DISPOSITION OF PROPOFOL AT CAESAREAN SECTION AND IN THE POSTPARTUM PERIOD

T. GIN, G. YAU, W. JONG, P. TAN, R. K. W. LEUNG AND K. CHAN

SUMMARY

We have compared the pharmacokinetics of a bolus dose of propofol 2 mg kg⁻¹ in eight patients undergoing Caesarean section with those in eight postpartum patients undergoing sterilization by mini-laparotomy. The Caesarean section group had a total body clearance of (median) 31.5 (range 24.4-53.3) ml min⁻¹ kg⁻¹, apparent volume of distribution at steady state 5.10 (2.46-6.61) litre kg⁻¹ and mean residence time 161 (52.3-251) min; values for the postpartum group were 33.8 (21.5-47.2) ml min⁻¹ kg⁻¹, 5.17 (3.47-8.09) litre kg⁻¹ and 163 (92.3-238) min, respectively. The 95% confidence interval for the umbilical venous to maternal venous ratio of propofol at delivery was 0.62-0.86. Plasma protein binding studies showed there was less unbound propofol in maternal plasma (1.28-2.29%) compared with umbilical plasma (2.08-3.88%) (P < 0.01). Neonatal concentrations of propofol were greater than maternal concentrations at 2 h and were in the range 0.05-0.11 µg ml⁻¹ at 4 h.

KEY WORDS

Propofol has been used for induction and maintenance of anaesthesia during Caesarean section because of the potential for rapid maternal and neonatal recovery [1-6]. Some studies using larger doses of propofol have reported lower Apgar and neurobehavioural assessment scores in neonates [1, 7]. Concentrations of propofol in neonatal heel prick blood samples 2 h after delivery were small [4], but there are no data on the protein binding or neonatal elimination of propofol.

The total body clearance of propofol was found to be increased in patients undergoing Caesarean section compared with non-pregnant patients undergoing laparoscopic operations [8]. The increase in clearance may have been caused by removal of fetal and placental tissues at operation, or by the physiological changes of pregnancy, with increased cardiac output or enzyme induction leading to increased metabolism of propofol.

Women in the immediate postpartum period possess many of the physiological changes of pregnancy [9, 10], but do not have the blood loss, fluid replacement and loss of fetal compartment that complicate pharmacokinetic analysis in women undergoing Caesarean section. A pharmacokinetic study of propofol in postpartum patients may provide clues to determine the cause of the increased clearance found at Caesarean section.

PATIENTS AND METHODS

The study was approved by the Research Ethics Committee of the Chinese University Faculty of Medicine and informed consent was given by all patients. We studied eight healthy patients with uncomplicated, singleton pregnancies for elective Caesarean section and eight ASA I patients, 2-3 days postpartum, for sterilization by mini-laparotomy tubal ligation.

In both groups, ranitidine 150 mg was given the night before and on the morning of surgery, with 0.3-mol litre⁻¹ sodium citrate 30 ml given 15 min...
before operation. Routine monitoring included pulse oximetry and end-tidal capnography. Patients underwent preoxygenation for 3 min before rapid sequence induction of anaesthesia with propofol 2 mg kg\(^{-1}\) over 20 s followed by suxamethonium 1.5 mg kg\(^{-1}\). After tracheal intubation, neuromuscular block was maintained with atracurium 0.5 mg kg\(^{-1}\). In the Caesarean section group, anaesthesia was maintained with 50% nitrous oxide and 1% enflurane in oxygen. At delivery, the inspired gas mixture was changed to 70% nitrous oxide and 0.5% enflurane in oxygen, an oxytocin infusion was started and morphine 0.2 mg kg\(^{-1}\) given i.v. The postpartum patients received 70% nitrous oxide and 1% enflurane in oxygen throughout the operation and no opioid drugs were administered.

Venous blood samples (2 ml) were taken before induction and at 2, 4, 6, 8, 10, 20, 30, 60, 120, 240, 360, 480 and 600 min in both groups. Additional maternal venous (MV), umbilical venous (UV) and umbilical arterial (UA) blood samples were taken at delivery in the Caesarean section group. Venous blood samples were taken from the neonate at times that coincided with the maternal samples. Neonatal blood samples were taken at 30, 60 and 120 min (n = 4), 30, 60 and 240 min (n = 2) or 30, 120 and 240 min (n = 2). Blood concentrations of propofol were measured by high pressure liquid chromatography with fluorescence detection as described previously [8]. The blood concentration–time profiles of propofol were analysed according to a model independent method [11] to give the following pharmacokinetic variables: apparent volume of distribution at steady state (V\(^{\text{app}}\)), mean residence time, elimination half-life (\(T_{\text{1/2}}\)) and total body clearance. Non-compartmental analysis was used because the removal of fetal and placental tissues at Caesarean section would have an unpredictable effect on a compartmental model [8].

