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A profile of intravenous nitroglycerin use in cardiopulmonary bypass surgery

We studied the indications for use, time to onset of effect, approximate effective concentration and therapeutic success of commercially prepared intravenous nitroglycerin (NTG) in 50 patients undergoing cardiopulmonary bypass (CPB) surgery. Nitroglycerin was used to treat systemic or pulmonary hypertension, myocardial ischaemia and ventricular failure. Twenty-one patients had more than one indication for NTG use. Nineteen of 22 patients with pulmonary hypertension, 12 of 13 patients with ischaemic changes, and 13 of 15 patients with ventricular failure improved during intravenous NTG administration. Hypertension during CPB was ameliorated in only six of ten instances. The time to onset of effect ranged from 4.1 ± 0.8 to 7.8 ± 2.8 minutes and the mean approximate effective NTG concentration varied from 1.7 ± 0.3 to $2.9 \pm 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (doses only approximate due to our use of an infusion system which absorbs NTG). Complications from intravenous NTG administration were not seen. We conclude that this NTG preparation facilitates treatment of prebypass hypertension, pulmonary hypertension, myocardial ischaemia and ventricular failure but is less effective for the treatment of hypertension during CPB.

Key words

PHARMACOLOGY: nitroglycerin; SURGERY: cardiac;
BLOOD PRESSURE: pulmonary hypertension,
systemic hypertension.

Intraoperative use of nitroglycerin by sublingual,¹ intramuscular,² and intravenous^{3,4,5} administration is not new to coronary artery bypass graft surgery. Its use in surgery for patients with aortic insufficiency has been advocated to improve cardiac function.^{6,7} It has also been administered intravenously in orthopedic⁸ and neurosurgery⁹ to induce controlled hypotension, and in obstetrics to prevent exacerbation of hypertensive conditions.¹⁰

We have used intravenous nitroglycerin during cardiac surgery for approximately seven years to treat worsening myocardial ischaemia. The drug was prepared by dissolving 0.6 mg tablets in 5 per cent Dextrose in water, which was passed through a 22 micron millipore filter and diluted to a volume of 250 ml resulting in a concentration of $240 \mu\text{g} \cdot \text{ml}^{-1}$. The preparation of the drug in this manner resulted in questionable concentration, was time-consuming, and the sterility of the preparation could not be guaranteed especially with regard to viral contamination. The advent of standardized,^{11,12} sterile intravenous nitroglycerin preparations should facilitate controlled pharmacological intervention in patients undergoing surgery. A one per cent sterile solution of nitroglycerin was made available to us and facilitated the intraoperative use of the drug. We studied the indications for use, the approximate dose range, and the effectiveness of intravenous nitroglycerin in patients undergoing open heart surgery.

Methods

The clinical trial of a new intravenous nitroglycerin preparation was approved by the Ethics Committee for Clinical Study of the Royal Victoria Hospital and informed consent was obtained from patients participating in the evaluation. During cardiopulmonary bypass surgery, intravenous nitroglycerin

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TABLE I Therapeutic profile of intravenous nitroglycerin

Indication	Systemic hypertension		Ischaemia	Pulmonary hypertension	Ventricular failure
	Pre-bypass	Bypass			
Single indication	13	10	2	3	1
Multiple indications	9	—	11	15	14
Total indications	22	10	13	18	15
Nitroglycerin success	19/22	6/10	12/13	17/18	13/15
Dose in those responding $\mu\text{g}^{-1}\cdot\text{kg}\cdot\text{min}^{-1}$ (mean $\pm$ SEM)	2.9 $\pm$ 0.7	1.7 $\pm$ 0.3	2.1 $\pm$ 0.5	1.8 $\pm$ 0.3	2.0 $\pm$ 0.3
Time to onset of effect minutes (mean $\pm$ SEM)	4.1 ($\pm$ 0.8)	7.8 ($\pm$ 2.8)	5.8 ($\pm$ 0.9)	7.5 ($\pm$ 1.3)	6.7 ($\pm$ 1.2)

as prepared by Hamon Laboratories,* was administered by infusion. This one per cent solution was mixed in a 250 ml glass bottle^{12,13} of five per cent Dextrose in water and resulted in concentrations of either 80 or 160 $\mu\text{g}\cdot\text{ml}^{-1}$. The infusion was given by an I.V.A.C.† infusion pump through a short¹⁴ 1.8 meter polyvinylchloride administration set (Baxter Travenol Laboratories‡) into a polyurethane central venous line (Cordis Corporation§) representing a mode of administration common to clinical practice. Patients were monitored as usual for cardiac surgery in our institution,¹⁵ with placement of electrocardiographic, venous, arterial, and thermidilution pulmonary artery catheters from which control values were recorded before induction of anaesthesia. When intravenous nitroglycerin was infused incrementally, the concentration used, the time to effect, the duration of infusion and the total dose of drug was recorded. It was used to treat:

