Propofol
An Update on Its Clinical Use

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IN 1989, Sebel and Lowdon published a comprehensive review article in ANESTHESIOLOGY describing the pharmacology of propofol (Diprivan, Zeneca Pharmaceuticals, Macclesfield, UK). Since its approval by the Food and Drug Administration and introduction into clinical practice in 1989, over 300 articles on propofol have been published in the peer-reviewed anesthesia literature. Although propofol was initially approved for use as an induction and maintenance hypnotic agent, its clinical uses have expanded greatly over the past 4 yr to include indications for neurosurgical and pediatric anesthesia, monitored anesthesia care and intensive care sedation. Propofol has rapidly become the drug of choice for induction of anesthesia in outpatients undergoing ambulatory procedures, and is becoming increasingly popular for pediatric anesthesia. Propofol's unique antiemetic and mood-altering properties may lead to further clinical applications in the future.

In this review article, we have focused on the more recently published literature relating to the clinical use of propofol. Detailed information regarding propofol's pharmacokinetic and pharmacodynamic properties has facilitated the use of this drug in clinical practice. As expected, there is a wide variability in the responses of patients to propofol during the perioperative period. Therefore, the dosage and rate of propofol administration should be titrated to the individual needs of the patient. Factors which influence the propofol dosage requirements include age, weight, preexisting medical conditions, type of surgical procedure, and concomitant medical therapy. As part of a balanced or a total intravenous anesthetic (TIVA) technique, infusion rates of 75–300 μg · kg⁻¹ · min⁻¹ are usually required, whereas adequate sedation can be maintained with infusion rates of 25–100 μg · kg⁻¹ · min⁻¹ (fig. 1). It has become possible to define "target plasma concentrations" for hypnosis (2–6 μg · ml⁻¹) and sedation (0.5–1.5 μg · ml⁻¹) during a variety of clinical conditions (fig. 2). Pharmacokinetically based delivery systems can rapidly achieve "targeted" plasma concentrations of propofol; however, careful titration to the desired clinical effect is essential because of the inherent pharmacokinetic and pharmacodynamic variability which exists among patients. In addition, the therapeutic propofol concentration is highly dependent on the surgical stimulus.

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The purposes of this review article are to update the reader on the more recently approved indications for using propofol and to discuss new information regarding propofol’s pharmacologic and physiologic effects in man. The relevant literature relating to the use of propofol for ambulatory, pediatric, cardiac, and neuroanesthesia has been extensively reviewed. Clinical applications of propofol infusions for sedation during local and regional anesthesia, as well as outside the operating room (e.g., intensive care unit [ICU] or radiologic suite) are also discussed. Emphasis has been placed on clinical trials involving propofol rather than anecdotal case reports.

**Pharmacokinetics of Propofol**

Several investigators have examined the pharmacokinetics of propofol in healthy adults and children, as well as in a variety of disease states. The pharmacokinetics and pharmacodynamics of propofol were reviewed in 1988 and the more recently published studies are summarized in Table 1. The pharmacokinetic properties of propofol are unique, and contribute to its favorable clinical characteristics. Of greatest importance is the rapid metabolic clearance of propofol, which is approximately ten times faster than that of thiopental. The metabolic clearance of propofol exceeds hepatic blood flow, which has led to the suggestion that propofol is also metabolized in extrahepatic sites. Evidence for this hypothesis is provided by the detection of propofol metabolites after administration of propofol during the anhepatic phase of orthotopic liver transplantation.

After an initial bolus of propofol, plasma levels decline rapidly mainly because of redistribution of propofol from the brain and other highly perfused tissues into less-well-perfused sites (e.g., muscle). The initial distribution clearance of propofol (3–4 L·kg\(^{-1}·\text{min}^{-1}\)) is similar to that of thiopental, and initially, plasma levels of thiopental and propofol decrease at similar rates. Subsequently, the decrease in propofol level is much more rapid than that of thiopental because of its high metabolic clearance rate.

