Propofol: A New Intravenous Anesthetic

Peter S. Sebel, M.B., B.S., Ph.D., FFARCSI,* Jane D. Lowdon, M.D.†

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Propofol is a new intravenous anesthetic agent chemically unrelated to barbiturate, steroid, imidazole, or eugenol agents. It is one of a series of alkyl phenols, found to have anesthetic properties in animals.1 The structure of propofol, 2,6-diisopropylphenol (ICI 35868) is shown in figure 1. It is also known as Diprivan (trade name) and was previously known as disiproflo. The group of hindered phenolic compounds, of which propofol is one, exists as oils at room temperature. These compounds can

* Associate Professor of Anesthesiology.
† Research Fellow.

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Address reprint requests to Dr. Sebel: Associate Professor of Anesthesiology, Emory University School of Medicine, 1564 Clifton Road, NE, Atlanta, Georgia 30322.

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be administered intravenously in aqueous solution with the solubilizing agent Cremophor EL (polyoxyethylated castor oil) or other similar substance. Initial studies were carried out using a 2% formulation in 10% Cremophor EL, then a 1% solution in 16% Cremophor EL. Due to a high incidence of pain on injection, and to the association between Cremophor EL and anaphylactoid reactions2,3 and one reported case of an anaphylactoid reaction,4 an alternative formulation of propofol in 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide, is now available. This review deals exclusively with the emulsion formulation unless specifically noted.

Pharmacology

Animal Data

The anesthetic activity of propofol in Cremophor formulation was investigated in a variety of species (mice, rats, rabbits, cats, pigs, monkeys).5 Propofol was found to produce rapid onset of anesthesia, and a sleeping time similar to that obtained with thiopental and slightly longer than that obtained with methohexitol. Mice regained coordination following propofol much more rapidly than following thiopental. In the pig, propofol produced a decrease in mean arterial pressure similar to that produced by thiopental. It was found to have no effect on bronchomotor tone. Excessive doses of the drug (20 mg/kg) in the cat produced severe hypotension; however, the cat survived. EEG changes produced by propofol in the rat indicated that the drug produced profound but rapidly reversible depression of cerebral activity at the anesthetic dose. It was also used with a variety of preanesthetic medications, inhalational agents, and neuromuscular blocking drugs, and no unexpected interactions were observed.6

A slight decrease in activity of the emulsion formulation in mice and rats suggested that the preparation may prove to be somewhat less potent than the Cremophor formulation. The behavioral effects in rats also suggested that there was less discomfort on injection of the emulsion form. In contrast to the Cremophor formulation, the emulsion formulation of propofol did not result in any histamine release in dogs or in the minipig.6
In further studies of the effects of propofol in animals, Glen and colleagues found that propofol had no anticonvulsant effects, in contrast to thiopental. No potentiation of propofol anesthesia was found following pretreatment with diazepam or alcohol. It was found to be inactive orally in mice. Acute administration of beta-receptor antagonist was tolerated during anesthesia with propofol. Propofol was found to have no effect on ADP-induced platelet aggregation or whole-blood clotting time. Similarly, bronchomotor tone and gastrointestinal motility were unaffected. Propofol has been used for total intravenous anesthesia in the horse and in the dog.

**Pharmacokinetics and Pharmacodynamics**

A multicenter study determined that the dose of propofol required to induce anesthesia measured by loss of eyelash reflex in 95% of healthy unmedicated patients was 2.5 mg/kg. The range of induction times was 22–125 s. Several authors have conducted pharmacokinetic analysis using the emulsion formulation following a single bolus injection of propofol, in volunteers, normal patients, heptatically, and renally impaired patients. These data are summarized in table 1. The decay of propofol concentration in blood plasma decay following a single intravenous injection in both young and elderly patients is shown in figure 2.13 The pharmacokinetic profile of propofol in emulsion formulation can be described by the sum of three exponential functions. Generally, clearance exceeds the capacity of the liver blood supply, suggesting that extrahepatic mechanisms contribute to the clearance of propofol from blood.

When a subanesthetic dose of C-labelled propofol was administered to volunteers, 88% of the radioactivity was excreted in the urine, while the feces contained less than 2%. Less than 0.3% was excreted unchanged, the remainder consisting of the 1 and 4 glucuronide and 4-sulfate conjugates. In patients with renal or hepatic (cirrhotic) disease, no statistically significant alterations in pharmacokinetic parameters were found, suggesting propofol can be used in both groups of patients. In the elderly patient, the clearance of propofol was significantly lower than in the younger patient. The volume of the central compartment in the elderly patient was also significantly smaller than in the younger patient. There were no differences in the volumes of distribution at steady-state or in the half-lives of distribution and elimination; these pharmacokinetic differences can be explained by decreases in cardiac output and hepatic blood flow in the elderly. These findings would suggest that propofol be used in reduced doses in the elderly, and this is borne out by clinical experience. Lower induction doses of propofol (1.25–2.25 mg/kg, compared with 1.5–3.0 mg/kg) are required in the elderly.

The interaction of continuous infusion of propofol (6 mg·kg⁻¹·h⁻¹) and alfentanil (target 300 ng/ml) have been studied. The disposition kinetics of propofol are unaffected by the administration of alfentanil. However, the plasma alfentanil concentration was significantly higher than expected values during the infusion. The authors suggest that coadministration of propofol with alfentanil may affect alfentanil kinetics either by a decrease in the volume of distribution or by decreased elimination. They did not, however, use a control group who

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**Table 1. Pharmacokinetics of a Single Bolus Injection of Propofol**