1. systemic hypertension (increase of systolic blood pressure 20 per cent greater than control or a

mean arterial pressure greater than 13.3 kPa on minimally accepted cardiopulmonary bypass flow rates);

2. pulmonary hypertension (an increase of systolic pressure 20 per cent greater than control);

3. myocardial ischemia (ST changes in the modified V_s electrocardiogram);

4. ventricular failure (increasing pulmonary capillary wedge pressure with decreasing cardiac index).

The anaesthetic technique was not standardized; however, all patients received high dose fentanyl anaesthesia which has been shown to minimize haemodynamic instability.¹⁵ On occasion this basal anaesthetic technique was supplemented with other anaesthetics, volatile and intravenous.

Results

Intravenous nitroglycerin was administered to fifty patients undergoing cardiopulmonary bypass (CPB) for either coronary artery bypass grafting (40 patients), cardiac valve replacement (eight patients) or a combination of the two (two patients). There were 13 women and 37 men in the group, and the mean age and weight were 56.9 years ($\pm$ 1.7) and 71.4 kg ($\pm$ 1.6) respectively. The results are shown in Table I. Twenty-one patients had more than one indication for use of the drug. Nitroglycerin was

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§Cordis Corporation, Miami, Florida, U.S.A.

INDICATIONS FOR INTRAVENOUS USE OF NITROGLYCERIN

FIGURE 1 A Venn Diagram is used to represent the indications for the use of intravenous nitroglycerin in 50 patients undergoing cardiopulmonary bypass surgery. Overlapping of circles reflects shared indications. Each number represents a patient in the study.

used to treat prebypass systemic hypertension on 22 occasions, hypertension during CPB on ten occasions, pulmonary hypertension on 18 occasions and ventricular failure on 15 occasions. The drug was highly effective in treating pulmonary hypertension, myocardial ischaemia, and only slightly less effective in managing prebypass systemic hypertension and ventricular failure. It was least effective in treating systemic hypertension during CPB. The approximate effective concentrations ranged from $1.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to $2.9 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. These, or concentrations as great as $7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ were unsuccessful on eleven occasions. The shortest time to onset of effect was 4.1 ± 0.8 min and the longest time was 7.8 ± 2.8 min. The majority of the patients had more than one indication for nitroglycerin treatment. The overlap in indications is represented in a Venn diagram (Figure 1).

Discussion

The mechanism of action and use of intravenous nitroglycerin has recently been reviewed with some

reference to surgical indications⁷ and the beneficial effects on the ischaemic myocardium when compared with other hypotensive agents have been discussed.¹⁶

Kaplan *et al.*⁴ found that use of intravenous nitroglycerin produced significant decreases in systemic blood pressure, pulmonary capillary wedge pressure and systemic vascular resistance, while cardiac index, stroke index and heart rate remained unchanged. In his study, indices of myocardial oxygen demand (i.e. rate pressure product and tension time index) were improved by nitroglycerin and in 50 per cent of patients ST segment depression returned to normal. Tobias⁵ also demonstrated a reduction in myocardial oxygen demand and improvement in ventricular performance and concluded that myocardial contractility was unaffected by nitroglycerin. Indeed, Cottrell *et al.*⁶ have suggested the use of intravenous nitroglycerin in patients with severe aortic incompetence to improve cardiac function. Nitroglycerin also appears to confer electrophysiological stability to the ischaemic myocardium whether by a direct or indirect effect and thus prevents adverse arrhythmias.¹⁷⁻¹⁹ Ventricular fibrillation threshold is elevated and this beneficial effect is probably caused by some action of nitroglycerin other than reduction in myocardial oxygen consumption.

