Nitroglycerin as a Hypotensive Drug during General Anesthesia

Nabil R. Fahmy, M.D.*

Circulatory variables and arterial partial pressure for oxygen (Pao₂) were compared in 91 anesthetized patients who received infusions of either nitroglycerin (TNG) or nitroprusside (SNP) to induce hypotension for the purpose of decreasing intraoperative blood loss. At comparable systolic arterial blood pressures, the mean and diastolic arterial blood pressures were significantly higher with TNG. Electrocardiographic changes suggestive of ischemia occurred in 18 patients who received SNP, whereas none were detected in patients given TNG. Both drugs significantly decreased Pao₂ and rate-pressure product, an indirect index of myocardial oxygen consumption. No untoward response to TNG occurred. No clinical evidence of myocardial infarction, renal damage, or cerebral vascular complication was encountered in the postoperative period in any patient. Thus, TNG is an effective hypotensive drug that may prove superior to currently available agents. (Key words: Anesthetic techniques, hypotension, induced: nitroprusside; nitroglycerin. Surgery, orthopedic.)

Deliberate hypotension, as an adjunct to general anesthesia, provides a relatively bloodless surgical field, decreases operative blood loss, and diminishes the need for and risks of blood transfusion. The drugs currently employed for this purpose include ganglionic-blocking drugs and sodium nitroprusside (SNP). Hypotension induced with ganglionic-blocking drugs is associated with undesirable side effects related to blockade of parasympathetic ganglia and development of tachyphylaxis. The widespread usage of SNP has made it apparent that this drug is not free of adverse effects; tachyphylaxis, cyanide toxicity and death have all been reported. Therefore, the search for an effective and safe drug continues.

Since nitroglycerin (TNG) has been used effectively to decrease peripheral vascular resistance in patients in heart failure and after acute myocardial infarction, and to control hypertension during coronary-artery surgery, I evaluated the effects of intravenously administered nitroglycerin for production of controlled hypotension during general anesthesia for major orthopedic surgical procedures.

Methods and Materials

Subjects of the study were 91 adult patients† scheduled for total hip replacement during general anesthesia with induced arterial hypotension. Their ages ranged from 18 to 72 years (average 46 years), and their mean (±SE) weight was 68 ± 4 kg. All were American Society of Anesthesiologists physical status I or 2. None had a history or clinical evidence of cardiovascular, pulmonary or metabolic disease. They were randomly allocated into two groups according to the hypotensive drug used: 44 patients received TNG and 47 had SNP. The groups were comparable with regard to age, sex distribution and weight. A sterile (Swinnex filter) aqueous solution of TNG (1 mg per ml of 0.9 per cent saline solution) was prepared by the hospital pharmacy; this was diluted further to a 0.01 per cent solution. Nitroprusside (Nipride, Roche) was also used as a 0.01 per cent solution.

A standard technique of anesthesia was employed for both groups of patients. Premedication consisted of morphine, 0.1 mg/kg, and scopolamine, 0.3 mg/70 kg, given intramuscularly one hour before induction of anesthesia. Sodium thiopental, 3–5 mg/kg, was used for induction of anesthesia, followed by succinylcholine, 1 mg/kg, to facilitate endotracheal intubation. Anesthesia was maintained with halothane, 0.5 to 1 per cent inspired concentration, in nitrous oxide and oxygen, 3–2 l/min, using a semiclosed system with a carbon dioxide absorber. In each patient, the inspired halothane concentration was maintained constant before and during administration of the hypotensive drug, and mean inspired halothane concentrations (0.7 per cent) were similar for the two groups. Ventilation was controlled to maintain arterial carbon dioxide partial pressure (Paco₂) between 35 and 40 torr, as determined by repeated measurements. Arterial hypotension was induced before incision of the skin by continuous intravenous infusion‡ of SNP or TNG. Infusion was begun at 20 μg/min and was then adjusted to decrease and maintain systolic arterial blood pressure at about 75 torr. This level was compatible with a "dry" operative field as determined by an observer who did not

*Assistant Professor in Anesthesia, Harvard Medical School; Assistant Anesthetist, Massachusetts General Hospital.

†All patients gave informed consent to the study, and the protocol was approved by the Subcommittee on Human Studies at the Massachusetts General Hospital.