<table>
<thead>
<tr>
<th>Number of Volunteers</th>
<th>Subgroup</th>
<th>(t_{1/2a}) (min)</th>
<th>(t_{1/2b}) (min)</th>
<th>(t_{1/2c}) (min)</th>
<th>Clearance (ml/min)</th>
<th>Central Compartment Volume (l)</th>
<th>Volume of Distribution (l)</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td>2.3 ± 0.2</td>
<td>50 ± 3</td>
<td>286 ± 36</td>
<td>1.8 ± 0.13</td>
<td>39.2 ± 5.7</td>
<td>755 ± 109</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>N₂O/O₂</td>
<td>2.9 ± 0.7</td>
<td>45 ± 5</td>
<td>284 ± 40</td>
<td>1.9 ± 0.37</td>
<td>41.3 ± 13.0</td>
<td>722 ± 34</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Fentanyl</td>
<td>1.8 ± 0.6</td>
<td>34 ± 8</td>
<td>208 ± 30</td>
<td>1.3 ± 0.05</td>
<td>21.8 ± 6.7</td>
<td>387 ± 59</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>Halothane</td>
<td>4.1 ± 2.6</td>
<td>34 ± 6</td>
<td>184 ± 15</td>
<td>1.8 ± 0.27</td>
<td>34.5 ± 0.1</td>
<td>460 ± 57</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>Young</td>
<td>2.04 ± 0.27</td>
<td>52.4 ± 9.2</td>
<td>674 ± 122</td>
<td>1.8 ± 0.12</td>
<td>25.3 ± 2.9</td>
<td>771 ± 236</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>Elderly</td>
<td>1.84 ± 0.25</td>
<td>69.3 ± 8.7</td>
<td>834 ± 170</td>
<td>1.4 ± 0.09</td>
<td>19.6 ± 5.2</td>
<td>691 ± 139</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>1.4 ± 0.1</td>
<td>21.0 ± 9.0</td>
<td>226 ± 52</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>2.8 ± 1.0</td>
<td>39.0 ± 9.0</td>
<td>404 ± 119</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>Normal</td>
<td>3.2 ± 1.3</td>
<td>37.0 ± 10</td>
<td>249 ± 56</td>
<td>2.2 ± 0.6</td>
<td>0.5 ± 0.5*</td>
<td>11.8 ± 2.4*</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>Normal</td>
<td>2.9 ± 0.7</td>
<td>39.0 ± 18</td>
<td>315 ± 70</td>
<td>1.7 ± 0.6</td>
<td>0.4 ± 0.2*</td>
<td>12.5 ± 6.8*</td>
<td>14</td>
</tr>
<tr>
<td>Volunteers 6</td>
<td></td>
<td>8</td>
<td>109</td>
<td>—</td>
<td>2.2</td>
<td>76</td>
<td>322</td>
<td>15</td>
</tr>
</tbody>
</table>

Data are mean ± SD.  

* Data are 1/kg.
received alfentanil alone. Thus, their interpretation is open to doubt. Using bolus pharmacokinetic data to predict infusion regimes may result in a different plasma drug concentration than predicted.‡

Pharmacokinetic modelling, using microprocessor-controlled infusions to produce linearly increasing propofol levels, have been assessed judging the hypnotic effect by clinical signs and electroencephalographic behavior. Measured propofol concentrations during the infusion were higher than those predicted by pharmacokinetic data obtained after bolus injection. This may suggest that propofol has a smaller volume of distribution and a lower total body clearance than detected by pharmacokinetic analysis following bolus injection. Alternatively, the pharmacokinetic data used in the program for the computer controller may have been inappropriate for the infusion approach utilized.

The dose requirements of propofol by infusion during nitrous oxide anesthesia in man have been studied with both morphine and lorazepam premedication. The data are shown in table 2. The effective dose of drug to stop movement on skin incision in 95% of patients was higher in patients premedicated with lorazepam (20.9 mg · kg⁻¹ · h⁻¹) than those receiving morphine premedication (6.7 mg · kg⁻¹ · h⁻¹). These infusion rates are higher than might be expected in general clinical practice because no intraoperative opioid supplementation was administered.

**CARDIOVASCULAR EFFECTS**

The cardiovascular effects of propofol were investigated in four different studies of premedicated patients. An induction dose of 2 mg/kg resulted in a statistically significant decrease in systolic blood pressure of approximately 30% (table 3). The changes in heart rate were variable and insignificant. Cardiac output decreased, but the decrease (approximately 30%) was statistically significant in only two studies, and only during steady-state anesthesia before surgical stimulation. In one of the studies, patients sustained a significant reduction in vascular resistance (21%). Stroke volume did not change significantly. Claes and coworkers concluded that the major hemodynamic effect of propofol was a decrease in arterial pressure, and that blood pressure decreased because of lowered systemic vascular resistance, not because of reduced stroke volume or cardiac output.

The effects of propofol on the baroreceptor reflex show...
TABLE 2. Propofol Dose Requirements to Supplement Nitrous Oxide Anesthesia

<table>
<thead>
<tr>
<th>Premedication</th>
<th>(ED_{50}) mg·kg(^{-1})·hr(^{-1})</th>
<th>(ED_{95}) mg·kg(^{-1})·hr(^{-1})</th>
<th>Propofol Conc at Incision at (ED_{50}) (\mu g/ml)</th>
<th>Propofol Conc at Incision at (ED_{95}) (\mu g/ml)</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>3.2</td>
<td>6.7</td>
<td>1.66</td>
<td>3.39</td>
<td>20</td>
</tr>
<tr>
<td>0.15 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>7.8</td>
<td>20.9</td>
<td>2.5</td>
<td>5.92</td>
<td>21</td>
</tr>
<tr>
<td>0.04 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

that propofol does reset the baroreceptor reflex to allow slower heart rates, despite a decrease in arterial pressure.\(^{26,27}\) Propofol appears not to affect the baroreflex sensitivity.\(^{26,27}\) Studies of the direct effects of propofol on the sinoatrial node and atrioventricular conduction are incomplete in dogs and nonexistent in humans.\(^{28}\)