The elimination half-life of propofol is long, yet recovery from its clinical effects is rapid, even after prolonged administration. The reason for this apparent discrepancy is that the long elimination half-life is related to slow elimination from the highly lipophilic tissue compartments (e.g., fat) and is largely irrelevant in clinical situations. Hughes et al. introduced the concept of “context-sensitive half-time” to describe recovery from anesthetic infusions of varying duration. The “half-time” is the time required for the drug concentration in the central compartment to decrease by 50% after discontinuation of drug administration. The “context” relates to the duration of drug infusion before its discontinuation. Propofol has a context-sensitive half-time of less than 25 min after infusions lasting as long as 3 h, and the half-time is still only 50 min after prolonged infusions. If the propofol infusion is titrated to effect, so that the plasma propofol concentration has to decline by only 10–20% to permit awakening, recovery is very rapid.
Hughes et al. provide a comprehensive description of how the pharmacokinetic parameters of propofol interact to permit such rapid recovery. Propofol has a large steady-state volume of distribution, indicating extensive redistribution of the drug into muscle, fat and other poorly perfused tissues. The capacity of these sites is large; however, their rate of equilibration with the central compartment is very slow. When an infusion of propofol is terminated, the concentration in the central compartment is much higher than that in these peripheral compartments, and hence redistribution continues to occur. Thus, the concentration in the central compartment declines both from metabolism (elimination) and from continuing redistribution. Because the capacity of these peripheral compartments is so large, redistribution from the central compartment can still occur even after prolonged drug administration. The net result is a rapid decline in propofol concentration to levels below those required for hypnosis (or deep sedation), permitting rapid awakening. Eventually, the concentration in the central compartment becomes lower than that of the peripheral sites, and drug will then begin to move back into the central compartment. However, the rate of this transfer is slow (resulting in a long elimination half-life), such that the concentration of propofol in the central compartment will remain at subtherapeutic levels. The complete elimination of propofol from the body (dependent on the elimination process) may take many hours or even days but has little (if any) effect on clinical recovery.

The effects of age and a variety of disease states on propofol pharmacokinetics are summarized in table 1. Analogous to the barbiturates, the elderly have a reduced dose requirement for propofol which appears to be related to pharmacokinetic rather than pharmacodynamic factors. Four published pharmacokinetic studies have been performed in children. Variations between these four studies may be attributable to differences in sampling intervals (which influences the size of the central compartment), small numbers of patients, the effects of adjunctive anesthetic drugs, and the use of different modeling techniques. Despite these intrastudy differences, all four studies demonstrated that the volume of propofol’s central compartment is larger (on a per kg body weight basis) in children than in adults. The clearance rate of propofol is also higher in children. Therefore, children will require a larger induction dose and an increased maintenance infusion rate (per kilogram body weight) than adults. As in adults, other factors (e.g., the infusion duration) also influence the effect of propofol on recovery in children.
Table 2. Comparison of Propofol for Induction and Maintenance of Outpatient Anesthesia with “Conventional” Intravenous–Inhalation Techniques

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Adjuvants</th>
<th>Propofol Administration</th>
<th>Comparative Group</th>
<th>Principal Findings†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding et al.46‡</td>
<td>44 laparoscopies</td>
<td>Fentanyl</td>
<td>VRI</td>
<td>Thiopental Enflurane</td>
<td>Faster emergence; later recovery equal</td>
</tr>
<tr>
<td>Millar and Jewkes27</td>
<td>130 outpatients</td>
<td>Alfentanil</td>
<td>IB</td>
<td>Thiopental Enflurane</td>
<td>Faster emergence and discharge</td>
</tr>
<tr>
<td>Price et al.26</td>
<td>98 D &amp; Cs</td>
<td>Fentanyl</td>
<td>VRI</td>
<td>Thiopental Enflurane</td>
<td>Faster recovery at 15–30 min</td>
</tr>
<tr>
<td>Puttick and Rosen79</td>
<td>38 children</td>
<td>IB</td>
<td>VRI</td>
<td>Thiopental Halothane</td>
<td>Faster emergence and discharge</td>
</tr>
<tr>
<td>Sear et al.30</td>
<td>50 outpatients</td>
<td>Papaveretum</td>
<td>VRI</td>
<td>Thiopental Halothane</td>
<td>Faster emergence</td>
</tr>
<tr>
<td>Doze et al.31</td>
<td>80 outpatients</td>
<td>Meperidine</td>
<td>VRI</td>
<td>Thiopental Isoflurane, 1 MAC</td>
<td>Earlier discharge from recovery room</td>
</tr>
<tr>
<td>Gold et al.32</td>
<td>60 outpatients</td>
<td>Morphine</td>
<td>FRI</td>
<td>Thiopental Isoflurane</td>
<td>Faster emergence and amelioration</td>
</tr>
<tr>
<td>Korttla et al.93</td>
<td>41 outpatients</td>
<td>Fentanyl</td>
<td>FRI</td>
<td>Thiopental Isoflurane, 0.5%</td>
<td>Faster emergence and discharge</td>
</tr>
<tr>
<td>Lim and Lov26</td>
<td>50 dental</td>
<td></td>
<td>FRI</td>
<td>Thiopental Isoflurane</td>
<td>Faster emergence and amelioration</td>
</tr>
<tr>
<td>Marais et al.36</td>
<td>100 outpatients</td>
<td>Not reported</td>
<td>VRI</td>
<td>Thiopental Isoflurane</td>
<td>Faster emergence and discharge</td>
</tr>
<tr>
<td>Sung et al.36</td>
<td>99 females</td>
<td>Fentanyl</td>
<td>VRI</td>
<td>Thiopental Isoflurane</td>
<td>Faster recovery and discharge</td>
</tr>
</tbody>
</table>

