VASODILATOR PROPERTIES OF NITROGLYCERIN AND ISOSORBIDE DINITRATE DURING CARDIOPULMONARY BYPASS†

O. MUUKU, M. HYNYNEN, M. SALMENPERÄ AND J. HEINONEN

SUMMARY
In a placebo-controlled trial, we have studied the vasodilator properties of bolus doses of nitroglycerin (TNG) and isosorbide dinitrate (ISDN) in 32 patients during cardiopulmonary bypass with a constant pump flow. Blood volume of the venous reservoir and mean arterial pressure were recorded for 10 min after drug administration to detect changes in venous capacitance and arteriolar resistance, respectively. The venous capacitance-increasing effects of TNG 200 µg and ISDN 1600 µg were initially identical and significant at 2 and 3 min after the bolus. Thereafter, the effect of TNG began to decline, while that of ISDN remained significant until the end of the study. TNG 200 µg decreased arterial pressure slightly more than ISDN 1600 µg, but the effect of both drugs lasted for only 1–2 min. TNG and ISDN were equipotent in increasing venous capacitance when administered in a bolus dose ratio of 1:8 during CPB, but the venodilator effect of ISDN lasted longer than that of TNG. The duration of the arteriolar dilator effect was very short with both drugs.

KEY WORDS

Organic nitrates are commonly given i.v. for the treatment of myocardial ischaemia and pulmonary and systemic hypertension, in addition to providing controlled hypotension in surgical patients [1, 2]. In general, nitrates have a predominant effect on the venous side of the vasculature, with less effect on arteries. Thus nitrates decrease cardiac filling pressures relatively more than systemic vascular resistance, arterial blood pressure and cardiac output. However, there are in vitro [3, 4] and in vivo [5] studies showing that various organic nitrates have different potency and selectivity in their effects on the venous and arterial beds, although the results are in part conflicting. In some situations, for example in the presence of increased myocardial oxygen consumption in association with systemic hypotension as a consequence of ischaemia-induced left ventricular failure and dilatation of the heart, it may be beneficial to give a nitrate which is more selective in its effect on the venous than on the arterial vascular bed. In man it is possible to evaluate concomitantly the venous/venular and arterial/arteriolar vascular effects of drugs during the constant flow conditions of cardiopulmonary bypass (CPB) by observing changes in the volume of blood returning into the venous reservoir and by measuring systemic arterial pressure, respectively [6-11]. In this study, we have compared the vasodilator properties of two organic nitrates available for i.v. use (nitroglycerin (TNG) and isosorbide dinitrate (ISDN)). These two nitrates have been reported to have a differing selectivity in their in vitro vascular effects [3].

PATIENTS AND METHODS
Patients
Forty-one patients were admitted originally to the study. They were studied double-blind after informed consent and Ethics Committee approval. They were allocated randomly to four groups to receive placebo (0.9% sodium chloride), TNG 200 µg (Nitro, Orion Pharmaceutica, Espoo, Finland), ISDN (Nitrosid, Pharmacal, Helsinki, Finland) 800 µg or ISDN 1600 µg. Chronic medication (long-acting nitrates, calcium channel blockers and beta adrenergic receptor blockers) was continued until the morning of surgery. Only patients meeting the following criteria were included in the study: absence of vasoactive drugs before or during the study; absence of mechanical problems in venous return during CPB; mean arterial pressure (MAP) 50-80 mm Hg at the time of the test drug administration; MAP less than 100 mm Hg during the study. On the basis of these criteria, 32 patients were studied; nine of the original 41 patients were excluded from the trial—three patients because of technical problems in venous return during CPB, mean arterial pressure (MAP) 50–80 mm Hg at the time of the test drug administration; MAP less than 100 mm Hg during the study. On the basis of these criteria, 32 patients were studied; nine of the original 41 patients were excluded from the trial—three patients because of technical problems in venous return, three because of hypertension during the study (MAP > 100 mm Hg) and three patients because of the need to give an additional dose of cardioplegic solution during the study.