TABLE 3. Cardiovascular Changes of Propofol

<table>
<thead>
<tr>
<th>Time from Induction to Measurements (min)</th>
<th>Induction Dose (mg/kg)</th>
<th>*Infusion Rate</th>
<th>Heart Rate (% change)</th>
<th>Systolic Blood Pressure (% change)</th>
<th>Diastolic Blood Pressure (% change)</th>
<th>Cardiac Output (% change)</th>
<th>Stroke Volume (% change)</th>
<th>Systolic Vascular Resistance (% change)</th>
<th>Premedication</th>
<th>Comments</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
<td>3.24–3.9</td>
<td>−1</td>
<td>−32.6</td>
<td>−20.3</td>
<td>−6.4</td>
<td>NR</td>
<td>NR</td>
<td>Morphine 150 μg/kg</td>
<td>Study not evaluated with statistics. Maintenance anesthesia with 67% (N_2O) in (O_2) with propofol at two infusion rates, begun immediately after induction. (ED_{50} = 54 \mu g·kg^{-1}·min^{-1}) (ED_{95} = 41 \mu g·kg^{-1}·min^{-1})</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>6.48–</td>
<td>NC</td>
<td>−36.6</td>
<td>−23.4</td>
<td>−11.1</td>
<td>NR</td>
<td>NR</td>
<td>Morphine 150 μg/kg</td>
<td>Elderly patients for peripheral vascular surgery. Maintenance anesthesia with 67% (N_2O) in (O_2) with propofol infusion, started immediately after induction; spontaneous ventilation.</td>
<td>23</td>
</tr>
<tr>
<td>SVNS</td>
<td></td>
<td>3.24</td>
<td>−18</td>
<td>−45</td>
<td>−31</td>
<td>−30</td>
<td>−20</td>
<td>−14</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVNS</td>
<td></td>
<td>6.48–7.8</td>
<td>−7</td>
<td>−44</td>
<td>−33</td>
<td>−16</td>
<td>−12</td>
<td>−28</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>NC</td>
<td>−29†</td>
<td>−22†</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Morphine 150 μg/kg</td>
<td>Elderly patients for peripheral vascular surgery. Maintenance anesthesia with 67% (N_2O) in (O_2) with propofol infusion, started immediately after induction; spontaneous ventilation.</td>
<td>23</td>
</tr>
<tr>
<td>SVNS</td>
<td></td>
<td>3.24</td>
<td>−NS</td>
<td>−47†</td>
<td>−31†</td>
<td>−31†</td>
<td>−NS</td>
<td>−NS</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVNS</td>
<td></td>
<td>6.48</td>
<td>−NS</td>
<td>−45†</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3.24</td>
<td>+NS</td>
<td>−24†</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>Morphine 150 μg/kg</td>
<td>Healthy ASA I–II patients. Maintenance anesthesia with 67% (N_2O) in (O_2) with propofol infusion. Note Infusions were started immediately after bolus.</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>6.48</td>
<td>+NS</td>
<td>−32†</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVNS</td>
<td></td>
<td>3.24</td>
<td>−NS</td>
<td>−35†</td>
<td>−29†</td>
<td>−32†</td>
<td>−NS</td>
<td>−NS</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVNS</td>
<td></td>
<td>6.48</td>
<td>−NS</td>
<td>−45†</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>−NS</td>
<td>Morphine 150 μg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6</td>
<td>−27†</td>
<td>−20</td>
<td>−NS</td>
<td>−21†</td>
<td>NC</td>
<td>−30†</td>
<td>Lorazepam 1 mg iv Glycopyrrolate 0.4 mg im</td>
<td>ASA II–III patients for total hip replacement. Maintenance anesthesia = spontaneous ventilation on room air with propofol infusion begun immediately after bolus.</td>
<td>25</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>6</td>
<td>−32†</td>
<td>−27†</td>
<td>−NS</td>
<td>−30†</td>
<td>NC</td>
<td>−NS</td>
<td>Lorazepam 1 mg iv Glycopyrrolate 0.4 mg im</td>
<td>ASA II–III patients for total hip replacement. Maintenance anesthesia = spontaneous ventilation on room air with propofol infusion begun immediately after bolus.</td>
<td>25</td>
</tr>
</tbody>
</table>

NR = Not Recorded; NS = Not Statistically Significant; SVNS = Steady-state anesthesia spontaneous ventilation—No surgery (prior to surgery); + = increase; − = decrease.

\* Rate = mg·kg\(^{-1}\)·hr\(^{-1}\).

† \(P < 0.05\).
The administration of propofol to patients with good left ventricular function undergoing myocardial revascularization was reported to cause consistent, significant decreases in blood pressure, variable changes in heart rate, and no statistically significant changes in cardiac output or cardiac index (figs. 3 and 4).29-31 Although Patrick et al. found significant changes in rate pressure product (RPP)29 after induction with propofol, this index may be a poor approximation of myocardial oxygen demand in anesthetized patients.32 No evidence of regional myocardial ischemia was noted by intraoperative ECG and pulmonary artery catheter findings.29,31 Stephan et al. measured myocardial blood flow and myocardial metabolism.30 A significant decrease (31%) in left ventricular oxygen consumption and a corresponding (26%) decrease in myocardial blood flow were found, but coronary sinus lactate production was increased in two of 12 patients.30 Lactate production by the myocardium reflects an imbalance of myocardial oxygen supply and demand, and a degree of myocardial ischemia.30 Although propofol can be administered to patients with coronary artery disease, it must be given with careful attention to hemodynamic changes. Administration of propofol in combination with a potent opioid may constitute safer practice and offer more effective blunting of autonomic sympathetic responses.30

Larsen and coworkers studied a geriatric population, a subgroup presumed to have diminished cardiovascular reserve.33 In these patients undergoing major upper abdominal surgery, significant decreases in myocardial oxygen consumption and myocardial blood flow were found. Although two studies used the same techniques to detect ischemia (including ECG, pulmonary artery pressures, and myocardial lactate production), Stephan et al. found an imbalance in myocardial oxygen supply and demand,30 whereas Larsen et al. did not.33 The differences between these two studies are probably related to the absence of documented coronary artery disease in the elderly and to the use of a lower dose (1.5 mg/kg vs. 2 mg/kg) of propofol.

Cardiovascular data obtained in the elderly conflict. Claey s et al. studied patients (age 50–75 yr) undergoing orthopedic surgery and found no significant reduction in cardiac output or stroke volume, but a decrease in systemic vascular resistance.25 Patients in this study received glycyrorylrate which may affect hemodynamic responses. These data are consistent with the findings of other studies in adult patients.29,30 Larsen et al., however, found a significant decrease in cardiac index which they attributed to a negative inotropic effect of propofol.33 In elderly patients undergoing peripheral arterial surgery, reductions in cardiac output up to 33% and systemic vascular resistance up to 42% were observed.23 In the worst case, this responded to head-down tilt and volume infusion.
is therefore likely that the difference in findings between these two groups of studies may be attributed to differences in volume status between study groups. In the absence of surgical stimulation, cardiac output is affected more than systemic vascular resistance.\textsuperscript{22,23}

The cardiovascular effects of propofol are manifested as systemic hypotension resulting from a reduction in systemic vascular resistance. Cardiac index is not consistently affected. These findings suggest that propofol should be used with caution in patients with compromised cardiovascular function, in the elderly, and in hypovolemic patients.

Induction of anesthesia with propofol is not usually associated with disturbances of cardiac rhythm.\textsuperscript{23,24,34,35} Although transient supraventricular tachycardia, ventricular ectopy, and nodal rhythms have been noted during intubation,\textsuperscript{36} the most serious conduction disturbance following propofol was a cardiac arrest, which occurred after a period of bradycardia during a dilatation and curettage procedure.\textsuperscript{37} The patient was resuscitated with atropine and external cardiac massage.\textsuperscript{37} Bradycardia persisting into the postoperative period has also been reported.\textsuperscript{38}