‡Volumetric Infusion Pump, IMED Corporation.
TABLE 1. Mean Circulatory and $P_{\text{O}_2}$ Values before, during and after Infusion of Nitroglycerin (TNG) or Nitroprusside (SNP)

<table>
<thead>
<tr>
<th>Blood pressure (torr)</th>
<th>Before Hypotension (Control)</th>
<th>During Hypotension</th>
<th>After Blood Pressure Returned to 10 Per Cent of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNG</td>
<td>SNP</td>
<td>TNG</td>
</tr>
<tr>
<td>Systolic</td>
<td>102</td>
<td>105</td>
<td>78*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75</td>
<td>74</td>
<td>55*</td>
</tr>
<tr>
<td>Mean</td>
<td>84</td>
<td>84</td>
<td>63*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Right atrial pressure (torr)</td>
<td>9</td>
<td>10</td>
<td>3*</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>6,936</td>
<td>7,455</td>
<td>5,538*</td>
</tr>
<tr>
<td>$P_{\text{O}_2}$ (torr)</td>
<td>175</td>
<td>188</td>
<td>118*</td>
</tr>
</tbody>
</table>

* $P < 0.05$ versus control.
Values obtained at 15, 45 and 75 min are not shown, for purposes of clarity.

know which drug was being administered. Drug infusion was discontinued, and arterial pressure allowed to return to prehypotension values before wound closure to secure hemostasis.

Lactated Ringer's solution was infused at a rate of 7 ml/kg/hr. Albumin, 5 per cent in saline solution, and packed erythrocytes were administered to replace measured blood loss, determined by weighing sponges and measuring the volume of blood in suction bottles.

Prior to induction of anesthesia, an 18-g Teflon catheter was inserted percutaneously into a radial artery, and a 16-g catheter was inserted percutaneously into the right atrium (confirmed by chest roentgenogram) from an antecubital vein. A 14-g peripheral venous catheter was inserted into the dorsal of each hand for fluid and drug administration. Pressures were measured by transducers (Hewlett-Packard type 267 BC) and recorded continuously on a Sanborn multichannel pen recorder and display oscilloscope. The baseline for the transducers was taken at the level of the right atrium. Mean pressures were obtained by electrical integration. Heart rate was derived from the electrocardiogram. Pre- and postoperative (on five consecutive days) 12-lead electrocardiograms were obtained for each patient. In addition, seven leads were recorded intraoperatively: the three standard limb leads, three augmented limb leads, and lead V5. Arterial blood-gas and $pH$ values were measured using appropriate electrodes.

The rate-pressure product (RPP, product of heart rate and systolic arterial blood pressure) was employed to evaluate relative changes in myocardial oxygen consumption ($\text{MV}_{\text{O}_2}$). This product provides a satisfactory predictor of $\text{MV}_{\text{O}_2}$ in subjects with and without coronary-artery disease.

For all patients, the circulatory and blood-gas values were obtained before induction of anesthesia, after induction but prior to initiation of hypotension, at 15-minute intervals for 90 min during hypotension, and when arterial pressure had recovered to within 10 per cent of the control value.

Data were examined statistically using an analysis of variance (ANOVA) and Student's t test for paired data when ANOVA indicated significant differences. Data from the two groups were compared using the uncorrelated Student's t test. $P < 0.05$ was considered significant.

**Results**

Although systolic blood pressure was decreased to comparable values with the two drugs, mean and diastolic arterial blood pressures were significantly higher with TNG than with SNP (table 1). Nitroglycerin produced approximately equal decreases in systolic (25 per cent) and diastolic (29 per cent) blood pressures, whereas SNP decreased diastolic pressure (42 per cent) more than the systolic (29 per cent) from pre-drug values. The mean rates of infusion of SNP and TNG were 175 $\mu$g/min (range 85 to 260) and 320 $\mu$g/min (125 to 498), respectively. Durations of hypotension were 112 ± 11 min (mean ± SE) for TNG and 117 ± 9 min for SNP. Upon discontinuation of infusion, blood pressure returned to within 10 per cent of control in 5 (range 2 to 8) and 9 (4 to 22) min for SNP and TNG, respectively. There was no patient in whom hypotension could not be induced. However, some patients who received SNP needed increasing doses of the drug to maintain the hypotension.

Fifteen minutes following TNG administration, a significant increase in heart rate occurred; subsequent changes were not significant. Nitroprusside administration was associated with significant increases in heart rate (from pre-drug values) at 15, 30, 45 and 60 min.

Right atrial pressure was significantly lower with TNG than SNP; the decrease in right atrial pressure
was presumably secondary to dilation of peripheral capacitance vessels. Arterial oxygen tension decreased significantly following the use of either drug. The mean (±SE) intraoperative blood loss in the TNG group was 578 ± 82 ml, compared with 762 ± 93 ml for the SNP group. The difference was statistically significant. Significant decreases in rate-pressure product occurred with both SNP and TNG, indicative of decreases in $MV_{\text{O}_2}$.