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Anaesthesia

All patients were premedicated i.m. with hyoscine and morphine in doses of 6 and 200 µg kg⁻¹, respectively. Before induction of anaesthesia, intravascular catheters were inserted under local anaesthesia. Anaesthesia was induced with fentanyl 30 µg kg⁻¹ and diazepam 0.1 mg kg⁻¹. Tracheal intubation was facilitated with pancuronium 0.1 mg kg⁻¹. Anaesthesia was maintained with an infusion of fentanyl 0.3 µg kg⁻¹ min⁻¹ until the start of CPB, when the dose was reduced to 0.15 µg kg⁻¹ min⁻¹. During surgery before CPB, anaesthesia was supplemented with enflurane or halothane, and incremental doses of pancuronium were given when needed. After induction of anaesthesia, the lungs were ventilated mechanically with a mixture of oxygen and air (FIO₂ = 0.5) and normocapnia was maintained by monitoring end-tidal carbon dioxide concentration and by intermittent blood-gas analyses. During CPB the lungs were disconnected from the ventilator.

Cardiopulmonary bypass

The aorta and superior and inferior venae cavae were cannulated and the left ventricular decompression tube was introduced through a pulmonary vein. CPB was conducted with a semi-occlusive roller pump (Stöckert, Munich, FRG) and a bubble oxygenator (S100A, Shiley, Irvine, USA). The CPB circuit was primed with 2000 ml of Ringer's acetate-gluconate solution and heparin 5000 u. During CPB, heparin was given to maintain the activated clotting time greater than 480 s. A non-pulsatile pump flow of 2.4 litre min⁻¹ m⁻² was used during the cooling and rewarming phases. After achievement of moderate hypothermia (29 °C nasopharyngeal temperature), the pump flow was maintained at 1.8 litre min⁻¹ m⁻². Oxygen 1 litre per litre of pump flow, was added into the oxygenator. Myocardial protection during aortic cross-clamping was achieved with systemic hypothermia, topical cooling of the heart and cold crystalloid cardioplegic solution (Plegisol, Abbot, North Chicago, U.S.A.). The cardioplegic solution was given at 20-min intervals.

Study design

The study was undertaken during stable hypothermia between administration of two doses of cardioplegic solution and maintaining the blood flow and the left ventricular decompression force constant. MAP and the blood level in the reservoir (venous return) were measured. Although the pump flow was non-pulsatile in nature, a small pulse pressure, 10 mm Hg on average, was generated. MAP was determined from the mid-point of the pulse pressure curve. During the 15-min study, radial artery pressure was recorded continuously (Nihon Kohden, Tokyo, Japan) and venous return was noted at 1-min intervals. Before administration of the test drug, arterial pressure and venous return were monitored for 5 min. After this control period, one of the test drugs was given as a bolus dose from a glass syringe into the venous side of the CPB circuit and haemodynamic effects were recorded for 10 min. The drugs were dissolved in 10 ml of 0.9% saline solution.

Statistical analyses

Two-way analysis of variance (ANOVA) for repeated measures was used to assess the significance of overall haemodynamic changes between the groups. This assessment was used separately for the data of the control period and those of the study period proper. After this, the effects of each drug were compared with placebo by two-way analysis of variance. At each 1 min of the study period, the differences between the groups in changes in MAP and reservoir blood volume were tested with one-way analysis of variance. Frequencies were compared using one-way analysis of variance. Frequencies were compared with the χ² test. P < 0.05 was considered statistically significant. The results are presented as mean (SEM).
Table II. Study conditions before drug administration (mean (SEM)). TNG = Nitroglycerin; ISDN = isosorbide dinitrate