VRI = variable-rate infusion; FRI = fixed-rate infusion; IB = intermittent bolus doses.

* Volatile agent titrated to clinical endpoints, unless otherwise stated.
† Findings are expressed with respect to the propofol group.
‡ This study was multiple-group comparisons but has been subdivided for ease of interpretation.

Although dosage adjustments are clearly indicated in severely debilitated patients, the clinical duration of effect of propofol does not appear to be greatly effected by obesity, moderate hepatic or renal dysfunction. Because considerable interpatient variability exists in both healthy and sick patients, careful titration of the propofol dose to effect will minimize adverse effects such as hypotension while permitting a rapid recovery from its central effects.

Ambulatory Anesthesia

The ideal anesthetic technique for ambulatory surgery should provide rapid onset and stable operating conditions while ensuring rapid recovery of protective reflexes and of cognitive and psychomotor functions. In evaluating recovery from anesthesia in the outpatient setting, it is common to divide the recovery process into three distinct phases. Early recovery is usually referred to as emergence, and describes the time at which the patient awakens from anesthesia and obeys simple commands. Intermediate recovery (or simply “recovery”) describes the return of cognitive and psychomotor function sufficient to permit discharge. Late recovery describes a complete return to the preoperative state and resumption of normal activities.

Anesthetic techniques used in the ambulatory setting should be associated with a low incidence of postoperative side effects because they can delay the patient's discharge and result in unanticipated hospital admissions. Since its introduction into clinical practice, propofol has become an extremely popular intravenous anesthetic for ambulatory surgery procedures because of its predictable recovery and favorable side effect profile. Recovery is not only rapid after a single bolus dose, but also after repeated doses or a titrated continuous infusion, thereby allowing propofol to be effectively used for maintenance of anesthesia during short ambulatory surgical procedures.

Many of the early clinical trials involving propofol compared its use for induction and maintenance of anesthesia with “traditional” techniques involving thiopental for induction and a volatile anesthetic agent for maintenance of anesthesia. Despite considerable variation in patient populations, type and duration of operative procedures, use of adjuvant agents, and methodology for titrating the anesthetics, the results were remarkably consistent (table 2). Most investigators have reported a more rapid recovery from a propofol-based anesthetic than a barbiturate–volatile anesthetic technique. For example, Millar and Jewkes27 studied 130 spontaneously breathing patients undergoing short (<30 min) outpatient procedures. Patients
receiving propofol for induction and maintenance of anesthesia awakened and reached recovery milestones significantly faster than a control group receiving a thiopental–enflurane combination. As a result, patients receiving propofol were fit for discharge 40–50 min earlier than the control group. However, this difference was decreased when either technique was supplemented with alfentanil. After discharge, propofol-treated patients were less likely to “feel unwell” during the journey home, resumed normal alimentation sooner, and reported significantly less drowsiness, dizziness and weakness on the 1st postoperative day.27

In a study involving 99 women undergoing breast biopsy procedures, Sung et al.36 compared a propofol bolus followed by a variable-rate continuous infusion with a thiopental–isoflurane combination. All patients received fentanyl 1 μg·kg⁻¹ intravenously, and nitrous oxide (N₂O). In addition to a shortened recovery time and earlier discharge, propofol-treated patients were able to resume normal activities sooner and also reported returning to work one-half day earlier (1.5 ± 0.1 vs. 2.0 ± 0.1 days) than those in the thiopental–isoflurane group.

Shorter recovery times have led some authors to speculate on the potential cost savings resulting from the use of propofol-based anesthetic techniques. Sung et al.36 suggested that extrapolating their results to a 4,000—case-per-year outpatient facility would save 1,000 h of nursing per year. Using the results of two separate comparisons of continuous propofol with thiopental–isoflurane, Marais et al.33 suggested that widespread use of propofol-based techniques could reduce the requirement for recovery room nurses by as much as 25%. This evaluation was based on the shorter recovery time after propofol-based anesthetics, as well as the reduced workload imposed on recovery room nurses as a result of the lower incidence of side effects (in particular, nausea and vomiting). However, the authors comment that actual savings would vary considerably depending upon site-specific factors such as case mix and volume, as well as decisions on minimum (nursing) staffing requirements in the postanesthesia care unit.