When the hemodynamic effects of various induction agents are compared, propofol appears to cause a greater reduction in blood pressure than most other agents. In adults, an induction dose of propofol (2.5 mg/kg) resulted in more significant decreases in arterial pressures than an equipotent dose of thiopental (4–5 mg/kg)\textsuperscript{39–41} at certain time intervals (1–8 min) after administration.\textsuperscript{54,62–66} When compared to methohexitol (1.5–2.0 mg/kg), most investigations have found an induction dose of propofol (2.0–2.5 mg/kg) to result in greater decreases in arterial pressures\textsuperscript{40–49} with one exception.\textsuperscript{50} From limited investigation (one study in 20 elderly patients) propofol and etomidate appear to cause similar decreases in arterial pressure, heart rate, and cardiac index.\textsuperscript{39} Equipotent doses of propofol and etomidate have not been established, and this study administered a fairly low dose of propofol (1.5 mg/kg) and a standard dose of etomidate (0.29 mg/kg).\textsuperscript{53} Data comparing propofol with thiamylal are limited and conflicting.\textsuperscript{51,52}

**Response to Tracheal Intubation**

During general anesthesia, the hemodynamic responses to tracheal intubation can be profound and deleterious.

with serious cardiovascular and cerebral effects.\textsuperscript{51-55} In the studies examining this issue, the administration of an induction dose of propofol resulted in a significant decrease ($P < 0.05$) in systolic arterial pressure (greater than thiopental or etomidate).\textsuperscript{29,33,36} After laryngoscopy and intubation, the arterial pressures of the patients who received propofol returned to approximately baseline values.\textsuperscript{29,33,36} In contrast, the arterial pressures of patients receiving thiopental exceeded baseline values after intubation.\textsuperscript{29,36} Although the induction dose of propofol decreased arterial pressure, the sympathetic stimulation of intubation reversed this decline, the net effect of these events being a return to preinduction hemodynamic status. The finding that propofol limits the hemodynamic response to intubation is confirmed by a series of studies without control groups.\textsuperscript{23,24}

**Respiratory Effects**

Most authors agree that propofol is a profound respiratory depressant. Different studies reported changes in respiratory rate as variable\textsuperscript{54} or decreased.\textsuperscript{55,56} After induction with propofol, apnea of greater than 30 s duration\textsuperscript{46,48,54,56-61} was reported in $13\%$\textsuperscript{58} to $83\%$\textsuperscript{60} of patients. Thiopental and propofol are not statistically different in the percentage of patients experiencing such apnea.\textsuperscript{57-60,62} Propofol (2.0 mg/kg) caused more patients to become apneic for a longer duration than did methohexital (1.4 mg/kg)\textsuperscript{61,63} or ketamine (2 mg/kg).\textsuperscript{54} These differences reached statistical significance with ketamine\textsuperscript{64} but not with methohexital.\textsuperscript{50,63}

Propofol was found to cause significant decreases in minute volume, especially in the first 4 min after administration and in patients receiving an opioid premedication.\textsuperscript{55,56} Noninvasive measurements of the respiratory cycle (inductance plethysmography and the pneumotachograph) have demonstrated that propofol causes significant decreases in tidal volume,\textsuperscript{55,65} mean inspiratory flow rate,\textsuperscript{55} and functional residual capacity.\textsuperscript{55} The changes in breathing pattern may suggest that the ventilatory depression of propofol results from a decrease in central inspiratory drive as opposed to a change in central timing.\textsuperscript{55}

Ventilatory depression is reflected clinically by an increase in end-tidal carbon dioxide ($ET\textsubscript{CO}_2$). Propofol increases $ET\textsubscript{CO}_2$\textsuperscript{53,54,54,54,54,65} more profoundly after opioid premedication\textsuperscript{54} than without premedication.\textsuperscript{54,65} The pattern of increase in $ET\textsubscript{CO}_2$ by propofol approximates thiopental\textsuperscript{54,54,65} (with one exception noted 6 min

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**Fig. 4.** Systemic vascular resistance and heart rate changes following propofol (1.5 mg/kg) or thiopental (2 mg/kg) used as the induction agent for patients scheduled for coronary artery surgery. \textsuperscript{*}$P < 0.05$ for differences between groups. Propofol causes a greater decrease in systemic vascular resistance than thiopental. Graph drawn from data in Patrick et al. 1985. Used with permission of the authors. Postgrad Med J 61(Suppl):23-7, 1985.
after induction) and by methohexital. Propofol was also found to blunt the ventilatory response to an increase in inspired CO₂. Although Goodman and coworkers found much variability between patients, a significant decrease in sensitivity to CO₂ was found between the awake and anesthetized states. The relationship between CO₂ sensitivity and depth of anesthesia is probably not linear and remains undefined. It should also be noted that these patients had received a subarachnoid block. Painful surgical stimuli may counteract the ventilatory depressant effect of propofol.

**Effects on Cerebral Blood Flow and Intracranial Pressure**

In patients without intracranial pathology, propofol decreases cerebral blood flow (CBF) by 26% to 51% and increases cerebrovascular resistance (CVR) by 51% to 55%. Propofol was also found to decrease cerebral metabolic requirement for oxygen (CMRO₂) to a significant degree (36%) in one study, but insignificantly (18%) in another study, which combined a propofol infusion with nitrous oxide (65%), oxygen, and enflurane (0.5%). The reactivity of the cerebral vessels to changes in P<sub>CO₂</sub> seems to be maintained during anesthesia with propofol.

Changes in intracranial pressure (ICP) have not been measured directly during propofol administration. However, Ravussin and coworkers studied patients undergoing intracranial surgery without elevated ICP and measured lumbar CSF pressure directly under the assumption that it would reflect ICP if there was no obstruction to CSF flow. After induction with propofol (1.5 mg/kg), fentanyl, and pancuronium, anesthesia was maintained with propofol by bolus and an infusion at 6 mg·kg⁻¹·h⁻¹. Propofol administered in this manner maintained cerebral perfusion pressure (CPP) above 70 mmHg despite significant decreases in CSF pressure and mean arterial pressure. There were no significant increases in CSF pressure or mean arterial pressure above baseline during intubation, application of the pin holder, or skin incision.

The effects of propofol in patients with elevated ICP have been studied with propofol (2 mg/kg) administered to six comatose patients with ICP greater than 25 mmHg. In this group of patients, ICP decreased significantly. However, the cerebral perfusion pressure also decreased in four of six patients below the minimum safe CPP of 50 mmHg due to a decrease in arterial pressure.

Although propofol seems to be a reasonable agent for neuroanesthesia, its effects on ICP and CBF are incompletely elucidated, especially in patients with intracranial pathology. We feel, therefore, that it should be used with caution in patients with increased ICP and unstable cardiovascular status.

