EFFECT OF PROPOFOL ON PERIPHERAL VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

F. BOER, P. ROS, J. G. BOVILL, P. VAN BRUMMELEN AND J. VAN DER KROGT

SUMMARY

Twenty-eight patients undergoing elective coronary artery bypass surgery were allocated randomly to receive either propofol 2 mg kg\(^{-1}\) or an equivalent volume of its vehicle during cardiopulmonary bypass with constant pump flow. Peripheral vascular resistance (PVR) was calculated from perfusion pressure and pump flow. After propofol, PVR decreased from 1767 (SD 415) dyn s cm\(^{-5}\) to a minimum of 1263 (283) dyn s cm\(^{-5}\) at 2 min, and remained significantly less than the control value until 12.5 min after administration of propofol. In the group given the vehicle, PVR did not change significantly. In a second study in 10 patients, venous blood samples were withdrawn before and 2, 4, 6, 8, 10, 20 and 30 min after injection of propofol 2 mg kg\(^{-1}\) during cardiopulmonary bypass, for measurement of blood concentrations of propofol. Concentrations were greater than predicted by a computer simulation based on published pharmacokinetic data. The decrease in PVR may be an important factor in the hypotension caused by propofol during induction of anaesthesia.

KEY WORDS

Propofol, given as an i.v. bolus for induction of anaesthesia, commonly causes hypotension which is dose related, and is less when the drug is administered slowly [1]. Propofol appears to cause more hypotension than equivalent doses of thiopentone [1—3]. This may be related to the greater decrease in peripheral vascular resistance (PVR) caused by propofol [4]. The decrease in PVR is comparable to the decrease in arterial pressure, suggesting that vasodilatation may be a major factor in propofol-induced hypotension.

Other contributing factors may be a lesser increase in heart rate in response to hypotension and impairment of myocardial contractility. Propofol causes resetting of the baroceptor reflex control of heart rate without depression of baroreflex sensitivity [5]. This allows low heart rates to be sustained despite a decrease in arterial pressure. Both in patients without cardiac disease and in those with severe coronary artery disease, propofol causes about a 20% decrease in cardiac index [6—8] which is similar to that caused by thiopentone [7]. There is evidence that propofol does not alter left ventricular performance in patients with coronary artery disease and good left ventricular function [8]. However, other studies in cardiac surgical patients suggest that the drug may cause some myocardial depression in addition to vasodilatation [7, 9]. This may be secondary to a reduction in coronary artery blood flow consequent upon hypotension [10].

Cardiopulmonary bypass has been used as a model to study the isolated effects of drugs on the peripheral circulation [11—14]. We have used this model to investigate the effect of propofol on PVR in two consecutive studies. The first study was a double-blind comparison of the effects of propofol and its vehicle on PVR. In the second study, the changes in blood concentrations of propofol were measured also.

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PATIENTS AND METHODS

After informed consent had been obtained, we studied patients undergoing elective aorto-coronary bypass grafting surgery. Both studies were approved by the local Ethics Committee.

Study one

Twenty-eight patients were premedicated with lorazepam 2–4 mg sublingually, 90 min before arriving in the operating theatre. Anaesthesia was induced with sufentanil 4–8 µg kg⁻¹. Pancuronium 100 µg kg⁻¹ was given for muscle relaxation and, after intubation of the trachea, the lungs were ventilated with an oxygen–air mixture (FIO₂ = 0.5). Anaesthesia was maintained with sufentanil 0.05–0.1 µg kg⁻¹ min⁻¹, but during cardiopulmonary bypass the infusion of sufentanil was reduced to 0.025 µg kg⁻¹ min⁻¹. Cardiopulmonary bypass was conducted with a membrane oxygenator using non-pulsatile flow and moderate hypothermia (26–27 °C). The circuit prime consisted of Ringer’s solution 1400 ml, human albumin 200 ml and 20% mannitol 100 ml. In all patients, systemic arterial pressure measured in a radial artery was taken to indicate perfusion pressure during cardiopulmonary bypass.

