain control, although the p value for this change fell short of statistical significance. On the other hand, patients in the NAC treatment group experienced a greater incidence of adverse effects, particularly severe hypotension, than the control group. A number of factors may have contributed to these findings.

Unstable angina pectoris occurs in a heterogeneous group of patients in whom the presence or absence of episodes of ischemic pain at rest, the frequency and severity of ischemic episodes, and the presence of electrocardiogram changes during episodes of pain differ. Available evidence suggests a markedly variable short-term prognosis within this group. Factors that may be markers of increased risk of continuing ischemia include the presence of fluctuating ST segment depression during pain and lack of response of symptoms to treatment with calcium antagonists and cutaneous NTG. Thus, it was predictable that the patients enrolled in this study would have a high incidence of symptomatic myocardial ischemia and a substantial short-term risk of acute myocardial infarction. While 10 patients in the placebo group developed acute myocardial infarction, infarcts were relatively small, as judged by peak CK levels of less than 2500 IU/liter, in all but one patient, in whom cardiogenic shock developed rapidly.

The effect of NAC on responsiveness to NTG may be predicted from a number of studies in vitro and in vivo. Activation of guanylate cyclase by NTG is potentiated by SH-containing materials, but most markedly by cysteine. NAC potentiates the systemic and coronary hemodynamic effects of NTG, possibly by reversing tissue SH depletion associated with prior nitrate therapy. Tolerance to the hemodynamic effects of NTG, which may develop during prolonged intravenous therapy, may be limited by coadministration of NAC as regards both the systemic and coronary vasodilator effects of NTG.

Furthermore, NAC has been shown to markedly potentiate the antplatelet effects of NTG, probably via the formation of S-nitroso-NAC. Each of these factors is of potential importance in the management of patients with severe unstable angina pectoris, in whom there is a high incidence of associated intracoronary nonocclusive thrombi, as well as an increased incidence of coronary vasospasm. Finally, there is increasing evidence that sulfhydryl donors such as NAC may protect against myocardial damage and dysfunction during periods of ischemia and reperfusion.

Analysis of the frequency of episodes of ischemic pain revealed no difference between the NAC and placebo groups, while the trend toward fewer increments in NTG infusion rate in the NAC group fell short of being statistically significant. This may represent a II error, or alternatively, the frequency of discrete episodes of ischemic pain in the placebo group may have been reduced somewhat because of the frequent development of acute myocardial infarction in these patients. The question of NTG/NAC effects on the frequency of ischemia therefore remains unanswered at this stage, and needs to be addressed in further studies with a larger sample size.

Somewhat unexpectedly, on an intention-to-treat basis, three patients in the NAC group and 10 in the placebo group developed acute myocardial infarction during the study period; this difference was statistically significant. Of the three patients in the NAC group in whom acute myocardial infarction occurred, only two received NAC (see above). In both of these cases, onset of infarction followed severe hypotension, which developed approximately 60 min after the infusion of NAC. It is therefore possible that infarction in these patients was precipitated by potentiation by NAC of the hemodynamic effects of NTG. This is supported by the
observation that most cases of hypotension in the NAC group occurred 30 to 60 min after the infusion of NAC. On the other hand, the majority of patients treated with NTG/NAC developed no significant hypotensive effects. The factors responsible for the development of hypotension in seven patients in the NAC group therefore require further elucidation. In the absence of marked reductions in the frequency of ischemic episodes in the NAC group, we postulate that the reduced incidence of acute myocardial infarction reflects the antiplatelet effects of NTG/NAC, mediated via formation of S-nitroso-NAC. However, the previously documented effects of NAC in potentiating coronary vasodilator responses to NTG and abolishing coronary vasoconstriction in combination with NTG may have played a role in producing this change.