Use of Propofol for Induction of Anesthesia

The major criticism of the previous studies is that they compared propofol-based techniques with a combination technique involving a barbiturate and a volatile anesthetic. Such comparisons are usually justified on the grounds that they are comparing a new technique with a “standard practice.” However, the substitution of propofol for other induction agents should be studied independently of its effects as a maintenance agent. In comparisons with thiopental, emergence from anesthesia induced with propofol has generally been more rapid irrespective of the maintenance agent used (table 3). However, Sanders et al. failed to detect a significant difference when halothane was used for maintenance of anesthesia.45

Several investigators have reported improved performance on postoperative psychomotor tests when patients received propofol for induction of anesthesia compared with those receiving thiopental.40,43,44 Although psychomotor tests are intended to assess the patient’s ability to cope without supervision and to aid in determining the appropriate time for discharge after ambulatory surgery, there is no agreement on the most useful measure of these important endpoints.47 Nevertheless, using traditional discharge criteria, the use of propofol (vs. thiopental) for induction of anesthesia may allow for an earlier discharge from the ambulatory facility after brief outpatient procedures.39,42

When propofol was compared with induction agents other than thiopental for outpatient anesthesia, smaller differences were observed. In comparison with methohexitol, propofol was reported to be associated with greater alertness, reduced ataxia and improved choice reaction times during the first 20 min after isoflurane anesthesia.37 However, by 40 min these differences were no longer significant. In a comparison with etomidate, propofol induction resulted in only moderate improvements in psychomotor performance after 20–30 min of isoflurane–N₂O anesthesia.43 Compared with induction of anesthesia with midazolam followed by reversal with flumazenil at the end of anesthesia, induction with propofol was associated with significant improvement in performance on postoperative psychomotor testing when anesthesia was maintained with isoflurane.46 Similar findings were obtained when comparing a propofol-based TIVA technique with a midazolam–isoflurane–flumazenil technique.48

Use of Propofol for Maintenance of Anesthesia

Outpatient investigations in which anesthesia was induced with propofol and maintained with either propofol or a volatile anesthetic agent are summarized in table 4. When propofol–N₂O was used to maintain outpatient anesthesia lasting approximately 3 h, recovery and discharge occurred significantly earlier compared with isoflurane–N₂O.54 However, when used for shorter
Table 3. Comparison of Propofol with Alternative Induction Agents for Outpatient Anesthesia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Adjuvants</th>
<th>Comparator</th>
<th>Maintenance</th>
<th>Principal Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Toole et al.\textsuperscript{27}</td>
<td>50 females</td>
<td>Methohexital</td>
<td>Isoflurane</td>
<td>Faster emergence, improved test results at 40 min</td>
<td></td>
</tr>
<tr>
<td>Valanne and Korttla\textsuperscript{28}</td>
<td>73 oral surgery</td>
<td>Methohexital</td>
<td>Enflurane</td>
<td>Similar times to orientation and ambulation</td>
<td></td>
</tr>
<tr>
<td>Chittleborough et al.\textsuperscript{29}</td>
<td>40 dental</td>
<td>Fentanyl</td>
<td>Thiopental</td>
<td>Faster emergence and discharge</td>
<td></td>
</tr>
<tr>
<td>Ding et al.\textsuperscript{28,\dagger}</td>
<td>40 laparoscopies</td>
<td>Fentanyl</td>
<td>Thiopental</td>
<td>Faster emergence, recovery times similar</td>
<td></td>
</tr>
<tr>
<td>Gupta et al.\textsuperscript{30}</td>
<td>30 arthroscopies</td>
<td>Alfentanil</td>
<td>Thiopental</td>
<td>Improved test results for first 90 min of recovery</td>
<td></td>
</tr>
<tr>
<td>Rolly and Versichelen\textsuperscript{41}</td>
<td>30 females</td>
<td>Fentanyl</td>
<td>Halothane/isoflurane</td>
<td>Faster emergence, later events not reported</td>
<td></td>
</tr>
<tr>
<td>Runcie et al.\textsuperscript{42}</td>
<td>102 children</td>
<td>Thiopental</td>
<td>Halothane/isoflurane</td>
<td>Faster emergence, earlier discharge in older children only</td>
<td></td>
</tr>
<tr>
<td>DeGrood et al.\textsuperscript{43}</td>
<td>30 laparoscopies</td>
<td>Fentanyl</td>
<td>Thiopental</td>
<td>Faster emergence and improved test results</td>
<td></td>
</tr>
<tr>
<td>DeGrood et al.\textsuperscript{44,\dagger}</td>
<td>30 laparoscopies</td>
<td>Fentanyl</td>
<td>Etomidate</td>
<td>Nonsignificantly faster recovery</td>
<td></td>
</tr>
<tr>
<td>Mackenzie and Grant\textsuperscript{45,\dagger}</td>
<td>40 urology</td>
<td>Thiopental</td>
<td>Thiopental</td>
<td>Greatly improved psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Mackenzie and Grant\textsuperscript{46,\dagger}</td>
<td>40 urology</td>
<td>Methohexital</td>
<td>Enflurane</td>
<td>Improved psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Sanders et al.\textsuperscript{47}</td>
<td>40 dental</td>
<td>Thiopental</td>
<td>Halothane</td>
<td>Similar emergence and recovery</td>
<td></td>
</tr>
<tr>
<td>Norton and Dundas\textsuperscript{48,\dagger}</td>
<td>40 vasectomy</td>
<td>Midazolam–flumazenil</td>
<td>Isoflurane</td>
<td>Improved psychomotor performance</td>
<td></td>
</tr>
</tbody>
</table>