**Neurophysiological Effects**

Studies of the electroencephalogram (EEG) produced by propofol are limited. In a study following a bolus injection of 2.5 mg/kg, followed by an infusion of 7-12 mg·kg⁻¹·h⁻¹, propofol was found to produce desynchronization of the awake physiological pattern approximately 1 min after the start of injection. Following an increase of alpha rhythm, delta and theta activity occurred. Rates of infusion above 9 mg/kg/h resulted in burst suppression lasting 15 s or longer. Following discontinuation of anesthesia, the EEG quickly returned to the awake state (mean 11.1 min). Propofol alters posterior tibial somatosensory-evoked cortical potentials. Following propofol anesthesia, the latency of the P40 was significantly increased and its amplitude was decreased. Similar effects were found on median nerve somatosensory-evoked potentials. Like the other intravenous anesthetics, althesin and etomidate, propofol appears to have no effect on the latencies of the brain stem auditory evoked potential. It does, however, cause significant attenuation of the amplitude and increase in latency of the cortical middle latency potential of the auditory response.

**Adrenal Steroidogenesis**

Using a preparation of guinea pig-dispersed adrenal cells, thiopental, propofol and etomidate all inhibited ACTH-stimulated production of cortisol. Thiopental and propofol were much less potent than etomidate in reducing cortisol secretion. Thiopental appears, like etomidate, to inhibit the final enzymatic step of cortisol synthesis 11 β-hydroxylase, whereas propofol probably acts between ACTH binding and pregnenolone production. Similar data were obtained in another in vitro model using isolated bovine adrenocortical cells. Etomidate was a potent inhibitor of cortisol production, thiopental slightly reduced production, whereas propofol did not affect production.

In man, when used as a single induction dose of 2.5 mg/kg, propofol did not block cortisol and aldosterone secretion in response to surgical stress or ACTH. In contrast, using the same dose of propofol for induction, followed by a continuous infusion (4.4 mg·kg⁻¹·h⁻¹), Kay and colleagues found a transient decrease in plasma cortisol concentration 30 min after induction of anesthesia. However, by 3 h after induction, cortisol concentration was not significantly different from baseline. Studies on steroidogenesis have also been carried out following an 8 h infusion for sedation in the intensive care unit. An infusion of 1-3 mg·kg⁻¹·h⁻¹ was given through a central vein and the infusion continued for 8 h. Cortisol estimations were made at 4 h and 8 h, then a Synacthen test was performed. The Synacthen test is a challenge with synthetic adrenocorticotropic hormone,
TABLE 5. Pain on Induction with Propofol in Emulsion Formulation

<table>
<thead>
<tr>
<th>Site of Injection</th>
<th>Dorsum of Hand</th>
<th>Antecubital Fossa</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propofol</td>
<td>Thiopental</td>
<td>Methohexital</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
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<td>NR</td>
<td>NR</td>
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<tr>
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<td>25%</td>
<td>NR</td>
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<td>2.5%</td>
</tr>
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<td>NR</td>
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<td>73%</td>
<td>NR</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>0%**</td>
</tr>
</tbody>
</table>

NR = Not Reported.
* Propofol given after 10 mg of iv lidocaine—17.5% of injections caused pain.
† Injecting lidocaine (unspecified amount) or mixing lidocaine (unspecified amount) with propofol decreased incidence of pain to 8.8%.
‡ Phlebitis was reported in two of 50 (6.7%) patients 24 h postoperatively and thrombosis in one of these.
§ Phlebitis in one of 72 patients (1.4%) after injection resolved within 24 h.
†† Incidence of phlebitis and thrombosis was 0.6% and 0.2%, respectively, in 1,238 patients in the immediate postoperative period. Incidence of phlebitis and thrombosis was 0.2% and 0.5%, respectively, in 562 at 24 h postoperatively.
** P < 0.05.

which normally results in cortisol secretion. In these five patients, propofol was found to have no effect on plasma cortisol concentrations, and the response to the Synacthen was normal, with a significant increase in cortisol concentrations 30 and 120 min after Synacthen administration. Considering these studies together, propofol appears to have in vitro potential for affecting adrenal steroidogenesis; however, in clinical practice, this does not appear to be a problem.79

Effects on Hepatic and Renal Function

Propofol has minimal adverse effect on liver function, as evidenced by the absence of change in liver function tests such as aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase, up to 15 days after a general anesthetic with propofol and nitrous oxide.60 After reviewing a large series of patients, Stark et al. found no patients to have elevated AST (128 patients tested) or ALT (155 patients) greater than twice the upper limit of normal and less than 1% of patients to have similar elevations in bilirubin or alkaline phosphatase.81 Propofol has not been reported to have adverse effects on renal function (by tests of creatinine and blood urea nitrogen).81

Effects on Coagulation

The emulsion in which propofol was reformulated resembles Intralipid, which has been associated with alterations of blood coagulation.82–84 With one possible exception,79 studies have failed to show that propofol changes the coagulation profile as measured by thrombin time, prothrombin time, partial thromboplastin time, fibrinogen titer, fibrin degradation products, and platelet count.78,85 The study that found an alteration in coagulation involved 8 h infusions of propofol for sedating mechanically ventilated patients, most of whom had undergone surgery and had ongoing pathophysiologic processes to explain a coagulopathy.76 In addition, propofol was found to have no apparent effects on platelet function.86

Effects at Site of Injection

The incidence of pain reported after intravenous injection of propofol varied from 10%67 or less if the cannula was in the antecubital fossa12,50,81,87,88 and up to 58%69 (range: 22.560–58%68) if the cannula was placed in the dorsum of the hand159,60,81,88–90 (table 5). The prior administration of lidocaine intravenously may81 or may not159,88 lessen the discomfort of injection. The incidence of thrombosis or phlebitis after intravenous injection of propofol is quite low, with several series reporting less than 1%.81,87,94 The one case of an intra-arterial injection reported transient hyperemia and pain with no function deficit or permanent sequelae.95

Allergic Reactions

Although anaphylactoid reactions were attributed to agents dissolved in Cremophor,4,96 the emulsion for-
mulation of propofol appears to be devoid of anaphylactoid side effects. The administration of propofol did not cause significant increases in plasma histamine,

97,98,99 immunoglobulin, or complement C3 levels.98

Clinical Use

TOTAL INTRAVENOUS ANESTHESIA

The ideal intravenous induction agent possesses characteristics which include rapidity of onset and recovery, reliability of action (smooth onset without excitatory effects or respiratory distress), water solubility, lack of allergic responses and tissue toxicity, and lack of hemodynamic effects.100 The suitability of propofol as an induction agent has been assessed in different anesthesia protocols: as a bolus, as a bolus followed by an infusion, with oxygen or supplemented with nitrous oxide, and with or without opioids.

