CARDIOVASCULAR ACTIONS OF TRIMETAPHAN NITROPRUSSIDE  
Comparison with Sodium Nitroprusside in Greyhounds

M. R. J. SURY, M. D. J. DONALDSON, M. STRINGER, C. J. VESEY  
AND P. V. COLE

Sodium nitroprusside (SNP) remains one of the most popular, short-acting hypotensive agents for use in intensive care and anaesthesia. Despite its potency, resistance to hypotension may occur in young healthy subjects as a result of compensatory haemodynamic mechanisms [1]. Successful control of arterial pressure may, therefore, only be achieved either by using high doses of SNP, with the accompanying risk of cyanide toxicity [1, 2], or by the addition of agents such as beta-adrenoceptor blocking drugs [1, 3]. Trimetaphan is a vasodilator and blocker of autonomic ganglia which also suppresses the renin–angiotensin response [4, 5]. Unfortunately, it is less evanescent than SNP and elicits progressive resistance [6].

The combination of SNP and trimetaphan can produce satisfactory control of arterial pressure without the disadvantage of reflex increases in cardiac output [7], and with correspondingly lower doses of nitroprusside and blood cyanide (HCN) concentrations [8].

Trimetaphan nitroprusside (TNP) is a new compound that combines one ion of nitroprusside with two of trimetaphan to form a stable molecule. The aim of this study was twofold: to determine the dose–response and haemodynamic effects of TNP, and to establish whether TNP has any advantage over SNP under equi-hypotensive conditions in a greyhound model.

METHODS

General procedure

Healthy greyhounds were starved overnight, but had free access to water. Anaesthesia was induced with thiopentone 20–25 mg kg⁻¹ i.v. and maintained with alpha-chloralose (initial bolus dose 40 mg kg⁻¹, then 10 mg kg⁻¹ every 2 h) and phenoperidine (initial bolus dose 1 mg, then infused i.v. at 1 mg h⁻¹). Intubation of the trachea immediately followed induction and the lungs were mechanically ventilated with 70% nitrous oxide in oxygen. Adequate fluid balance was ensured by an infusion of 5% dextrose in 0.9% saline 4 ml kg⁻¹ h⁻¹, and normothermia was maintained using a heating blanket.

Arterial pressure was measured directly from the femoral artery. A flow-directed thermo-
dilution catheter was used to measure pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac output and temperature. Cardiac index, stroke volume index, systemic vascular resistance index and pulmonary vascular resistance index were determined using standard formulae (see Appendix). Left ventricular dP/dt max was measured with a pig-tailed catheter placed in the left ventricle. All cardiovascular variables were recorded by means of an Ormed MT6 recorder. Acid–base balance and blood-gas tensions were measured at 10-min intervals during the hypotensive period. Sixty minutes after instrumentation, two baseline sets of measurements were taken to ensure haemodynamic stability.

Solutions of SNP and TNP were prepared in 5% dextrose in 50-ml foil-wrapped syringes and infused from a Vickers infusion pump. The precise timing of the entry and exit of the drug was controlled by first infusing it through an externally primed 16-gauge cannula and then inserting and removing this at will through a shorter 14-gauge cannula placed in the external jugular vein.

Dose–response study

A TNP infusion lasting 50 min was administered to five dogs to determine the dose response. The rate of the infusion was increased step wise at 10-min intervals (1, 2.5, 5, 10 and 20 μg kg⁻¹ min⁻¹). Measurements of cardiovascular function and blood-gas tensions were recorded before the end of each 10-min infusion period when haemodynamic equilibrium had been established. In two dogs the infusion of TNP was repeated after a period of 2 h to ascertain whether the first infusion affected the response to the second.

Comparison of SNP and TNP under equi-hypotensive conditions

In a randomised within-dog comparison, SNP and TNP were alternately infused to produce equi-hypotensive conditions. Three dogs received TNP first and SNP second; a further three dogs received the drugs in the reverse order. Each drug reduced the mean arterial pressure by 30% within the first 10 min and thereafter doses were adjusted to maintain this degree of hypotension for a further 20 min. Two hours always elapsed between each infusion. Subsequent comparison included the doses of drugs used, HCN concentrations measured, and the cardiovascular effects observed. Following the discontinuation of the infusion, the times taken for the heart rate and arterial pressure to return to baseline values (±10%) were recorded.