* Findings are expressed with respect to the propofol group.
\dagger This study was multiple-group comparisons but has been subdivided for ease of interpretation.

Table 4. Comparison of Propofol for Induction and Maintenance of Outpatient Anesthesia with a Propofol–Volatile Anesthetic Combination

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Adjuvants</th>
<th>Propofol Administration</th>
<th>Comparative Maintenance*</th>
<th>Principal Findings†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hervegos et al.\textsuperscript{49,\dagger}</td>
<td>40 arthroscopies</td>
<td>FRI</td>
<td>Isoflurane, 1%</td>
<td>Similar emergence and psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Larse et al.\textsuperscript{50}</td>
<td>74 arthroscopies</td>
<td>FRI</td>
<td>Isoflurane</td>
<td>Impaired psychomotor performance in first 30 min</td>
<td></td>
</tr>
<tr>
<td>Marshall et al.\textsuperscript{51}</td>
<td>114 females</td>
<td>Alfentanil</td>
<td>FRI</td>
<td>Similar emergence and psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Milligan et al.\textsuperscript{52}</td>
<td>60 D &amp; Cs</td>
<td>Alfentanil</td>
<td>IB</td>
<td>Faster emergence, recovery times similar</td>
<td></td>
</tr>
<tr>
<td>Nightingale and Lewis\textsuperscript{53}</td>
<td>50 D &amp; Cs</td>
<td>Alfentanil</td>
<td>IB</td>
<td>Improved psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Valanne\textsuperscript{54}</td>
<td>50 dental</td>
<td>FRI</td>
<td>Isoflurane</td>
<td>Faster emergence, recovery, and discharge</td>
<td></td>
</tr>
<tr>
<td>Zuurmond et al.\textsuperscript{56}</td>
<td>40 arthroscopies</td>
<td>FRI</td>
<td>Isoflurane, 0.9%</td>
<td>Similar emergence and psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Ding et al.\textsuperscript{57,\dagger}</td>
<td>38 laparoscopies</td>
<td>Fentanyl</td>
<td>VRI</td>
<td>Similar emergence and psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Rapp et al.\textsuperscript{58,\dagger}</td>
<td>45 orthopedic</td>
<td>Fentanyl</td>
<td>VRI</td>
<td>Similar emergence and psychomotor performance</td>
<td></td>
</tr>
<tr>
<td>Van Hemelrijk et al.\textsuperscript{59,\dagger}</td>
<td>46 females</td>
<td>Fentanyl</td>
<td>VRI</td>
<td>Similar emergence and psychomotor performance</td>
<td></td>
</tr>
</tbody>
</table>

