Intravenous Nitroglycerin for Acute Myocardial Infarction

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Intravenous nitroglycerin (IV TNG) has been increasingly used in the setting of acute myocardial infarction. The seven randomized trials comparing IV TNG with placebo, and one trial comparing IV isosorbide dinitrate with furosemide, were reviewed for evidence of beneficial clinical effects. IV TNG in low dosage is safe in the setting of acute myocardial infarction and modestly effective in relieving chest pain. Favorable hemodynamic effects are most pronounced in patients with congestive heart failure. Limited evidence suggests that IV TNG, particularly when administered early, reduces both infarct size and mortality when given prophylactically. (Henry Ford Hosp Med J 1991;39:206-9)

Nitrates have been used in the treatment of heart disease for more than 120 years (1). The recent development of intravenous nitroglycerin (IV TNG) (2) has found widespread application in treating acute ischemia syndromes and, in particular, acute myocardial infarction (MI). Therapeutic goals have included alleviation of symptoms, reduction of preload and afterload, limitation of infarct size and preservation of left ventricular (LV) function, and prevention of mortality. A total of seven randomized trials (3-9) have compared the effect of IV TNG with that of placebo on these endpoints. One trial compared IV isosorbide dinitrate (ISDN) with furosemide (10). These studies are briefly reviewed and guidelines for the use of IV TNG in the treatment of acute MI are discussed.

Nitrates for Symptomatic Relief

Sublingual and oral forms of nitroglycerin are well established for symptomatic relief of chronic angina. The efficacy of IV TNG in relieving chest pain during acute MI was examined in several of the randomized trials. Lis et al (8) found that 22% of patients receiving IV TNG required morphine for pain control during the first 24 hours of hospitalization, while 54% of patients in the placebo group required morphine, a significant difference. This finding was confirmed in the study of Bussmann et al (4), who found that 39% of 31 patients in the IV TNG group required morphine for pain control during the first 24 hours of hospitalization, while 66% of patients in the control group required morphine, a significant difference. The difference in morphine administration appeared to be limited to the patients in whom IV TNG was initiated within 8 hours of symptom onset. In contrast, in the study of Jaffe et al (5), morphine requirements averaged 11.4 mg/patient in the IV TNG group and 12.2 mg/patient in the control group, a difference which was not significant. Since staff members caring for patients in these trials were either not blinded to treatment or would be expected to discern treatment assignment during dose titration, it is possible that bias may have influenced the results. Two studies (2,6) have shown a decrease in ST segment elevation (measured by precordial mapping) in response to IV TNG, suggesting a decrease in myocardial ischemia, but neither study compared ST changes to degree of symptomatic relief.

Preload and Afterload Reduction

Nitrates have long been recognized as preload-reducing agents and, to a lesser extent, as afterload-reducing agents. Through an action to increase venous capacitance, ventricular filling pressure falls, especially when elevated above normal. A reduction in LV filling pressure may decrease LV volume, an effect which decreases wall stress and thereby myocardial oxygen consumption. Decreased diastolic volume may also increase coronary blood flow independent of coronary vasodilatation (11). In 12 patients with LV failure complicating acute infarction, low doses of IV TNG sufficient to lower mean arterial pressure by only 7 mm Hg, or 7%, caused mean LV filling pressure (measured as the pulmonary-capillary wedge pressure) to fall from 22 to 12 mm Hg, a 43% reduction. This reduction was associated with a minimal decrease in cardiac index and no change in stroke work index (2). In patients with normal LV filling pressures, such effects are discernible but not as pronounced.

The hemodynamic profile of IV nitrates was contrasted with that of furosemide-induced diuresis in a study reported by Nelson et al (10). In this protocol, 30 patients with LV failure complicating acute infarction were randomized to receive either furosemide at a dose of 1 mg/kg IV or IV ISDN titrated to reduce mean arterial pressure by 10 mm Hg. For similar reductions in LV filling pressure, IV ISDN produced a fall in arterial pressure and systemic vascular resistance with no change in cardiac index, whereas furosemide produced no change in arterial pres-
A smaller infarct size as a result of IV TNG therapy may translate into preserved ventricular function. Only two of the IV TNG trials examined LV function prior to discharge as a clinical endpoint. Flaherty et al (7) found no effect of IV TNG overall or in the subset of patients given IV TNG within 10 hours from symptom onset. Only when patients receiving early IV TNG treatment were further divided into those with initially normal (> 50%) or impaired (< 50%) ejection fractions was an effect discovered: the former group had no change while the latter group had an 11% increase in ejection fraction from the initial to predischARGE study.

This issue was more powerfully addressed by Jugdutt and Warnica (9) in a study of 310 patients prospectively designed to measure LV regional and global function as an endpoint. Treatment was begun an average of 8.1 hours after symptom onset in the placebo group and 9.0 hours in the treatment group, with about one-fifth of patients receiving therapy within 4 hours. IV TNG was titrated in order to lower mean arterial pressure by 10% (30% if initial pressure was greater than 140/90 mm Hg). Echocardiography was performed before treatment and then serially until discharge, with overall LV function measured as ejection fraction and regional wall motion defined by extent of asynergy, by endocardial segment length in the infarct zone, and by a derived expansion index and thinning ratio.