Any patient who had been given a vasoactive drug before or during cardiopulmonary bypass was excluded from the study. When nasopharyngeal temperature and pump flow had been stable for 5 min during cardiopulmonary bypass, with a perfusion pressure greater than 50 mm Hg, a bolus of 0.2 ml kg⁻¹ of a coded solution containing either propofol 10 mg ml⁻¹ or Intralipid was injected over 30 s into the venous inflow line of the oxygenator. Perfusion pressure, pump flow and temperature were recorded at 30-s intervals for a minimum of 10 min. Measurements were continued until cardioplegic solution was given, the pump flow was changed, or the aortic clamp was released.

Venous blood samples were withdrawn for measurement of plasma concentrations of adrenaline and noradrenaline immediately before administration of the study drug and either at the time of maximum decrease of perfusion pressure or 5 min after administration of drug. A 3-ml blood sample was placed in a cooled tube containing 60 µl of a solution of reduced glutathione 60 mg ml⁻¹ and EDTA 50 mg ml⁻¹. The samples were stored in melting ice and the plasma separated within 15 min in a refrigerated centrifuge (4 °C). Plasma was stored at −20 °C until assayed. Catecholamines were assayed radioenzymatically [15].

Study two

This study involved 10 patients. The technique of anaesthesia and cardiopulmonary bypass and the pre-study conditions were the same as those for study one. When stable conditions had been present during cardiopulmonary bypass for 5 min, propofol 2 mg kg⁻¹ was injected over 30 s into the venous inflow line of the oxygenator. Perfusion pressure, pump flow and temperature were measured as described above.

Venous blood samples were withdrawn from the internal jugular vein before and 2, 4, 6, 8, 10, 20 and 30 min after injection of propofol for measurement of blood concentrations. Samples were stored at 4 °C until assayed. Propofol concentrations were measured in blood by a modification of the method described by Adam and colleagues [16, 17].

PVR was calculated as:

\[
\text{PVR} = \frac{\text{Perfusion pressure (mm Hg)} \times 80 \text{ dyn s cm}^{-6}}{\text{Pump flow (litre min}^{-1})}
\]

Data were analysed by two-way analysis of variance for repeated measures. When indicated, differences within or between groups were tested using paired and unpaired t tests with Bonferroni correction for multiple comparisons. P < 0.05 was accepted as statistically significant. Results are presented as mean (SD).

RESULTS

There were no significant differences in patient data, pre-drug pump flow, perfusion pressure, PaO₂ or packed cell volume between the two groups of patients in study one, or between patients in the two studies (table I).

Study one

Data were collected from all patients for 8 min after administration of propofol, and in 10 patients for 12.5 min. In the Intralipid group, data were collected from all patients for 6 min and from 10 patients for 8.5 min. Following administration of propofol, PVR decreased, reaching a minimum value of 1263 (283) dyn s cm⁻⁶ at 2 min. This was
TABLE I. Demographic data and pre-drug conditions in studies one and two (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Study one</th>
<th>Study two</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>60.4 (6.6)</td>
<td>64.4 (9.3)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>81.8 (13.0)</td>
<td>76.1 (8.2)</td>
</tr>
<tr>
<td><strong>BSA (m²)</strong></td>
<td>1.94 (0.175)</td>
<td>1.89 (0.15)</td>
</tr>
<tr>
<td><strong>Perfusion pressure (mm Hg)</strong></td>
<td>65.8 (10.9)</td>
<td>68.9 (8.9)</td>
</tr>
<tr>
<td><strong>Flow (litre min⁻¹)</strong></td>
<td>3.16 (0.29)</td>
<td>3.16 (0.13)</td>
</tr>
<tr>
<td><strong>P*o₂ (kPa)</strong></td>
<td>22.3 (9.7)</td>
<td>19.7 (6.9)</td>
</tr>
<tr>
<td><strong>PCV</strong></td>
<td>0.26 (0.03)</td>
<td>0.26 (0.03)</td>
</tr>
</tbody>
</table>