There was no change in the electrocardiograms of patients who received TNG. With SNP, however, six patients had flattening or inversion of the T wave, and 12 had depression of the ST segment (0.5–1.2 mm), together with T wave changes. These alterations were transient and resolved in one to five days. In both groups, there was no clinical evidence of myocardial infarction, renal damage, or cerebral vascular complications throughout the postoperative periods (average 18 days). Furthermore, untorward responses to nitrates, e.g., prolonged hypotension, headache, etc., were not observed.

**Discussion**

The present study demonstrates that TNG can be effective as a hypotensive drug during general anesthesia. It readily produced a "dry" operative field that was, in all cases, acceptable to the surgeons. Nitroglycerin-induced hypotension was directly related to the rate of infusion, and the response of the patients was rapid. Upon discontinuation of drug infusion, return of arterial blood pressure to control values was moderately slower following TNG (average 9 min) than SNP (average 5 min). Throughout the series there was no evidence of tachyphylaxis or tolerance to the action of TNG. With SNP, however, some patients required increasing infusion rates with time. It is known that repeated exposure of man to organic nitrates leads to a decreased responsiveness to the pharmacologic effects of these agents.

Nitroglycerin-induced hypotension is related primarily to a direct effect of the drug on vascular smooth muscle. Both resistance and capacitance vessels are dilated, but the effect on the latter is predominant. SNP, however, has a relatively balanced effect on the arterial and venous vessels and has no direct effect on the myocardium. The magnitude of the decrease in diastolic pressure was more pronounced and significant with SNP. This observation may assume clinical importance since coronary perfusion is dependent upon the arterial diastolic pressure. It suggests that TNG may have a more beneficial effect than SNP in the preservation of adequate myocardial perfusion during the low-pressure phase. In addition, TNG is known to increase coronary blood flow in animals and in man without coronary-artery disease, and has a greater dilator effect on coronary collateral vessels than SNP. These properties of TNG, together with a relatively slower heart rate, can explain the absence of electrocardiographic change following its use in my study. Transient changes in ST segments and T waves occurred in 18 of 47 patients who received SNP. Simpson et al. found transient ischemic changes in nine of 20 patients during comparable levels of hypotension induced by SNP. Chiarello and co-workers have recently demonstrated in patients with acute myocardial infarction that, although TNG and SNP caused similar hemodynamic changes, TNG decreased while SNP intensified myocardial ischemic injury. They have also found, in the dog, that when SNP or TNG was administered at a rate sufficient to cause a modest decrease in systemic arterial pressure, SNP decreased transmural coronary blood flow, whereas TNG increased it. They concluded that, although TNG and SNP caused similar hemodynamic changes, they apparently exert opposite effects on myocardial blood flow.

Despite the fact that systolic arterial blood pressures were similar with the two drugs, blood loss was statistically less, although not clinically important, with TNG. Since most bleeding during operation is of venous origin, it may well be that the lower venous pressure associated with TNG was partly responsible. Davis et al. have reported that, in patients undergoing total hip replacement during deliberate hypotension, the average volume of blood replacement (intra- and postoperative) was 1,150 ml, compared with 2,250 ml for normotensive anesthesia. Lawson et al. found an average blood loss (intraoperative) of 475 ± 100 ml in hypotensive patients, compared with 1,475 ± 200 ml for controls. Both groups of investigators employed anesthetic sequences similar to that used in this study.

Concomitant with the beneficial effects of decreased blood loss induced by TNG, this drug also favorably influenced an index of myocardial energetics. The rate-pressure product decreased significantly with both TNG and SNP. This suggests that $MV_{\text{O}_2}$ was decreased during the hypotensive state. Recent evidence suggests that these drugs decrease preload and afterload, leading to a decrease in left ventricular work and $MV_{\text{O}_2}$. In addition, TNG has been shown to increase coronary blood flow in animals and in normal man.

Nitroglycerin seems to offer certain advantages over SNP. It produces a smooth and gradual decrease in blood pressure, and it is easy to control the dose and blood pressure response with minimal danger of producing severe hypotension. The "peaks and valleys" of blood pressure seen during SNP admin-
istration are not seen with TNG. Although the dose of TNG employed in this study was four times that used by Kaplan, no untoward response that could be attributed to the drug occurred. The beneficial effects of TNG on the coronary circulation and protection of the myocardium against injury have been recently reported. Unlike trimethaphan, TNG does not affect parasympathetic (or sympathetic) ganglia and, according to this study, does not produce tachyphylaxis.

On the basis of the results of this study, intravenously administered nitroglycerin is an effective hypotensive drug that is easy to administer and has a rapid, reversible action with absence of side effects. Experience with its use would seem to justify further trials in situations where deliberate hypotension during anesthesia is indicated.

The author thanks Drs. W. John Powell, Jr., and David J. Greenblatt for reviewing the manuscript.

References