A commercial preparation of glyceryl trinitrate for i.v. administration was assessed under both experimental and clinical conditions. The overall haemodynamic effects were beneficial during coronary artery grafting and aortic valve replacement, when the drug was given at a rate of 0.8 \mu g \text{kg}^{-1} \text{min}^{-1} at which dose there was no appreciable effect on resistance vessels. No adverse side-effects occurred. There was no change in the activity of the preparation, whether diluted or not, over a 6-h period.

Hypertension unresponsive to analgesia or sedation may occur during heart surgery, particularly coronary artery by-pass grafting (CABG) and replacement of severely stenosed aortic valves (AVR). This increases left ventricular work, compromises suture lines and may be indicative of myocardial ischaemia as demonstrated by a decreased endocardial viability ratio (EVR) (Olinger et al., 1975; Kaplan, Dunbar and Jones, 1976):

\[
\text{EVR} = \frac{\text{(mean DAP - LVEDP)} \times \text{diastolic time}}{\text{mean SAP} \times \text{systolic time}}
\]

where LVEDP = left ventricular end diastolic pressure; DAP = diastolic arterial pressure; SAP = systolic arterial pressure. It has become accepted as a useful indicator of subendocardial perfusion (which takes place exclusively in diastole) and carries a prognostic value (Hoffman and Buckberg, 1975, 1978). EVR less than 0.5 indicates that diffuse subendocardial necrosis will occur unless measures are taken to improve the myocardial oxygen supply/demand ratio, for example by intraaortic balloon pumping.

Many of the drugs used to control hypertension have serious disadvantages. Long acting vasodilators may result in unwanted hypotension at a later stage, phenothiazines and butyrophenones have sedative effects and compound respiratory depression from narcotics. Sodium nitroprusside (SNP) may cause cyanide intoxication if used over a prolonged period and has been reported by Armstrong and others (1975) to produce an adverse effect on EVR by reducing diastolic pressure and increasing intracoronary steal by its arteriolar dilator action.

A crushed glyceryl trinitrate (GTN) tablet in the buccolabial groove of such patients will transiently control such hypertension. The effect, however, is variable and not easy to adjust. Until very recently no preparation of i.v. GTN has been available and with additional controls imposed upon hospital pharmacies an ad hoc local preparation has not been feasible, so there is no available published work on the drug in the context of current U.K. practice.

A study was undertaken under experimental and clinical conditions to evaluate some of the haemodynamic effects of GTN during AVR and CABG. Permission was obtained from the Leicestershire Area Ethics Committee.

**METHODS**

The drug was supplied by Arnar-Stone Laboratories as a sterile, non-pyrogenic solution in 10-ml glass ampoules. The solution has the following composition: nitroglycerin* 0.5 mg ml\(^{-1}\); lactose, US* 4.5 mg ml\(^{-1}\); alcohol, USP 0.1 ml ml\(^{-1}\) (10% v/v); monobasic potassium phosphate, USP 13.6 mg ml\(^{-1}\) (0.1 mmol ml\(^{-1}\)). (*From nitroglycerin 10% (w/w) in lactose USP.)

**Experimental study**

Ten patients were studied in detail while in a steady state at the conclusion of surgery (AVR, three patients; CABG, seven). After a control
period GTN was infused i.v. at a constant rate of 0.8 μg kg⁻¹ min⁻¹ until a further steady state was obtained, whereupon further measurements were made. The infusion was then discontinued, and observation continued until there was a return to control values. GTN was administered by placing the contents of one 5-mg ampoule into a Travenol 100-ml burette diluted with 5% dextrose 90 ml. A Sorenson “Dial-a-flow” was used to control the rate of infusion.

Clinical use
We have used i.v. GTN over a 6-month period for the following:

(1) In at least 10 patients for the treatment of acute perioperative hypertension in the presence of adequate analgesia (morphine 3–4.5 mg kg⁻¹) and normocarbia. Hypertension was defined as an arterial systolic pressure greater than 160 mm Hg or a diastolic pressure greater than 100 mm Hg, or both. In four of these patients the drug was administered as an infusion of GTN concentrate given from a 50-ml syringe gun over a period of 6 h. In the remainder of the patients the mode of administration was as described for the experimental study.