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>TNG 200 µg</th>
<th>ISDN 800 µg</th>
<th>ISDN 1600 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump flow</td>
<td>1.78 (0.03)</td>
<td>1.79 (0.02)</td>
<td>1.74 (0.05)</td>
<td>1.76 (0.03)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>64 (4)</td>
<td>66 (3)</td>
<td>62 (3)</td>
<td>73 (2)</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>30.3 (0.5)</td>
<td>30.8 (0.4)</td>
<td>29.7 (0.5)</td>
<td>30.9 (0.3)</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>27 (1)</td>
<td>26 (2)</td>
<td>24 (1)</td>
<td>25 (1)</td>
</tr>
<tr>
<td>Change during the 5-min control period</td>
<td>+7.5 (2.9)</td>
<td>+7.5 (2.1)</td>
<td>+7.5 (2.6)</td>
<td>+10.6 (2.2)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reservoir volume (ml)</td>
<td>-189 (46)</td>
<td>-216 (77)</td>
<td>-223 (37)</td>
<td>-173 (59)</td>
</tr>
</tbody>
</table>

DISCUSSION

The present study was performed to evaluate the vasodilator properties of bolus doses of TNG and ISDN during hypothermic CPB. We showed that TNG and ISDN, when administered in a dose ratio of 1:8, were equipotent in respect to the peak venodilator effect, but that the duration of effect was longer with ISDN. In this dose ratio, TNG caused more rapid arteriolar dilatation than ISDN.

Because the cardiac responses to changes in peripheral vascular tone are eliminated during CPB, this procedure allows the investigation of both arteriolar and venous effects of drugs in cardiac surgical patients. However, the use of CPB as a method of evaluating vascular effects of drugs requires steady state conditions. Therefore, we maintained pump flow constant during the measurements. Furthermore, no additional cardio-plegic solution was given between the two administrations of the study period and the suction force exerted on the left ventricular decompression tube was maintained constant. Particular attention was paid to eliminating technical problems with venous return by avoiding any major manipulation and positioning of the heart during the study. In addition, the trial was performed after reaching steady state hypothermia and the infusion of fentanyl was continued unaltered throughout the study. In spite of these efforts to stabilize conditions, there was a continuous increase in arterial pressure and a decrease in reservoir blood volume during CPB [6, 9], and therefore we compared our data with a control group. With this study design, acute changes in arterial pressure and venous return reflect drug-induced changes in vascular tone of arterial and venous beds, respectively.

Venodilatation is maximal with small doses of nitrates, only little additional dilatation occurring when the dose is increased [12]. Systemic arteries begin to dilate also with small doses but, in contrast to veins, arteries continue to dilate with increasing doses. Arteriolar dilatation occurs only with large doses of nitrates [12]. The increase in venous capacitance indicates decreased preload and reduction in heart size and ventricular wall tension. Arterial and arteriolar dilatation lead to a decrease in systemic arterial pressure and systemic vascular resistance [2, 12]. The decreases in preload and afterload cause a reduction in myocardial oxygen demand.

Change in mean arterial pressure (fig. 2)

TNG 200 µg decreased MAP more than the other drugs at 1 min after the drug bolus. At 2 min after injection, both TNG 200 µg and ISDN 1600 µg decreased MAP more than placebo. The effect of ISDN 800 µg on MAP was not significantly different from placebo.

2–4 min and ISDN 1600 µg at 2–10 min after drug administration. Although the overall decrease with time for ISDN 800 µg was significant compared with placebo according to two-way ANOVA, the exact timing of this decrease could not be determined by one-way ANOVA as analysed at each 1 min.

FIG. 1. Change in reservoir volume (venous return) after a bolus dose of placebo, nitroglycerin (TNG) and two doses of isosorbide dinitrate (ISDN).

FIG. 2. Change in mean arterial pressure (MAP) after a bolus dose of placebo, nitroglycerin (TNG) and two doses of isosorbide dinitrate (ISDN).
Further more, nitrates improve myocardial oxygen supply by dilating epicardial coronary arteries and by increasing subendocardial blood flow as a result of reduced ventricular wall tension [12]. All these changes improve myocardial oxygen balance and are beneficial for ischaemic heart.