Biochemical and pharmacokinetic changes. NTG is thought to activate guanylate cyclase via a series of enzymatic bioconversions involving initial denitration, formation of nitric oxide, and possibly formation of S-nitrosothiols. At steady state, there is an arteriovenous NTG concentration gradient, consistent with continuous metabolism of NTG by tissues. The onset of hemodynamic tolerance to NTG is associated with reduced arteriovenous NTG concentration gradients, consistent with decreased rates of bioconversion in target organs. NAC might accelerate NTG bioconversion, particularly by acting as a cofactor for the action of organic nitrate ester reductase, or might lead to increased formation of S-nitrosothiols.

However, there was no significant effect of NAC on venous NTG concentrations in the small number of patients in whom these could be assessed. Further studies using simultaneous determination of arterial and venous concentration may help to elucidate this issue, but no clear-cut evidence of a pharmacokinetic interaction between NTG and NAC can be adduced from the currently available data. Furthermore, NAC induced no significant changes in the tissue redox state, as assessed from venous lactate-pyruvate ratios.

Limitations of study. There are a number of potential limitations to the current study. Since incidence of acute myocardial infarction was a secondary end point of the study, the observation of reduced incidence in patients treated with NTG/NAC needs further confirmation in a larger number of patients. Currently we are performing an open-label study using a modified NTG/NAC treatment regimen. Twenty consecutive additional patients with severe unstable angina pectoris have been treated with intravenous NTG at an initial infusion rate of 2.5 μg/min and concomitantly infused NAC (10 g/24 hr). Patients treated in this manner experienced 38 episodes of chest pain over the first 24 hr of treatment and required 18 increases in NTG infusion rate for control of pain. Seven patients remained pain free; only one developed acute myocardial infarction (peak CK 1086 IU/liter). Thus, the incidence of development of acute myocardial infarction in the randomized and open-label NAC groups was similar (12.5% and 5%, respectively) and both were significantly lower than the placebo group from the randomized portion of the study. No patient developed symptomatic hypotension. While this open-label experience is consistent with the observed reduction in incidence of acute myocardial infarction with NTG/NAC, absolute validation of this finding can be made only with a larger randomized controlled study.

The concomitant use of other antianginal agents such as calcium-channel blockers may have modified responses to NTG (and to NAC). However, such concomitant therapy is the rule rather than the exception in current clinical practice. No patient received aspirin during the study period, despite evidence that aspirin therapy may reduce the incidence of acute myocardial infarction in patients with unstable angina pectoris. It is possible that concomitant aspirin therapy might have reduced the incidence of infarction in the placebo group and reduced the incremental effect of NAC.

Finally, a number of questions remain unanswered regarding the optimum regimen for administration of NAC. NAC has a relatively short half-life and it is therefore possible that a more satisfactory regimen would involve the continuous infusion of NAC (after a small loading dose); furthermore, the use of a smaller total dose of NAC and the concomitant avoidance of a phase of rapid infusion of NAC may reduce the risk of hypotension. Further studies are required to delineate the potential benefits of such regimens. The results in an additional 20 patients suggest that continuously infused NAC (10 g/24 hr) may reduce the risk of hypotension without increasing the incidence of acute myocardial infarction.

Clinical implications. Because the subset of patients with unstable angina pectoris similar to patients studied in the current investigation is at high risk of developing acute myocardial infarction, in-hospital management currently involves augmentation of the patient’s medical regimen to minimize myocardial oxygen demands and maximize myocardial blood flow. Intravenous NTG has assumed a pivotal role in achieving these goals, but is often suboptimal because of continued ischemia and the development of hemodynamic tolerance.
This study represents the first reported investigation of the role of NAC in the management of patients with ischemic heart disease who are receiving intravenous NTG. The results suggest that intravenous NAC augments the efficacy of NTG by reducing the need for increments in infusion rates and preventing the development of acute myocardial infarction.

This stabilization of a potentially high-risk group of patients may permit institution of interventional measures, including cardiac catheterization, angioplasty, and coronary surgery, on a more elective basis.

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