(2) To induce hypotension in cases of surgical difficulty: (a) slipping of the aortic side clamp (three patients); (b) to assist haemostasis under difficult conditions (two patients).

(3) To obtain sufficient haemodynamic improvement as to render aortic balloon counterpulsation unnecessary as judged by measuring EVR. The anaesthetic technique was the same in all patients (morphine, hyoscine and pancuronium, IPPV with a 50% oxygen in air mixture as described by May, Machin and Wyatt (1978)). Pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output were measured using a thermodilution Swan–Ganz catheter. Statistical analysis was performed using a paired Student’s t test.

RESULTS

Experimental study (table I)
I.v. GTN in a constant dose of 0.8 μg kg⁻¹ min⁻¹ produced a decrease in arterial systolic pressure not associated with an increase in heart rate or a decrease in diastolic pressure. No change in perfusion pressure could be demonstrated when GTN was administered with artificially generated pulsatile flow using a Stockert pump with the aorta cross-clamped and a venous pressure of zero, that is there appeared to be no effect on the resistance side of the circulation in the dose used. This is contrary to results published in the U.S.A. by Hempleman and others (1977).

There was a moderate but significant decrease in cardiac index (of the order of 10%) and, as a consequence, no significant changes in systemic or pulmonary vascular resistance were shown. The use of low doses of dopamine (3–5 μg kg⁻¹ min⁻¹) to restore the cardiac output did not abolish the beneficial effects of GTN. Myocardial supply : demand ratio as measured by EVR was significantly improved. In all patients onset of action appeared complete within 4 min and in no patient was any haemodynamic effect discernible 5 min after discontinuing the GTN.

Clinical use
In four patients (CABG), two of whom were studied in the experimental series, an infusion of GTN concentrate was given for 6 h at a rate of 0.8 μg kg⁻¹ min⁻¹. This proved effective in maintaining normotension with no instability of arterial pressure.

When bolus doses of GTN were used in an attempt to control brief periods of hypertension, doses of 50–100 μg were effective. With this method of administration a visible haemodynamic effect was seen within 1–2 min. This was followed by a continuous infusion. In three patients surgical difficulty because of slipping of the aortic side clamp was alleviated by the “bolus” technique and in two cases the induction of hypotension by GTN in previously normotensive individuals has, in conjunction with other measures, assisted in securing haemostasis under difficult conditions. In two instances sufficient haemodynamic improvement was obtained to render balloon counterpulsation unnecessary as judged by EVR. In one patient an improvement in cardiac output was observed after correction of a hypertensive state in the initial stages of a CABG surgery.

No adverse effects were observed. In particular, cerebral function as monitored with a Devices Cerebral Function Monitor was never compromised, no e.c.g. changes were seen, and there were no significant reductions in oxygen saturation or increase in shunt fraction. No methaemoglobin was detected on spectroscopic examina-
on the capacitance side of the circulation. This and Gilman, 1975), the effect being more marked on the capacitance side of the circulation. This promotes peripheral pooling of blood and decreases venous return, producing in turn a decrease in left ventricular pressure, myocardial wall tension, heart size and, ultimately, myocardial oxygen demand. As a result of the reduction in LVEDP subendocardial perfusion is decreased (Winbury, Howe and Hefner, 1969; and Gilman, 1975), the effect being more marked on the capacitance side of the circulation. This promotes peripheral pooling of blood and decreases venous return, producing in turn a decrease in left ventricular pressure, myocardial wall tension, heart size and, ultimately, myocardial oxygen demand. As a result of the reduction in LVEDP subendocardial perfusion is increased (Winbury, Howe and Hefner, 1969; GA, 1978).

**DISCUSSION**

The primary pharmacological action of GTN is relaxation of vascular smooth muscle (Goodman and Gilman, 1975), the effect being more marked on the capacitance side of the circulation. This promotes peripheral pooling of blood and decreases venous return, producing in turn a decrease in left ventricular pressure, myocardial wall tension, heart size and, ultimately, myocardial oxygen demand. As a result of the reduction in LVEDP subendocardial perfusion is increased (Winbury, Howe and Hefner, 1969; GA, 1978).