Fig. 1. Peripheral vascular resistance (PVR) after propofol 2 mg kg⁻¹ (•) or an equivalent volume of its vehicle (△) during cardiopulmonary bypass for aortocoronary bypass surgery.

significantly (P < 0.001) less than the average of values obtained in the 4 min before administration of drug (control value: 1767 (415) dyn s cm⁻⁶). PVR remained significantly less than the control value until 12.5 min after administration of propofol, but did not change significantly during the 10-min observation period following administration of Intralipid (fig. 1). There were no changes in plasma concentration of adrenaline or noradrenaline in each group (table II).

TABLE II. Plasma concentrations of adrenaline and noradrenaline (mean (SD)) before and after administration of propofol 2 mg kg⁻¹ or an equivalent volume of its vehicle (Intralipid). Blood samples for the measurement of post-drug concentrations were taken either at time of maximum decrease in perfusion pressure or at 5 min after administration of drug

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Intralipid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenaline (pmol ml⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>2.4 (2.2)</td>
<td>1.7 (1.5)</td>
</tr>
<tr>
<td>After</td>
<td>1.8 (1.5)</td>
<td>1.6 (1.4)</td>
</tr>
<tr>
<td><strong>Noradrenaline (pmol ml⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>3.0 (2.0)</td>
<td>4.1 (2.5)</td>
</tr>
<tr>
<td>After</td>
<td>2.5 (1.3)</td>
<td>3.6 (2.3)</td>
</tr>
</tbody>
</table>

TABLE III. Mean (SD) changes in peripheral vascular resistance (PVR) following propofol 2 mg kg⁻¹ in the two studies

<table>
<thead>
<tr>
<th>Time relative to administration (min)</th>
<th>Change in PVR (dyn s cm⁻⁶)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study one</td>
</tr>
<tr>
<td>Control</td>
<td>1767 (415)</td>
</tr>
<tr>
<td>2</td>
<td>1263 (283)</td>
</tr>
<tr>
<td>4</td>
<td>1328 (320)</td>
</tr>
<tr>
<td>6</td>
<td>1302 (330)</td>
</tr>
<tr>
<td>8</td>
<td>1310 (312)</td>
</tr>
<tr>
<td>10</td>
<td>1373 (235)</td>
</tr>
</tbody>
</table>
Fig. 2. Whole blood concentrations of propofol in 10 patients at timed intervals after administration of propofol 2 mg kg\(^{-1}\) during cardiopulmonary bypass for aortocoronary bypass surgery (—). The thicker, continuous line (—) is the change in propofol concentration following the same dose predicted by a computer simulation based on pharmacokinetic data [18].

**Study two**

The changes in PVR following administration of propofol were similar to those in study one (table III).

The changes in blood concentrations of propofol for individual patients are shown in figure 2. Initially, they decreased rapidly, presumably as a result of distribution, and then from about 6 min decreased more slowly. In all patients, blood concentrations of propofol from 8 min after administration were greater than that predicted by the pharmacokinetic model described by Gepts and colleagues [18].

**DISCUSSION**

Haemodynamic changes after induction of anaesthesia are the result of both direct and indirect effects on the myocardium and peripheral blood vessels. The indirect effects are mediated by changes in peripheral receptors and central control mechanisms. Under normal circumstances, it may be difficult to isolate the contribution that individual mechanisms make to the overall haemodynamic response to a drug. Cardiopulmonary bypass has been shown to be a useful model for studying the isolated effects of anaesthetic drugs on PVR; it has been used to study the effect of morphine [11], benzodiazepines [12], droperidol [13] and thiopentone [14]. Using this model, we have found that propofol 2 mg kg\(^{-1}\), given during cardiopulmonary bypass under stable conditions of perfusion pressure, flow and temperature, caused a rapid decrease of 28% in perfusion pressure and thus of PVR. This decrease is comparable to that observed in studies when propofol was given for induction of anaesthesia. Propofol 2 mg kg\(^{-1}\) given to patients undergoing elective general surgery caused a 18–22% decrease in PVR [19]. When propofol 1.5 mg kg\(^{-1}\) was used to induce anaesthesia in patients undergoing elective coronary artery bypass surgery, PVR decreased by 19% [20].