Some of the results from this study are shown in Table 2. All three primary measurements of LV function and volume were favorably influenced by IV TNG. In addition, IV TNG was found to reduce the expansion index and thinning ratio when treated patients were compared to controls. These important findings point toward the potential role of IV TNG to modulate ischemic damage and may explain the reduction in mortality seen in this trial and in pooled results from the smaller trials.

All of the clinical trials were conducted without IV thrombolytic therapy administration, which can also salvage myocardium. IV TNG has been found by several investigators to inhibit platelet aggregation (12,13). However, one group found that IV TNG diminished thrombolytic effectiveness of tissue plasminogen activator in a dog model of coronary thrombosis (14). IV TNG has been found by some (15,16) but not all (17,18) investigators to antagonize the anticoagulant effect of heparin. Careful monitoring of the partial thromboplastin time was recommended, particularly when changes were made in IV TNG infusion rates. Whether IV TNG demonstrates synergy or interference, or whether its additive effect is only marginal when administered together with thrombolytic and anticoagulant agents, is an important question not fully addressed by a clinical trial.

### Mortality Reduction

The effect of IV TNG on mortality was examined by Yusuf et al (19) using meta-analysis. This technique allows for the structured pooling of results from several smaller trials of similar but not identical study design to arrive at a combined result. All but two trials (4,9) showed a trend in favor of active treatment but lacked sufficient power to demonstrate a statistically significant result. When the results were combined, however, mortality was
Complications of IV TNG Therapy

The most predictable complication of IV TNG is dose-related hypotension. In the studies of Jaffe et al (5) and Lis et al (8), an excess of IV TNG patients became hypotensive compared to the placebo group. On occasion, hypotension is associated with bradycardia, a syndrome possibly mediated by vagal discharge and generally responsive to volume expansion, atropine, and decrease or interruption of the IV TNG infusion (20). This situation may particularly be encountered in inferior infarction. Reflex tachycardia is encountered rarely when IV TNG is titrated to a modest decrease in blood pressure; resting tachycardia is not a contraindication to IV TNG use. IV TNG should be used with caution in patients with right ventricular infarction, whose cardiac output is dependent on high right-sided pressures due to impaired right ventricular performance. In addition, volume-depleted patients may be sensitive to low doses of IV TNG and also prone to hypotension. Volume depletion can occur because of decreased oral intake and vomiting associated with the acute infarction. IV TNG is particularly useful in hypertensive patients, though may not suffice as a single agent to adequately lower blood pressure.

Tolerance to the effects of nitrates has been reported with increasing frequency (21). Tolerance is an important issue when chronic oral nitrates or sustained IV TNG infusions are used for unstable angina; when the goal is a 10% reduction in arterial pressure for 48 hours, tolerance is less often encountered. Jugdutt and Warnica (22) reported that of the 154 patients who received IV TNG, 24% required an increase in dose to maintain the reduction in blood pressure achieved by the initial titration.

The headache commonly encountered often responds to analgesia or dose reduction. Intoxication has been reported to result from the ethanol solvent of the TNG preparation, but only with doses of 2,000 µg/min or more (23).

The IV formulation is generally preferred to oral, topical, and sublingual nitrate preparations because of the ease of dose titration in the early and acute stages of infarction. After 48 hours, in stable patients, the IV infusion can be readily changed to chronic intermittent oral or topical administration.

Conclusions and Recommendations

Review of the seven randomized trials of IV TNG shows that this therapy is safe and well tolerated in the majority of patients with acute MI. While relief of chest pain can sometimes be achieved, IV TNG is no substitute for morphine or other analgesia. Favorable hemodynamic effects are seen in patients with symptoms of congestive heart failure or elevated LV filling pressures. IV TNG has the potential to limit infarct size and salvage myocardium; this may be one mechanism of the reduction in mortality demonstrated with treatment, especially when initiated early in the course of infarction. Effects of IV TNG have not been extensively evaluated in patients who have received thrombolytic therapy; it is possible that such patients may experience only marginal benefit when therapies are combined.

IV TNG should be considered a first-line agent—in addition to other, standard measures—in patients with acute infarction who have evidence of congestive heart failure or recurrent ischemia. In patients with uncomplicated infarction, IV TNG is most beneficial when started within 6 hours of the onset of symptoms. Its prophylactic use in all patients with uncomplicated infarction remains controversial. Despite the evidence reviewed, guidelines recently published by the Joint Task Force of the American College of Cardiology and American Heart Association did not recommend the prophylactic use of IV TNG in the absence of the specific indications discussed (24) (Table 3). Ongoing investigation should clarify the clinical settings in which IV TNG is most beneficial.

References

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