**Table 1. Haemodynamic values and statistical analysis of patients in the experimental study.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>SA (m²)</th>
<th>AP (mm Hg)</th>
<th>HR (beats min⁻¹)</th>
<th>PAP (mm Hg)</th>
<th>RAP (mm Hg)</th>
<th>PCW (mm Hg)</th>
</tr>
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<td>B D</td>
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<tr>
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<td>1.90</td>
<td>150/75</td>
<td>125/72</td>
<td>90 90 (paced)</td>
<td>22 16</td>
<td>11 8</td>
</tr>
<tr>
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<td>1.90</td>
<td>121/78</td>
<td>96/68</td>
<td>90 90</td>
<td>26 16</td>
<td>12 9</td>
</tr>
<tr>
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<td>100/44</td>
<td>80/42</td>
<td>90 92</td>
<td>22 16</td>
<td>18 16</td>
</tr>
<tr>
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<td>1.40</td>
<td>110/60</td>
<td>90/60</td>
<td>80 85</td>
<td>17 8</td>
<td>15 12</td>
</tr>
<tr>
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<td>160/60</td>
<td>130/60</td>
<td>105 100</td>
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<td>15 10</td>
</tr>
<tr>
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<td>159/85</td>
<td>140/85</td>
<td>105 105</td>
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<td>74 78</td>
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<td>14 12</td>
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<td>124/72</td>
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<td>16 15</td>
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<td>122/80</td>
<td>110/80</td>
<td>88 90</td>
<td>28 15</td>
<td>12 9</td>
</tr>
</tbody>
</table>

**Mean** Syst. 133.6 115.0 93.1 93.8 22.5 16 23 13.1 10.7 18.0 12 4

**SD** Syst. 19.85 13 54 4.46 2.99 4.10

**P** Syst. 0.01 n.s. 0.01 0.05 0.02

<table>
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<tr>
<th>Patient</th>
<th>SA (m²)</th>
<th>CO (litre min⁻¹)</th>
<th>CI (litre min⁻¹)</th>
<th>EVR</th>
<th>PVRI</th>
<th>SVRI</th>
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<td>0.13 0.86</td>
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<td>23.52 26.53</td>
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<tr>
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<td>7.98 6.08</td>
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<td>0.48 0.69</td>
<td>0.46 1.52</td>
<td>22.79 22.31</td>
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<tr>
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<td>2.15</td>
<td>5.73 5.38</td>
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<td>6.45 5.65</td>
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<td>1.31 1.26</td>
<td>27.20 30.02</td>
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<tr>
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<td>4.75 4.20</td>
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<td>1.73 1.50</td>
<td>30.03 35.28</td>
</tr>
<tr>
<td>9</td>
<td>2.05</td>
<td>6.07 5.00</td>
<td>2.96 2.44</td>
<td>0.59 0.68</td>
<td>3.15 3.00</td>
<td>27.24 30.41</td>
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<tr>
<td>10</td>
<td>1.80</td>
<td>4.60 4.29</td>
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<td>0.65 0.75</td>
<td>4.04 1.53</td>
<td>32.08 33.98</td>
</tr>
</tbody>
</table>

**Mean** 5.34 4.65 2.92 2.54 0.70 0.89 1.73 1.56 28.36 30.11

**SD** 1.05 0.49 0.20 0.05 1.04 7.57

**P** < 0.1 > 0.05 0.02 n.s. n.s.
Becker, Fortuin and Pitt, 1971; Mathes and Rival, 1971; Chiarello et al., 1976). A more favourable myocardial oxygen supply : demand ratio is thus achieved.

In the past few years the popularity of CABG operations has increased and has been accompanied by a high frequency (5-40\%) of perioperative myocardial infarction (Mundth and Austen, 1975). It is important that steps are taken to treat the factors which decrease the myocardial supply: demand ratio. (1) increased myocardial wall tension, secondary to either hypertension (increased afterload) or increased filling pressure (increased preload), (2) increased contractility and (3) increased heart rate (Awan et al., 1976).