Numerous studies have examined propofol as a single bolus92 or as a bolus followed by maintenance anesthesia with nitrous oxide and incremental doses of propofol.91,101,102 ** Induction was rapid with few excitatory effects, such as hypertonus, tremor, or hiccup (14%),62 or spontaneous movement (25%).91 When total dose and time of anesthesia were taken into account, researchers reported a wide range of dose requirements from 4.491 to 11.25 mg · kg⁻¹ · h⁻¹.100

The next stage of investigation evaluated an induction dose of propofol (2.0–2.5 mg/kg) followed by an infusion of propofol with nitrous oxide (60–66% inspired)12,22 or without nitrous oxide.103,104 All patients received an opioid either as premedication 60–90 min before induction or as pretreatment within 3–5 min of induction. Coates and coworkers described dose requirements in pharmacodynamic terms: effective dose 50 (ED50) which was 3.24 mg · kg⁻¹ · h⁻¹ and ED95 of 5.46 mg · kg⁻¹ · h⁻¹.22 The reader should note that these doses are applicable only to the setting in which they were generated, i.e., in patients with morphine 150 µg/kg for premedication and with 67% nitrous oxide to supplement the maintenance of anesthesia.22 The average rate of infusion varied and was reported as high as 11.5 mg · kg⁻¹ · h⁻¹.22

Infusions of propofol and an opioid (without nitrous oxide) have been combined as general anesthesia. Combined infusions were first reported in 1985 by DeGrood et al. using fentanyl and propofol with good success at controlling anesthetic depth and hemodynamic changes.105 Because of their similar pharmacodynamic characteristics (rapid onset and short duration of action), it seems that propofol and alfentanil would be ideal and complementary agents for total intravenous anesthesia. When these two agents were administered together for orthopedic106 or ENT88 procedures, anesthesia proceeded smoothly with predictable changes in hemodynamics after induction and intubation. Emergence from anesthesia was rapid (time from end of infusion until patient being oriented: 12.856–18.9 min).106 In the recovery room patients were described as fully alert86 and clear headed.106

If propofol is to be used by continuous intravenous infusion, then it is likely that sophisticated microprocessor-controlled infusion devices will allow stable plasma concentrations of the drug to be achieved rapidly. An initial assessment of such an infusion device, which was aimed at a constant blood level of 2.5 µg/ml, demonstrated that stable concentrations of the drug could be achieved.107 Taking the 20 patients studied as a group, induction of anesthesia was not associated with hypotension. The time taken by the microprocessor to achieve stable concentrations was not reported.107 A similar study was carried out using a different microprocessor system aiming for a target concentration of 3 µg/ml.108 This concentration was reached within 10 min. The blood pressure and heart rate decreased over the first 15 min of the study. It is also possible to achieve a stable plasma concentration rapidly using a manually controlled infusion scheme.109 This involved making four rate adjustments in the first 20 min, but achieved stable concentrations within 2 min of start of infusion. Again, these authors suggested that this technique provided better hemodynamic stability during induction than a loading dose of 2 mg/kg.109 This finding has yet to be confirmed by a prospective randomized trial. Computer-controlled infusion schemes will result in a stable mean concentration of drug in a group of patients. However, the standard deviation may be as large as 50% of the target level.108 Although these techniques may still be considered experimental, it is likely that computer-controlled devices for propofol administration will become more readily available in the future.

Comparisons of propofol and inhalational techniques for maintenance of anesthesia are limited. In a study comparing propofol infusions (12–15 mg · kg⁻¹ · h⁻¹) in oxygen with thiopental, nitrous oxide/oxygen, and enflurane anesthesia for day case surgery, use of propofol was found to be associated with less nausea and vomiting.108 Although the inhalational anesthetic group received nitrous oxide. Recovery times and Steward scores were not different between groups.105 When propofol by bolus and infusion was compared to thiopental-isoflurane anesthesia for ear surgery, patients given propofol demonstrated shorter recovery times, but there was no difference between groups in the incidence of side effects.110 Therefore, based on the limited data available, it is impossible to say whether propofol infusions will be better or worse than traditional

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techniques for maintenance of anesthesia. A bolus technique of propofol has been used for maintenance of anesthesia without nitrous oxide compared with propofol 2–2.5 mg/kg for induction followed by intermittent bolus of 10–20 mg. Concomitant alfentanil administration (bolus 1 mg, infusion 1 μg·kg⁻¹·min⁻¹) was used. Infusion regimes using 67% nitrous oxide have been suggested. Following a bolus injection of propofol 2 mg/kg, infusions of 3.2 mg·kg⁻¹·h⁻¹ or 6.5 mg·kg⁻¹·h⁻¹ were found to be satisfactory for maintenance of anesthesia. These doses should be reduced in the elderly.

INTERACTIONS WITH NEUROMUSCULAR BLOCKING AGENTS

Although the Cremophor formulation of propofol modified the activity of neuromuscular blocking agents, current information suggests that propofol in emulsion is devoid of such effects. Propofol in its current formulation has no effect on the actions of vecuronium, succinylcholine, or atracurium.

CHARACTERISTICS OF ANESTHETIC INDUCTION

Induction time is short with propofol and comparable to other agents. There were no statistically significant differences comparing propofol to thiopental, etomidate, or methohexitol when measuring the interval from beginning of injection to loss of eyelash reflex, or to loss of counting, with one exception. Like thiopental, propofol in adequate doses will induce anesthesia in one arm-brain circulation time. In one comparative study, propofol 2 mg/kg resulted in loss of eyelash reflex in 30.5 s, compared with thiopental 4 mg/kg which produced anesthesia in 34.6 s. The induction of anesthesia should not be only rapid but smooth, without excitatory phenomena, such as myoclonia, hypertonus, or involuntary movement. In this regard, propofol was intermediate between thiopental, the most desirable agent (0–6.7% excitatory phenomena), and methohexitol, where such side effects were noted in up to 90% of patients. In fact, excitatory effects following propofol are relatively low in frequency and minimal postoperative confusion. When compared to thiopental, propofol has been reported to have shorter recovery times by measurements such as time to open eyes on command, time to recall date of birth, and time to orientation, with some studies reporting exceptions to this data. Although data is limited, recovery characteristics of propofol and etomidate appear to be similar.

The Steward Score is another method of evaluating recovery from anesthesia by physical examination (consciousness, airway, and movement). Patients who received propofol and nitrous oxide exhibited faster recovery by Steward's scale than those given general anesthesia with thiopental, nitrous oxide, and halothane. As total intravenous anesthetics, patients recovered faster with propofol than with etomidate.

When technically sophisticated measurements of recovery from anesthesia are employed, such as choice reaction time (CRT) and the critical flicker fusion test (CFFT), patients who received propofol generally were found to have faster recovery, especially in the first half hour after surgery, than did patients who received thiopental, methohexitol, or isoflurane-nitrous oxide. Other investigators using the same methods (CRT and CFFT) did not find as clear a distinction between drugs.