The total dose (nmol kg⁻¹) of the drugs given over 30 min and the mean dose rate (nmol kg⁻¹ min⁻¹) over the last 20 min of hypotension were calculated (molecular weight of TNP = 956). Plasma and red cell HCN, together with whole blood lactate concentrations, were measured in 15-ml and 0.5-ml arterial blood samples,

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**Fig. 1.** Results of dose–response study. Mean arterial pressure (MAP), heart rate (HR) and cardiac index (CI) from five greyhounds (mean ± SEM) taken before (baseline) and at equilibrium during infusions of TNP. Each infusion rate (1, 2.5, 5, 10 and 20 μg kg⁻¹ min⁻¹) lasted 10 min. Significant differences from baseline: *P < 0.05; **P < 0.01.
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**RESULTS**

*Dose-response study*

The dose response to TNP (fig. 1) demonstrated a predictable stepwise decrease in mean arterial pressure. In addition, there was a significant increase in heart rate but, overall, no change in cardiac index. When the dose responses for TNP were repeated in two dogs after a 2-h rest, the haemodynamic changes were almost identical (fig. 2).

**Comparison of SNP and TNP under equi-hypotensive conditions**

A 30% reduction in mean arterial pressure was easily obtained by SNP and TNP in each respectively, which were taken at baseline and at the end of each infusion. Whole blood lactate concentration was determined using a fully enzymatic procedure (Boeringer Corp. Ltd), and HCN concentration by a previously described method [2, 9].

All data were normally distributed except for mean arterial pressure, drug doses, HCN concentrations and central venous pressures which were subsequently found to hold log skewed normal distributions. Student's t tests (paired and unpaired) were, therefore, applied and statistical significance inferred when $P < 0.05$.

### Table 1. Haemodynamic measurements taken at baseline (mean ± SEM) and times after start of infusion of SNP and TNP. *Significant change from baseline: $P < 0.05$*

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beat min⁻¹)</th>
<th>Cardiac index (ml min⁻¹ kg⁻¹)</th>
<th>Systemic vascular resistance index (mm Hg ml⁻¹ min kg⁻¹)</th>
<th>Mean pulmonary artery pressure (mm Hg)</th>
<th>Pulmonary artery occlusion pressure (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td><strong>SNP</strong></td>
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</tr>
<tr>
<td>Baseline</td>
<td>106 ± 9.9</td>
<td>119 ± 5.6</td>
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<td>11.3 ± 1.6</td>
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<tr>
<td>10</td>
<td>74 ± 6.3</td>
<td>116 ± 10.5</td>
<td>152* ± 6.4</td>
<td>10.3 ± 0.6</td>
<td>0.7*</td>
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<tr>
<td>20</td>
<td>73* ± 6.1</td>
<td>121* ± 8.6</td>
<td>155* ± 0.6</td>
<td>9.8 ± 0.5</td>
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<tr>
<td>30</td>
<td>73* ± 6.4</td>
<td>125* ± 10.6</td>
<td>166* ± 0.5</td>
<td>10 ± 0.5</td>
<td>0.3*</td>
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<tr>
<td><strong>TNP</strong></td>
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<tr>
<td>Baseline</td>
<td>107 ± 9.5</td>
<td>115 ± 8.5</td>
<td>11.2 ± 0.17</td>
<td>12.8 ± 1.2</td>
<td>5.5</td>
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<td>72* ± 6.2</td>
<td>143* ± 17</td>
<td>168 ± 0.58</td>
<td>12 ± 1.3</td>
<td>1.3*</td>
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<tr>
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<td>154* ± 18.3</td>
<td>150 ± 0.64</td>
<td>11.3 ± 0.8</td>
<td>0.8*</td>
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<tr>
<td>30</td>
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<td>155* ± 14.9</td>
<td>151 ± 0.64</td>
<td>10.8 ± 0.0</td>
<td>0.0*</td>
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</tr>
</tbody>
</table>
greyhound. No significant differences were found between the first and second infusions of either SNP or TNP in drug doses, blood HCN concentrations, cardiac index or heart rate.

The haemodynamic effects of TNP and SNP were then compared with their own baseline values (table I). Both drugs significantly increased the heart rate and decreased systemic vascular resistance index and pulmonary artery occlusion pressure. Each drug increased cardiac index, but only the change produced by SNP achieved statistical significance. Although both drugs decreased pulmonary artery pressure, this was significant only following TNP. Corresponding decreases in pulmonary vascular resistance index were significant only for SNP. Small but non-significant increases in left ventricular dP/dt_{max}

were seen for both drugs. Plasma lactate concentrations and blood-gas values remained within their normal ranges throughout each experiment.