Protein binding studies were carried out by equilibrium dialysis using a Dianorm apparatus (Diachem AG, Zurich, Switzerland). Plasma samples (1 ml) containing propofol were dialysed against 0.067-mol litre\(^{-1}\) phosphate buffer made isotonic with sodium chloride 1 ml (pH 7.4) without propofol in Teflon dialysis chambers separated by a Spectrapor dialysis membrane. An equilibrium between the two sides of the dialysis membrane was attained within 4 h at 37 °C with a rotation speed of 12 r.p.m. The samples were analysed for propofol content to give the percentage of protein bound and free propofol in plasma.

Neonates were assessed by cord blood-gas analysis, Apgar scores at 1 and 5 min and Neurologic and Adaptive Capacity Scores (NACS) at 15 min, 2 h and 24 h.

Between group comparisons were made using the Mann–Whitney test for the derived pharmacokinetic variables and the unpaired \(t\) test for measured data. The paired \(t\) test was used to compare maternal with neonatal concentrations of propofol. Results are expressed as mean (SD); \(P < 0.05\) was considered significant.

**RESULTS**

The patients in the Caesarean section group (27.4 (4.3) yr and 72.5 (9.1) kg) were heavier than those in the postpartum group (30.8 (4.3) yr and 62.0 (11.8) kg) \((P < 0.05)\). Duration of anaesthesia was shorter in the postpartum group (30.2 (8.7) min) compared with the Caesarean section group (43.1 (6.2) min) \((P < 0.01)\).

The concentration of propofol declined with time, but secondary peaks were observed in 11 patients shortly after the end of anaesthesia (fig. 1). Propofol was not detectable at 600 min in three patients in the Caesarean section group. Pharmacokinetic variables were similar between the groups (table I).

![Graph showing venous blood propofol concentrations](https://academic.oup.com/bja/article-abstract/67/1/49/283887/fig1)
TABLE I. Median (range) pharmacokinetic variables for patients undergoing Caesarean section or postpartum sterilization. \( V^* \) = Volume of distribution at steady state; \( CI \) = clearance; \( MRT \) = mean residence time; \( T^\beta \) = elimination half-life

<table>
<thead>
<tr>
<th></th>
<th>Caesarean section</th>
<th>Postpartum sterilization</th>
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<tbody>
<tr>
<td>( V^* ) (litre kg(^{-1}))</td>
<td>5.10 (2.46–6.61)</td>
<td>5.17 (3.47–8.09)</td>
</tr>
<tr>
<td>( CI ) (ml kg(^{-1}) min(^{-1}))</td>
<td>31.5 (24.4–53.3)</td>
<td>33.8 (21.5–47.2)</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>161 (52.3–251)</td>
<td>163 (92.3–238)</td>
</tr>
<tr>
<td>( T^\beta ) (min)</td>
<td>170 (60.7–275)</td>
<td>211 (117–345)</td>
</tr>
</tbody>
</table>

TABLE II. Total whole blood concentration of propofol and plasma protein binding data from maternal vein (MV), umbilical vein (UV) and umbilical artery (UA) at delivery. CI = Confidence interval

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV (µg ml(^{-1}))</td>
<td>0.79</td>
<td>0.24</td>
<td>0.54–1.21</td>
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<tr>
<td>UV (µg ml(^{-1}))</td>
<td>0.58</td>
<td>0.20</td>
<td>0.33–0.84</td>
<td></td>
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<tr>
<td>UA (µg ml(^{-1}))</td>
<td>0.60</td>
<td>0.14</td>
<td>0.47–0.89</td>
<td></td>
</tr>
<tr>
<td>UV MV</td>
<td>0.74</td>
<td>0.14</td>
<td>0.50–0.92</td>
<td>0.62–0.86</td>
</tr>
<tr>
<td>UA/UV</td>
<td>1.10</td>
<td>0.28</td>
<td>0.77–1.51</td>
<td>0.86–1.33</td>
</tr>
<tr>
<td>Unbound propofol (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>UV plasma</td>
<td>3.12</td>
<td>0.74</td>
<td>2.08–3.88</td>
<td></td>
</tr>
<tr>
<td>MV plasma</td>
<td>1.75</td>
<td>0.36</td>
<td>1.28–2.29</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Pharmacokinetic variables for propofol in patients undergoing Caesarean section were similar to those in patients during the immediate postpartum period. There was reduced protein binding of propofol in fetal plasma compared with maternal plasma. The concentration of propofol in the neonate exceeded that in the mother by 2 h and this suggested that the elimination of propofol was slower in the neonate than in the mother.