COMPARISON OF SIDE EFFECTS

Morbidity after anesthesia includes nausea, emesis, headache, restlessness, confusion, depression, and euphoria. The incidence of nausea and/or emesis after propofol ranged from 0% to 17%. In fact, some authors attribute an antiemetic effect of propofol. Although propofol seems to cause less nausea and emesis than methohexitol, there is little difference between propofol and etomidate or propofol and thiopental. Headache was reported in 12.5% of the time. Incidence of headaches can be generally related to the existence of preoperative migraine or a tendency towards headaches. Other authors offered anecdotal reports of restlessness, confusion, and depression.

SUPPLEMENTATION OF REGIONAL BLOCKADE AND INTRAVENOUS SEDATION

Because of its pharmacokinetic and pharmacodynamic profiles, propofol is a useful drug for intravenous sedation during procedures. As a light general anesthetic to accompany regional blockade, propofol offered smooth induction, satisfactory maintenance, and rapid recovery with reliable amnestic properties. In hypnotic doses, propofol may not be as potent an amnestic agent as midazolam, but this question remains unde-
cided. Although the equipotent doses of propofol and midazolam have not been clearly defined, recovery after propofol appears to be significantly more rapid than that after midazolam.\textsuperscript{126,127}

Propofol is also useful as a sedative in patients undergoing procedures such as endoscopy.\textsuperscript{35,128} Investigators reported good control of anesthetic depth with changes in stimulation, dose-dependent amnesia,\textsuperscript{35} and rapid recovery.\textsuperscript{35,128}

**SEDATION IN THE INTENSIVE CARE UNIT**

Sedation in the intensive care unit (ICU) is essential for patient comfort and safety. Etomidate was used by continuous infusion in the ICU, particularly for its effects on ICP, until reports of an associated increase in mortality in critically ill patients.\textsuperscript{129} This increase in mortality was related to suppression of the neuroendocrine axis peripherally\textsuperscript{130} and possibly centrally.\textsuperscript{131}

Two studies have been carried out using propofol infusions in different populations of ICU patients, infusions over a duration of 8–24 h.\textsuperscript{79,132} Newman and coworkers observed 10 patients being mechanically ventilated over an 8 h period. These patients required intensive care for various reasons, including respiratory failure from chronic obstructive pulmonary disease, septic shock after bowel surgery, and postoperative chest or great vessel surgery.\textsuperscript{79}

Of ten patients, three received a 1 mg/kg bolus of propofol. Infusions were started on all patients at a mean rate of 1.93 mg · kg\(^{-1}\) · h\(^{-1}\) (range: 1.03–2.81 mg · kg\(^{-1}\) · h\(^{-1}\)).\textsuperscript{79}

The acceptable level of sedation was defined as that state where the patient remained comfortable without periods of agitation.\textsuperscript{79} An average of four changes were made in the infusion rate over the 8 h period. Of the three patients who received a bolus of propofol, two exhibited marked decreases in mean arterial pressure of 40 and 53%. Articular pressures decreased over the first 4 h of infusion, reached their lowest point between 4 and 8 h \(P < 0.05\) difference from baseline for mean and diastolic pressures at 4, 7, and 8 h), and appeared to increase after the infusion was discontinued. Although most adjustments of infusion dose were made for changes in level of sedation, the infusion rate in three of eight patients was decreased because of a continuing decline in blood pressure. Oxy-

genation and ventilation were well-maintained during infusion. These researchers found propofol to be suitable for infusion in critically ill patients, but cautioned that the cardiovascular respiratory and sedative effects must be carefully monitored in this sensitive group of patients.\textsuperscript{79}

Grounds and coworkers studied a rather uniform group of patients, all of whom had undergone cardiac surgery and cardiopulmonary bypass.\textsuperscript{132} The anesthetic technique was standardized and included premedication with paveretum, hyoscine and droperidol, induction with thiopental (up to 4 mg/kg), and fentanyl (50 \(\mu\)g/kg) and pancuronium, and maintenance with nitrous oxide (60%) and oxygen. Hypertension was controlled with sodium nitroprusside. Upon arrival in the ICU, patients were given either midazolam in 2.5 mg increments intravenously or a continuous infusion of propofol.\textsuperscript{132} The mean doses of drugs given were 0.016 mg · kg\(^{-1}\) · h\(^{-1}\) of midazolam and 0.79 mg · kg\(^{-1}\) · h\(^{-1}\) of propofol.\textsuperscript{132} (Compare with Newman et al.'s 1.93 mg · kg\(^{-1}\) · h\(^{-1}\)).\textsuperscript{79} Patients in the midazolam group received significantly more papaveretum (0.298 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\)) than those in the propofol group (0.125 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) median doses, \(P < 0.05\)).\textsuperscript{132} The amount of sodium nitroprusside given was not different between the two groups.\textsuperscript{132} Level of sedation was assessed according to Ramsay et al.'s classification into six levels from anxious and agitated (level 1), to asleep with no response, to auditory stimuli or glabellar tap (level 6).\textsuperscript{133} All levels of sedation within these two extremes were deemed suitable in this setting.\textsuperscript{132} A satisfactory level of sedation was recorded in the propofol group 91% of the time while ventilator-dependent, as opposed to satisfactory sedation 81% in the midazolam group.\textsuperscript{132} Recovery times were markedly different between the two groups. Patients were weaned from ventilatory support according to the criteria of Klineberg et al. and Foster et al. for early extubation after cardiac surgery.\textsuperscript{134,135} The duration of ventilator dependence was significantly shorter in the propofol groups (mean–8.08 h) than in the midazolam groups (mean–11.12 h; \(P < 0.02\)). After the propofol infusion was stopped, the median time to spontaneous ventilation was 9.5 min (range: 1–54 min) in contrast to 202 min (range: 51–600 min), the corresponding time interval for midazolam \(P < 0.001\). Median time from stopping infusion to tracheal extubation was 20 min (range: 5–70) with propofol, compared to 237 min (range: 80–610) after midazolam.\textsuperscript{132} These researchers considered propofol by continuous infusion to be suitable in the postoperative cardiac ICU and cited the rapid changes in level of sedation as an advantage. They emphasized that propofol has no analgesic properties.\textsuperscript{132} This statement is in conflict with evidence from Briggs et al. who found that the Cremophor formulation of propofol had some analgesic properties in subhypnotic doses during tibial pressure algiesmetry.\textsuperscript{136}

An interesting side effect of prolonged infusion of propofol was the report of green urine. This unusual finding was noted on the third day of a propofol infusion in an asthmatic patient who required artificial ventilation.\textsuperscript{137} The dark green color persisted until the propofol infusion ended, when it rapidly cleared. The urine contained phenols\textsuperscript{137} which have been reported to cause green urine after other intravenous drugs.\textsuperscript{138} The discoloration did not affect renal function.\textsuperscript{137}
INTRAOCULAR PRESSURE

Propofol causes a significant decrease in intraocular pressure (IOP) ranging from 27% to 53%, although propofol was superior to thiopental in controlling IOP after rapid sequence induction. IOP was best controlled in those patients who received a second dose of propofol just prior to intubation, and who were administered a nondepolarizing neuromuscular blocking agent to facilitate intubation.