Within-subject comparisons of SNP and TNP showed that SNP caused a significantly greater increase in cardiac index at 30 min, but the heart rate was clearly higher during the infusion of TNP at 20 and 30 min (fig. 3). There were no significant differences between the drugs for systemic and pulmonary vascular resistance indices. Mean pulmonary artery pressure, pulmonary artery occlusion and central venous pressures were also similar.

At the end of the infusions mean arterial pressure returned more rapidly after TNP (mean times: TNP 2.8 min, SNP 8.3 min), although heart rate took longer to reach baseline values (mean times: TNP 14.2 min, SNP 6.8 min).

Higher molar doses of SNP were required to achieve equi-hypotensive conditions, but this did not achieve statistical significance (fig. 4). Nevertheless, the plasma and red cell HCN concentrations were significantly higher after SNP \( P = 0.007 \) and \( P = 0.047 \), respectively (fig. 4).

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DISCUSSION

The effectiveness of sodium nitroprusside and other potent vasodilator drugs is frequently reduced by reflex increases in heart rate and cardiac output [10, 11] with an associated increase in plasma catecholamine concentrations [5]. These compensatory mechanisms are usually undesirable in patients receiving either critical care or anaesthesia. The addition of beta-adrenoceptor blocking drugs may resolve this problem, but they are not short-acting and may compromise cardiac output and induce bronchospasm [12]. As an alternative to SNP, trimetaphan has a slower onset of effect, but the advantage of inhibiting sympathetic activation [5]. However, resistance to its action may occur [6] and return to normotension is often delayed [4]. The technique of combining SNP with trimetaphan was introduced by MacRae, Wildsmith and Dale [13], who mixed the two drugs in a weight ratio of 10:1, which corresponds to a molar ratio of 5:1. The administration of this mixture to anaesthetized patients considerably reduced the usual dose of either drug, and hypotension was achieved without a significant increase in cardiac output [7]. These findings have been confirmed by Fahmy [8] who found, in addition, that blood HCN concentrations were lower in patients receiving the mixture compared with those receiving SNP alone.

Trimetaphan nitroprusside is a compound manufactured solely for experimental trials. The lyophilized drug is a semihydrate which should be stored in the dark at a temperature of 0–5 °C. Forty milligrams of the drug is dissolved in 3 ml of 75 % ethanol and subsequently diluted with at least 50 ml of normal saline or 5 % glucose solutions and protected from light.

In this trial, we chose to compare TNP with SNP in greyhounds because they have cardiovascular systems capable of powerful compensatory mechanisms and so resemble those of healthy young adults. Using this model, with alpha-chloralose as the sole anaesthetic, Ross and Cole [14] reported a wide variation in baseline heart rate and arterial pressure and, consequently, the effects of SNP were extremely variable. We found that the addition of phenoperidine ensured that the baseline heart rates and arterial pressures were within the normal range for the conscious animal.

In order to minimize the possible influence of the effects of the first infusion upon the second, we ensured that the degree and duration of hypotension were compatible with full recovery to the baseline haemodynamic state, and that the doses of nitroprusside used were less than toxic, as reflected in acid-base status and blood lactate concentrations remaining normal throughout. Furthermore, the cardiovascular effects of TNP were shown to be almost identical with those of similar infusions given to the same dog 2 h later (fig. 2).

To produce equivalent degrees of hypotension, smaller doses of TNP (and, therefore, nitroprusside ions) were required. Lower HCN concentrations resulted (fig. 4), although neither drug produced potentially toxic HCN concentrations. In addition, TNP produced hypotension by reducing systemic vascular resistance without a significant increase in cardiac output, but with tachycardia which often persisted when the infusion ended.

The demand remains for a short-acting hypotensive drug which may be safely infused to patients without causing a reflex increase in heart rate and cardiac output, and without necessitating recourse to a beta-adrenoceptor blocker. In our opinion, in our animal model, TNP has not been shown to be significantly better than SNP for short term use. It may be more suitable, however, for long-term control of arterial pressure, particularly as the resultant cyanide concentrations would be appreciably lower.

APPENDIX

STANDARD FORMULAE

Cardiac index = \( \frac{\text{cardiac output}}{\text{body weight}} \)

Stroke volume index = \( \frac{\text{cardiac index}}{\text{heart rate}} \)

Systemic vascular resistance index = \( \frac{\text{mean arterial pressure}}{\text{cardiac index}} \)

Pulmonary vascular resistance index = \( \frac{\text{mean pulmonary arterial pressure}}{\text{cardiac index}} \)

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REFERENCES