VRI = variable-rate infusion; FRI = fixed-rate infusion; IB = intermittent bolus doses.
* Volatile agent titrated to clinical endpoints, unless otherwise stated.
† Findings are expressed with respect to the propofol group.
‡ This study was a multiple-group comparison but has been subdivided for ease of interpretation.
for individual variations in the anesthetic requirements, it is difficult to be certain that patients were at comparable depths of anesthesia. In the absence of an objective monitor of anesthetic depth, it is a common practice to titrate the anesthetic drugs using clinical signs (e.g., hemodynamic and respiratory variables), and to regard comparable cardiorespiratory stability as indicative of a similar depth of anesthesia. When propofol and isoflurane were administered using this clinical titration methodology, propofol was found to be associated with improved performance on psychomotor testing during the 1st h of recovery. Of interest, this difference was no longer apparent 2 h after the operation. In clinical comparisons with enflurane or desflurane, maintenance of anesthesia with propofol did not improve recovery times (fig. 3). Although it is possible that the use of intravenous adjuvants such as fentanyl and midazolam, and mask-diffused nitrous oxide, could have affected the results, the differences found in routine practice are indeed of little (if any) clinical significance. Finally, a large multicenter survey found that when isoflurane was used to supplement propofol–N₂O anesthesia, emergence times were slightly prolonged compared with propofol–N₂O alone; however, this effect was not clinically significant.

**Propofol versus Inhaled Induction**

When propofol induction and maintenance were compared with an inhalation induction using halothane followed by isoflurane for maintenance of pediatric anesthesia, recovery times were remarkably similar. However, the concomitant use of meperidine and diazepam premedication, as well as intraoperative morphine, may well have masked differences between the two study groups. Although the use of propofol for induction of anesthesia was associated with pain on injection, it significantly decreased the incidence of upper airway obstruction compared with halothane.

Induction of anesthesia with propofol was more rapid than inhalation induction in adults, even when newer volatile anesthetics with low blood-gas partition coefficients were used. Propofol induction was also associated with less airway irritation compared with desflurane, but not sevoflurane. Recovery times after use of propofol–N₂O for induction and maintenance were similar to those achieved with sevoflurane–N₂O or desflurane–N₂O. Use of desflurane–O₂ resulted in a more rapid emergence than propofol–N₂O (fig. 3); however, recovery times were similar.

**Propofol versus Alternative Total Intravenous Anesthetic Techniques**

Recovery after TIVA with propofol with recovery has been compared with recovery after other intravenous anesthetic agents (table 5). Most comparisons have shown that propofol is associated with a faster emergence and improvements in the patient's assessment of their recovery or enhanced performance in psychomotor testing. Comparisons with methohexital have tended to yield smaller differences than with other commonly used intravenous agents (e.g., thiopental, midazolam, etomidate). For outpatients undergoing dental surgery, recovery was reported to be faster after methohexital than after propofol. However, this finding may have been related to the comparatively large propofol dose (3 mg·kg⁻¹) used for induction of anesthesia. Unfortunately, most of these studies have not reported discharge times, an important measure of the efficiency of an outpatient anesthetic technique. Two investigations reported similar discharge times after propofol and methohexital for very short operations. A further investigation found similar discharge times for propofol and thiopental, although the preoperative use of diazepam may have delayed discharge in both groups.

Several investigators have commented upon the quality of anesthetic maintenance with propofol in comparison with other intravenous agents. TIVA with propofol has generally been reported as "smooth," with a reduced incidence of coughing and hiccupping, resulting in improved surgical conditions compared with barbiturates or etomidate. A further common finding with propofol has been a reduced incidence of postoperative nausea.