EFFECTS OF PREMEDICATION

The effects of various premedication regimens on the characteristics of propofol have been evaluated in several studies. In a double-blind, randomized study of patients undergoing minor gynecological procedures, Bilain and Desmonts found no difference between groups (isotonic saline, atropine 0.5 mg intramuscularly, hydroxyzine 100 mg intramuscularly) with respect to success of induction (2 mg/kg) induction times, times to eye opening and to orientation, decreases in arterial pressures, and excitatory side effects. In a similarly randomized study in gynecological patients, Briggs and White gave an induction dose of 2.5 mg/kg to patients who had received no premedication, diazepam 10 mg orally, or meperidine 50–75 mg intramuscularly and atropine 0.5 mg intramuscularly approximately 1 hour preoperatively. Anesthesia was successfully induced in all patients with mean induction times of less than 30 s in all groups. The systolic blood pressure decreased to a similar extent in all three groups. Premedication did not seem to affect the incidence of events such as spontaneous movement, excitatory effects, or respiratory upset.

Another study in gynecological patients (cervical dilation and curettage or termination of pregnancy) compared three premedications: lorazepam 1 mg, 2 h before surgery; papaveretum 10 mg intramuscularly with hyoscine 0.2 mg, 1 h before surgery; and no premedication. After a bolus of alfentanil 250 µg, induction proceeded with propofol until the eyelash reflex was abolished. Induction dose did not correlate with either age or weight of the patient, although the groups were comparable with respect to weight. The dose for induction was significantly higher in unpremedicated patients (126 mg) than in premedicated patients (101 mg, P < 0.01). The incremental doses required for maintenance of anesthesia, however, were not affected by the different premedication regimens. Furthermore, recovery time was related to the total dose of propofol, not to premedication.


Patients receiving an opioid premedication had more nausea or vomiting (17.5%) compared to the other patients (2.6%).

Premedication seemed to have few effects on the induction characteristics of propofol. The addition of an opioid to the premedication may decrease the induction dose of propofol. Various premedications had little effect on time to induction, extent of hemodynamic changes, and recovery.

SPEED OF INJECTION

Speed of injection may affect the induction of anesthesia by changing the dose requirement and rapidity of onset. The administration of an induction dose of propofol (2 mg/kg) produced a satisfactory level of anesthesia more rapidly and more reliably if injected over a short time (5 s) than a longer time (60 s). The speed of injection had no effect on the degree to which arterial pressures declined, or on the incidence or duration of apnea. Furthermore, when propofol in Cremophor formulation was studied, the speed of injection did not seem to affect recovery time (assessed by eye opening, sitting up, a pegboard test).

SPECIAL SETTINGS

The characteristics of propofol have not been described for every conceivable anesthetic setting. Although the porphyrogenic nature of propofol is not completely known, it has been administered safely on two separate occasions to a patient known to have acute intermittent porphyria. Preliminary studies on muscle biopsies suggest that propofol may be used in patients with malignant hyperthermia (MH). In another case report, propofol was used without incident during myocardial revascularization in a patient with a strong family history of MH.

The use of propofol in the puerperium has not been investigated closely. Dailland and coworkers anesthetized ten patients with propofol for cesarian section and found propofol in fetal blood. The ratio of drug in the umbilical vein (UV) to that in the maternal vein (MV) was 0.70 (compared to UV/MV of 1.08 for thiopental) and was not related to the interval following propofol administration. Furthermore, no relationship was found between propofol levels and Apgar scores at 1, 5, and 10 min. A preliminary study of women given propofol in the puerperium showed that propofol was secreted in the colostrum with a blood-to-colostrum ratio close to 1.

Propofol has not been extensively studied in the pediatric population. Purcell-Jones and coworkers compared propofol (2.0–2.5 mg/kg) with thiopental (4–5 mg/kg) for induction in 60 children age 3–16 yr. All children were premedicated with papaveretum 0.4 mg/kg (max-
imum dose 15 mg) and hyoscine 0.008 mg/kg (maximum dose 0.3 mg), given intramuscularly 90 min before operation. No statistically significant difference was found between groups with respect to pain on injection, induction times, spontaneous movements, or duration of apnea. Propofol caused a greater decrease in systolic blood pressure, but it was statistically significant only at 2 min after induction (P < 0.05). Although a blinded, independent assessor considered the quality of induction with thiopental good in all patients, quality of induction after propofol was rated poor because of moderate pain on injection (into an antebrachial vein), apnea, and mild involuntary movements.

Although investigation is limited, propofol has been used successfully for electroshock therapy (ECT) and been found to compare favorably with methohexital in this setting. In animal studies, propofol has neither convulsant nor anticonvulsant properties; human data is unavailable.

Interesting idiosyncratic responses were attributed to propofol in several letters. For example, three different anesthesiologists reported amorous advances from their female patients after anesthesia with propofol. Vivid and frightening hallucinations were experienced by one patient postoperatively. Another author reported facial sensations, (burning, numbness, or tingling) in 13 of 32 patients upon injection of the emulsion formulation of propofol.

Conclusion

Untoward effects of propofol have appeared in case reports and in a few formal studies. It is clear that the drug causes pain on injection but results in phlebitis or thrombosis quite infrequently. Other side effects of propofol are hypotension and respiratory depression on induction. Bradycardia, perhaps leading to cardiac arrest, has also been reported.

In healthy adults, the induction dose of propofol is 2.0–2.5 mg/kg, and is modified by factors such as premedication and state of hydration. A reasonable beginning rate of infusion is approximately 5–6 mg·kg⁻¹·h⁻¹ in the presence of nitrous oxide. Older or debilitated individuals require less propofol for induction (approximately 1.5 mg/kg) and for maintenance of anesthesia (3 mg·kg⁻¹·h⁻¹).

The most desirable features of the drug are rapid, clear emergence from anesthesia, and the lack of cumulation, which allows the drug to be given by prolonged infusion. It does not release histamine, nor has it been associated with anaphylactoid reactions in emulsion form.

Propofol is unlikely to supplant thiopental in routine practice. It is, however, likely to be extensively used for day-stay anesthesia, ophthalmic surgery (because of its beneficial effects on IOP), and sedation, both peripherally and in the ICU. Its use by continuous infusion for maintenance of anesthesia will increase with the development of more sophisticated administration devices.

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