The more sensitive response of veins and venules to nitrates compared with arteries and arterioles is evident in this study: the venous effect caused by nitrates lasted longer than that in the arterial bed and the venodilatory effect was significant with time also with the smaller dose of ISDN, while the pressure effect was not. The present study confirms our earlier observation that nitrates affect the venous side more than the arterial side of the vasculature during CPB, in spite of intra-arterial administration [6].

It is not clear if the venous responses to TNG 200 µg and ISDN 1600 µg were maximal. However, the acute venodilator response to ISDN 800 µg was less marked than that to ISDN 1600 µg or TNG 200 µg. Thus our results show that, on a weight basis, TNG is more than four times (possibly eight times) as potent as ISDN in its peak venodilator activity when given as a bolus during hypothermic CPB. Toyoda, Hisayama and Takayanagi [4] also found that the potency order of three nitrates in dilating isolated veins and arteries was TNG > ISDN > ISMN (isosorbide 5-mononitrate). The relative contributions of ISDN and its active metabolite, ISMN, to the vascular responses observed in the present study remain unclear. The greater potency of TNG as an arteriolar dilator compared with ISDN is supported by the findings of Durkin and associates [13], who compared the efficacy of TNG and ISDN infusions in the management of perioperative hypertension during coronary artery surgery. With a mean dose ratio of approximately 1:2, TNG was more successful than ISDN in decreasing arterial pressure.

There seem to be differences also in the selectivity of the effects of various nitrates on veins and arteries. Toyoda, Hisayama and Takayanagi [4] compared the relaxant effects of TNG, ISDN and ISMN on isolated femoral veins and arteries. All nitrates dilated both veins and arteries, but ISMN had the greatest venous selectivity. Stiefel and Kreye [3], studying the responses of isolated renal vessels of the rabbit, showed that ISDN and ISMN were 7–20 times more potent relaxants of veins than of arteries. The sensitivity of TNG was slightly greater in veins than arteries in small concentrations, but similar in veins and arteries in greater concentrations. Our results suggest that, in a dose ratio with about equipotent venodilator activity, TNG caused slightly more prominent decrease in arterial pressure than ISDN. This finding is consistent with those of Cintron and colleagues [14]. They administered TNG or ISDN to patients with acute myocardial infarction by an i.v. infusion in a mean dose ratio of approximately 1:4 and found that, after about 1 h of infusion with a similar decrease in pulmonary capillary wedge pressure and systolic arterial pressure, cardiac output had increased significantly more with TNG than with ISDN; this suggests that systemic vascular resistance may have decreased more with TNG than with ISDN. These results suggest that ISDN has a more selective action on venous vasculature than TNG. However, Rezakovic and colleagues [5], who compared TNG and ISDN in stoichiometrically equivalent doses by infusing them in a dose ratio 1:1.5 over 30 min in patients with acute myocardial infarction, found that TNG influenced predominantly pulmonary artery pressure and cardiac filling pressures, while ISDN affected cardiac output and systemic vascular resistance. They concluded that TNG is predominantly a venous dilator, while ISDN is a mixed vasodilator.

During the changing conditions of CPB, only short periods of relative stability are available for observation of drug effects. Therefore, we used bolus dose administration of drugs and our conclusions are applicable only to this mode of administration. Administering nitrates by an infusion would probably result in a different dose ratio, mainly because of the longer duration of action of ISDN/ISMN relative to TNG. Cintron and colleagues [14] found that, after producing a similar decrease in pulmonary capillary wedge pressure with TNG and ISDN in a dose ratio of 1:4 in patients with acute myocardial infarction, the maintenance of the decrease in the wedge pressure required progressive increase in TNG dosage, while the dose of ISDN remained essentially unchanged. Further, Davis and co-authors [15], giving continuous infusion of either TNG or ISDN during the prebypass period in patients undergoing coronary artery surgery, achieved a similar control of arterial pressure with a total dose ratio of approximately 1:1. Our results may have clinical significance, as a bolus dose of a nitrate may be a suitable way of rapidly increasing venous capacitance or decreasing systemic vascular resistance during the transient haemodynamic changes in patients undergoing CPB.