Intravenous nitroglycerin has been used to treat subendocardial ischaemia which can be detected by monitoring the V_5 electrocardiogram²⁰ or even earlier by careful observation of the pulmonary capillary wedge pressure.²¹ We were able to revert electrocardiographic changes suggestive of ischaemia on 12 of 13 occasions and decrease elevated pulmonary artery pressures on 17 of 18 occasions. Elevated pulmonary artery pressure may also reflect chronic ventricular dysfunction. In such cases the vasodilating effect of nitroglycerin on the pulmonary circulation has been shown to be of benefit.^{22,23} Nitroglycerin may improve cardiac function when ventricular hypokinesis or dysfunction is secondary to myocardial ischaemia whereas patients with cardiomyopathic or dyskinetic ventricles fail to improve haemodynamically with the drug.^{24,25} In this series we observed a decrease in ventricular filling pressures and increase in cardiac index in 13 of 15 patients. Some of these patients had valvular dysfunction and it has been shown that

low forward flow states associated with aortic and/or mitral valve dysfunction may improve with nitroglycerin therapy.^{7,26}

Systemic hypertension remains a threat to patients undergoing coronary revascularization surgery, regardless of anaesthetic technique, as it may be associated with myocardial ischaemia.^{15,27,28} Nitroglycerin has been advocated for the treatment of systemic hypertension in these instances³⁻⁴ and we noted a high degree of response when the drug was used for this indication.

The physiological response to cardiopulmonary bypass is an increase in plasma levels of catecholamines, glucocorticoids and antidiuretic hormone.²⁹ This is often manifest by an increase in mean arterial pressure at constant flow which can be treated by the administration of anaesthesia. Nitroglycerin was least effective in our series in attenuating the increase in mean arterial pressure on cardiopulmonary bypass, and corroborates the reports of others.³⁰ This may be due to the fact that while arteriolar dilatation is an effect of nitroglycerin³¹⁻³³ the predominant dilating effect is on the venous system;⁷ or it may simply be a reflection of the absorptive capacity of the polyvinylchloride tubing³⁴ of the cardiopulmonary bypass machine.

The mean dosages noted in Table I represent the amount of drug required for successful intervention of the indications cited. Controlled infusion devices allow more precise control of dosage and, with respect to intravenous nitroglycerin, avoid the variable haemodynamic effects of sublingual boluses.³⁵ As with most drugs, nitroglycerin should be titrated to achieve the desired effect. Determination of the exact administered intravenous concentration is made difficult by the changing concentration effect caused by adsorption to infusion sets.^{13,14} This effect is especially noted with polyvinylchloride plastics³⁴ and is directly proportional to the surface area of this plastic to which the infused nitroglycerin is exposed. The methodology of this clinical study reflects commonly employed administration methods. Consequently, the doses reported effective are approximations. Manufacturers of intravenous nitroglycerin will soon supply administration sets made of plastics with a low absorptive capacity for nitroglycerin and this may result in a decrease in the amount of drug required to achieve clinical effect.

Complications of administration were not seen with the use of intravenous nitroglycerin. We conclude that this preparation facilitates intervention in episodes of prebypass systemic hypertension, pulmonary hypertension, myocardial ischaemia and left ventricular failure but is less effective in treating systemic hypertensive episodes during cardiopulmonary bypass.

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Résumé

Chez 50 patients subissant une intervention chirurgicale avec l'emploi du cœur-poumon artificiel, nous avons étudié les indications, le temps d'action, l'approximation de la concentration effective et le succès thérapeutique de la nitroglycérine préparée commercialement et injectée par voie intraveineuse. La nitroglycérine fut employée pour traiter l'hypertension pulmonaire et systémique, l'ischémie du myocarde et la défaillance ventriculaire. Vingt-et-un des patients ont eu plus d'une indication d'emploi de nitroglycérine. Dix-neuf des 22 patients souffrant d'hypertension pulmonaire, 12 des 13 patients avec changements ischémiques et 13 des 15 patients souffrant de défaillance ventriculaire s'améliorèrent pendant l'administration par voie intraveineuse de nitroglycérine. L'hypertension s'améliora dans seulement six des dix cas pendant la circulation extra-corporelle. Le temps du début de l'effet de la nitroglycérine varia entre 4.1 ± 0.8 à 7.8 ± 2.8 minutes et la moyenne effective et approximative de la concentration de nitroglycérine varia entre 1.7 ± 0.3 à $2.9 \pm 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (ces doses sont seulement approximatives dû à l'emploi d'un système d'administration qui absorbe la nitroglycérine). On n'observa pas de complications avec la nitroglycérine administrée par voie intraveineuse. Nous concluons que cette préparation de nitroglycérine facilite le traitement de l'hypertension du pré-pontage cardiopulmonaire, de l'hypertension pulmonaire, de l'ischémie du myocarde et de la défaillance ventriculaire mais elle est moins efficace pour le traitement de l'hypertension pendant la circulation extra-corporelle.