Studies in postpartum patients may indicate the effect of late pregnancy on the pharmacokinetics of some drugs, even though these patients are no longer pregnant. Postpartum patients retain many of the physiological changes of pregnancy, some of which take up to 6 weeks to return to normal [9, 10]. In contrast with the pregnant patient at term, the puerperal patient no longer carries the fetus and placenta; however, these tissues contribute little to overall maternal drug metabolism and the absence of fetal and placental tissues should not have a significant effect on calculations of maternal \( V^* \) if pharmacokinetic variables are corrected for body weight and if the \( V^* \) is large for the drug being studied.

The puerperal period itself is also of interest, as patients may require anaesthesia and changes in the duration of action of some drugs have been reported. The decrease in pseudocholinesterase activity is greatest at this time [12] and the clinical duration of action of vecuronium was found to be longer in postpartum patients compared with non-pregnant patients [13].
The values for $V^{ss}$ and $T_\frac{1}{2}$ in the Caesarean section group are within the range of that found in other studies, but greater than that reported in our previous study [8] because the sampling period was longer in the present study [14]. The effect of different sampling periods generates uncertainty regarding the true pharmacokinetic values, with one study reporting a mean $V^{ss}$ of 771 litre and a $T_\frac{1}{2}$ of 674 min in young patients when a sampling time of 24 h was used [15]. However, this terminal $T_\frac{1}{2}$ is not directly comparable with our $T_\frac{1}{2}$ because the variables were calculated by different methods. The $T_\frac{1}{2}$ relates also to very small, clinically insignificant concentrations of propofol being redistributed back to the central compartment after a single bolus dose, and the effect of this terminal portion on the area under the concentration-time curve and subsequent calculations of clearance would be very small. A change in volume of distribution during pregnancy affects calculations of elimination half-life, so it is a less reliable index of the rate of metabolism and clearance is a more meaningful indicator [16].

The mean values for clearance of propofol in non-pregnant subjects are more consistent among studies, including those with long sampling times, but less than that found in our peripartum patients. The clearance in the non-pregnant group in our previous study (mean 1.57 litre min$^{-1}$) [8] was less than that in the Caesarean section group in this study ($P < 0.05$), but not significantly less than the clearance in the postpartum group ($P = 0.16$). Unfortunately, differences in methodology between the two studies render further conclusions difficult. Nevertheless, given the almost identical results between the two groups in this study, we believe that a trial with larger sample sizes may show that the pharmacokinetics of propofol in postpartum patients are closer to those in patients undergoing Caesarean section than those in non-pregnant patients.

We have postulated that pharmacokinetics in women undergoing Caesarean section may be influenced by both the physiological changes of pregnancy and the operative procedure. The findings in this study imply that the blood volume changes and loss of placental and fetal compartments at Caesarean section do not have a significant effect on the pharmacokinetics of propofol in women during the peripartum period. The increased clearance may be related to an increase in the extrahepatic metabolism of propofol by enzyme induction or increased blood flow to other organs where metabolism is suspected to occur. Another possibility is that the increased cardiac output in pregnancy may redistribute propofol back more quickly from peripheral tissues for metabolism as the terminal elimination of propofol is constrained normally by the slow return of propofol from peripheral compartments.

Maternal and fetal proteins have similar drug binding affinity and differences in concentrations of binding proteins or displacing substances are responsible for the fetal to maternal distribution of drugs at steady state [17]. Lower protein binding in the fetus is seen usually with basic drugs which bind to $\alpha_1$-acid glycoprotein. However, the situation is more complex and uncertain with propofol, as it is a very weak acid which binds to red blood cells and to plasma proteins. UV: MV and UA: UV ratios of propofol concentrations were similar to those reported and discussed in previous studies [2, 18]. The elimination of propofol in the neonate appears to be slower than that in the mother, but this is to be expected with most drugs, including thiopentone [19]. The $V^{ss}$ for propofol in the neonate has not been determined, but $V^{ss}$ is usually increased in neonates compared with adults [20]. It is likely that clearance of propofol may be decreased also, as neonatal glucuronidation is developed poorly, despite a sulphation activity which is similar to that found in adults [20]. Nevertheless, the neonatal concentrations of propofol were very small and neonatal assessment was satisfactory.

REFERENCES