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Table 5. Comparison of Propofol with Alternative Intravenous Techniques for Outpatient Anesthesia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Adjuvants</th>
<th>Administration</th>
<th>Comparator</th>
<th>Principal Findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeGroot et al.40†</td>
<td>31 laparoscopies</td>
<td>Fentanyl</td>
<td>FRI</td>
<td>Etomidate</td>
<td>Faster and more predictable recovery</td>
</tr>
<tr>
<td>Heath et al.41†</td>
<td>40 TOPs</td>
<td>Alfentanil</td>
<td>IB</td>
<td>Etomidate</td>
<td>Faster emergence, smoother induction</td>
</tr>
<tr>
<td>Cade et al.42</td>
<td>70 females</td>
<td>Fentanyl</td>
<td>IB</td>
<td>Methohexital</td>
<td>Faster recovery to ambulation</td>
</tr>
<tr>
<td>Cundy and</td>
<td>60 TOPs</td>
<td>Fentanyl</td>
<td>IB</td>
<td>Methohexital</td>
<td>Improved “quality” of anesthesia, less drowsy</td>
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<td>Arunasalam43</td>
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<td>Doze et al.44</td>
<td>60 females</td>
<td>Meperidine</td>
<td>VRI</td>
<td>Methohexital</td>
<td>Earlier orientation and ambulation</td>
</tr>
<tr>
<td>Heath et al.45†</td>
<td>40 TOPs</td>
<td>Alfentanil</td>
<td>IB</td>
<td>Methohexital</td>
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<td>Kay and Healy46†</td>
<td>60 cystoscopies</td>
<td>Alfentanil</td>
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<tr>
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<td>Methohexital</td>
<td>Slower emergence, similar recovery times</td>
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<td>Noble and Ogg49</td>
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<tr>
<td>Rieder and Misver47†</td>
<td>50 D &amp; Cs</td>
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<td>Edelfors51</td>
<td>90 TOPS</td>
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<td>Faster emergence and orientation</td>
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<td>40 TOPs</td>
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<td>IB</td>
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<td>60 D &amp; Cs</td>
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<td>IB</td>
<td>Thiopental</td>
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<td>Henriksson et al.54</td>
<td>120 D &amp; Cs</td>
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<td>Thiopental</td>
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<tr>
<td>Kortilia et al.56</td>
<td>12 volunteers</td>
<td>Diazepam</td>
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<tr>
<td>Nielsen et al.57</td>
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<td>Thiopental</td>
<td>Similar emergence and recovery times</td>
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<td>Rieder and Misver47†</td>
<td>50 D &amp; Cs</td>
<td>Alfentanil</td>
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<td>Ryom et al.58</td>
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</tr>
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<td>VRI = variable-rate infusion; FRI = fixed-rate infusion; IB = intermittent bolus doses.</td>
<td></td>
<td></td>
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<td>* Findings are expressed with respect to the propofol group.</td>
<td></td>
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<tr>
<td>† This study was multiple-group comparisons but has been subdivided for ease of interpretation.</td>
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</table>

and vomiting. This finding has been reported when using propofol both for induction and maintenance, as well as when it is used solely as an induction agent. 26–28,31,33,35,36,45,51,54,56,57,60,64,66,72

In summary, compared with traditional techniques involving barbiturate–volatile agent combinations, balanced anesthesia or TIVA with propofol may offer significant advantages in terms of more rapid recovery and reduced postoperative nausea and vomiting. However, some of this benefit appears to result from the substitution of propofol for barbiturates during the induction period. After short cases (<30 min), the maintenance technique appears to have less impact on recovery times. When propofol is used for induction of anesthesia, followed by maintenance with a volatile agent, there is only a small increase in direct costs with propofol. However, careful cost: benefit analysis may be needed to determine whether the additional cost when propofol is used for both induction and maintenance of anesthesia is justified in terms of reduced duration of hospital stay and fewer side effects.

Monitored Anesthesia Care

Monitored anesthesia care usually involves the administration of intravenous adjuvants to produce sedation, anxiolysis, and amnesia during minor diagnostic and therapeutic procedures or to supplement analgesia provided by local or regional anesthetic techniques. During monitored anesthesia procedures, patients are monitored to ensure their safety and comfort during the operation. With the optimum sedation technique, the chosen drug (or combination of drugs) has sedative–hypnotic, anxiolytic, and amnestic properties; produces a low incidence of perioperative side effects (e.g., respiratory depression, nausea and vomiting); and provides ease of titration to the desired level of sedation while providing rapid return to a “clearheaded” state on completion of the procedure.

Traditionally, benzodiazepines have been the most widely used drug for sedation during monitored anesthesia care. However, even drugs like midazolam and triazolam with relatively short elimination half-life values (2–4 h) may be associated with prolonged sedation,
and the resultant psychomotor impairment can delay recovery. 

Opioid analgesics (e.g., fentanyl and its newer analogues) are often administered in combination with sedative–hypnotic agents to reduce pain resulting from the injection of local anesthetic solutions and traction on deeper tissue structures. Although a combination of midazolam and fentanyl is very popular, this combination can produce profound respiratory depression. However, when used alone, the potent opioid analgesics generally do not produce adequate sedation and may be associated with undesirable side effects (e.g., itching, respiratory depression, nausea).