Studies of the effects of drugs on peripheral vascular tone commonly rely on estimates of vascular resistance, based on the ratio of pressure and flow (cardiac output), before and after drug administration. Valid conclusions based on these estimates depend on the assumption of a linear pressure–flow relationship that passes through the origin. This is often not the case [21], so that isolated resistance calculations cannot discriminate between changes in pressure caused by active changes in vascular tone and passive changes resulting from altered venous return [22]. However, this does not apply to our model in which flow is independent of venous return. Furthermore, all our studies were performed during constant flow rate conditions.

In our first study, the decrease in PVR caused by propofol lasted for more than 10 min. This is in contrast to other studies, in which the reduction in PVR was of short duration. However, in those studies patients underwent laryngoscopy and intubation of the trachea within a few minutes after administration of propofol. It is possible that, had this not occurred, the decrease in PVR would have been more prolonged. A possible explanation of the prolonged reduction of PVR in our patients could be altered propofol pharmacokinetics during cardiopulmonary bypass, resulting in greater concentrations in blood than would occur after the same dose given for induction of anaesthesia. In order to investigate this, we studied the changes in concentration of propofol following a bolus injection of propofol 2 mg kg\(^{-1}\) in a second group of patients. Although our results did not allow detailed pharmacokinetic analysis, they suggest that blood concentrations of propofol decreased more slowly during bypass than in patients given a similar dose of propofol for induction of anaesthesia.

It is reasonable to assume that the direct effects of propofol on vascular smooth muscle are proportional to its concentration in blood. The
greater blood concentration of propofol in our patients compared with those predicted in patients not subjected to cardiopulmonary bypass, may partly explain the prolonged reduction in PVR. Cardiopulmonary bypass is known to alter significantly the disposition of many drugs as a result of haemodilution, hypotension, hypothermia and altered regional blood flow [23]. It is also possible that hypothermia (26–27 °C) may have altered the sensitivity of vascular smooth muscle to the effects of propofol. The use of non-pulsatile flow also may have contributed to the duration of the resistance decrease. Videcoq and colleagues [13] found that the decrease in vascular resistance produced by droperidol was of shorter duration with pulsatile flow.

Propofol is a weak organic acid that is bound extensively to plasma albumin, with a free fraction of only 2–3 % [24]. Haemodilution during cardiopulmonary bypass is associated with proportional decreases in the concentrations of plasma proteins, and a 1.5–3 fold increase in the fraction of unbound propofol [25]. An increased free fraction of propofol could have contributed to the prolonged effect observed in our patients. The use of heparin during cardiopulmonary bypass causes an increase in non-esterified fatty acids because of activation of lipoprotein lipase [26]. Non-esterified fatty acids are thought to be responsible for the decrease in drug binding to plasma proteins after heparin [27]. This could be an additional explanation for our findings.

Unfortunately, because of the type of bypass circuit used in our study, we were not able to evaluate the effect of propofol on capacitance vessels. However, the finding that perfusion pressure and thus PVR decreased significantly after administration of propofol, with perfusion flow maintained constant, implies that propofol caused arteriolar vasodilatation. This could have been secondary to a reduction in sympathetic outflow caused by deepening of anaesthesia. However, the fact that catecholamine concentration did not change suggests that the haemodynamic effect of propofol was the result of direct action on blood vessels.

Although our results confirm the importance of changes in PVR to the overall haemodynamic response to propofol, they cannot be extrapolated directly to other clinical situations. Our results have been influenced by the special factors present during cardiopulmonary bypass, in particular haemodilution, hypothermia and the use of non-pulsatile blood flow. These should be taken into consideration when interpreting the findings of this study.

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REFERENCES