Sublingual GTN has been used for more than a century in the treatment of angina pectoris. Viljoen (1968) used i.m. GTN during internal mammary implantation surgery. Many studies have been undertaken in recent years on both i.v. and i.m. administration of GTN in the U.S.A. In these American studies GTN has been shown to reduce preload and afterload and improve blood flow to ischaemic areas of myocardium, whilst SNP reduces the flow (Chiarello et al., 1976). It is effective in relieving coronary artery spasm in patients suffering from Prinzmetal's variant angina pectoris, probably by a direct dilator effect on the coronary arteries (Oliva, Potts and Pluss, 1973; Krantz, Viljoen and Gilbert, 1980). GTN has also been shown to redistribute blood to the subendocardium (Becker, Fortuin and Pitt, 1971; Mathes and Rival, 1971; Chiarello et al., 1976). A reduction in pulmonary vascular resistance has been demonstrated by Hempleman and others (1977).

In this study GTN caused a reduction of preload and arterial systolic pressure without change in diastolic pressure or heart rate, thus improving EVR. A decrease in cardiac output, readily reversed by low-dose dopamine, was seen. Unlike the American experience, no demonstrable effect on systemic or pulmonary vascular resistance was observed, neither did we see any significant increase in shunt fraction. These differences may be partly explained by dissimilar anaesthetic technique; we used no inhalation anaesthetic agents such as halothane or nitrous oxide which have a negative inotropic effect and potentiate GTN. The absence of an increase in shunt fraction may be attributable to the regional hypoxic vasoconstrictor mechanism which regulates $V/Q$ balance, is abolished by nitrous oxide, but preserved with morphine. The absence of any effect on pulmonary vascular resistance is disappointing, but separate studies should be performed to determine if the drug affects abnormally increased resistance such as occurs in mitral valve disease.

REFERENCES


**EFFETS HEMODYNAMIQUES ET USAGE CLINIQUE DU TRINITRATE DE GLYCERYLE POUR LES INTERVENTIONS CHIRURGICALES AU COEUR**

**RESUME**

Une préparation commerciale de trinitrate de glycéryle pour administration par voie intraveineuse a été évaluée dans des conditions expérimentales et dans des conditions cliniques. Les effets hémodynamiques ont dans l’ensemble été bénéfiques lors d’une greffe de l’artère coronaire et du remplacement d’une valve aortique, alors que ce médicament était administré à raison de 0,8 μg kg⁻¹ min⁻¹, dose qui n’a pratiquement pas affecté les vaisseaux de résistance. Il ne s’est produit aucun effet secondaire adverse. Il n’y a eu aucun changement dans l’activité de la préparation, diluée ou non, au cours d’une période de 6 h.

**TRINITRATO DE GLICERILO INTRAVENOSO: EFECTOS HEMODINAMICOS Y USO CLINICO EN LAS OPERACIONES DE CORAZON**

**SUMARIO**

Se evaluó una preparación comercial de trinitrato de glucero a usar en administraciones intravenosas, tanto bajo condiciones experimentales como clínicas. Los efectos hémodinámicos globales fueron beneficiosos durante el injerto de la arteria coronaria y durante la sustitución de la válvula aórtica, cuando la droga se administro a un régimen de 0,8 μg kg⁻¹ min⁻¹, dosis a la que no se detectaron efectos apreciables en la resistencia de los vasos. No se presentaron efectos adversos. No hubo cambio alguno en la actividad de la preparación por espacio de 6 h, independientemente de que dicha preparación fuera diluida o no.

**INTRAVENÖS VERABREICHTES GLYZERYLTRINITRAT. HÄMODYNAMISCHE WIRKUNGEN UND KLINISCHE VERWENDUNG BEI HERZCHIRURGIE**

**ZUSAMMENFASSUNG**

Ein Handelspräparat von Glyzeryltrinitrat zur intravenösen Verabreichung wurde unter experimentellen und unter klinischen Bedingungen untersucht. Die allgemeinen hämodynamischen Wirkungen während Koronararterienverpflanzung und Aortenklappeneinsatz waren günstig, wenn die Droge mit 0,8 μg kg⁻¹ min⁻¹ verabreicht wurde, bei welcher Dosis sich keine erkennbaren Auswirkungen auf den Gefässwiderstand zeigten. Es kam zu keinen schädlichen Nebenwirkungen. Die Wirkung des Präparates, ob verdünnt oder nicht, veränderte sich über eine Periode von 6 Stunden nicht.