Because the use of low-dose propofol infusions is associated with a rapid recovery when used as part of a balanced anesthetic technique, there has long been interest in using propofol to produce sedation during local and regional anesthesia. The use of propofol for sedation was initially described by Mackenzie and Grant in 1987. These investigators used a variable-rate propofol infusion (mean dosage 63 µg·kg⁻¹·min⁻¹) to provide sedation for patients undergoing lower limb surgery under spinal anesthesia. This low-dose propofol infusion resulted in a sleeplike state from which patients were arousable with verbal commands. More importantly, maintenance of the desired sedation level was easily achieved by varying the propofol infusion rate. After completion of the operation, patients were awake within 4 min after terminating the propofol infusion, and rapidly became clearheaded with "a strong desire for food." The authors also commented on the ease with which the transition to general anesthesia could be made when the operation became more extensive than originally planned. In a follow-up study, these investigators compared infusions of propofol and midazolam when used to supplement spinal anesthesia. Propofol 62 µg·kg⁻¹·min⁻¹ provided sedation comparable to that provided by midazolam 4.5 µg·kg⁻¹·min⁻¹ but was associated with a significantly more rapid recovery. After discontinuation of the sedative infusions, patients receiving propofol were wide awake in 2.1 ± 0.3 min, compared with 9.2 ± 1.5 min after midazolam.

When propofol and midazolam infusions were evaluated during monitored anesthesia care, propofol was associated with decreased levels of residual sedation, drowsiness, confusion, clumsiness, and amnesia compared with midazolam (fig. 4). Impairment of cognitive function in the early postoperative period was significantly greater in the midazolam-treated patients. Although midazolam produced more effective intraoperative amnesia, residual amnesia persisted for 60 min (or longer) into the postoperative period. Fanard et al. also found that all patients had recovered to baseline levels within 15 min after discontinuing propofol 44 µg·kg⁻¹·min⁻¹, whereas 24% of those receiving midazolam 0.67 µg·kg⁻¹·min⁻¹ required more than 2 h to achieve comparable recovery endpoints. The clinical experience that has been gained using propofol for sedation has culminated in the recent approval by the Food and Drug Administration of this indication.

Low-dose propofol infusions have also been used as an adjunct to local infiltration anesthesia in patients undergoing central venous catheter placement, oral surgery, and superficial surgical procedures, including breast biopsy and herniorrhaphy procedures. Recovery was superior after propofol sedation compared with midazolam and diazepam. Even when the residual effects of midazolam were antagonized by flumazenil, recovery was no more rapid than after a propofol infusion. Ferrari and Donlon compared bolus injections of propofol 0.5 mg·kg⁻¹ with midazolam 0.02 mg·kg⁻¹ and methohexital 0.45 mg·kg⁻¹ for sedation during retrobulbar or peribulbar blocks for ophthalmologic procedures. Propofol was associated with the lowest incidence of awareness during injection.
of the local anesthetic block, and also resulted in more satisfactory sedation during the remainder of the surgical procedure. Additional advantages of propofol for this procedure include its ability to decrease intraocular pressure and reduce postoperative nausea. Furthermore, sedative doses of propofol had no adverse effects on tidal volume, minute ventilation, end-tidal carbon dioxide (CO₂) tension, or arterial blood gases. However, propofol can depress the ventilatory response to hypoxia in volunteers, suggesting that supplemental oxygen (O₂) should always be supplied.

Propofol sedation has also been used to provide satisfactory conditions for upper gastrointestinal endoscopic procedures. Use of an infusion of propofol 7.2 µg·kg⁻¹·min⁻¹ produced a cooperative patient with complete amnesia for the procedure while providing awakening and orientation in 4.8 ± 5.9 and 6.1 ± 5.7 min after discontinuing the infusion, respectively. Patterson et al. reported more rapid recovery and reduced hangover effects after propofol compared with midazolam when these drugs were administered for upper gastrointestinal endoscopic procedures. The short duration of hypnosis after a bolus dose of propofol resulted in more recall of the end of the endoscopic procedure. However, the use of one or more supplemental doses of propofol would have extended the period of unconsciousness and reduced recall. Because of its profound cardiovascular and respiratory depressant properties, propofol should always be administered by personnel trained in the administration of general anesthesia, and not by gastroenterologists, radiologists and surgeons.

Several investigators have commented upon the minimal degree of amnesia produced by hypnotic doses of propofol. Smith et al. administered four different bolus dose–infusion regimens to patients undergoing urologic procedures with regional anesthesia. Propofol infusion rates of 8, 17, 33, and 67 µg·kg⁻¹·min⁻¹ resulted in dose-related increases in the level of sedation (fig. 5). Recall was assessed by showing the patients a picture 30 min after the start of the propofol infusion. Amnesia was not evident in the two low-dose propofol groups, with 88% and 86% of patients recalling the picture. However, at the two highest propofol infusion regimens, recall was reduced to 65% and 18%, respectively.

Sedation, amnesia and anxiolysis are well-recognized pharmacologic features of benzodiazepines like midazolam; however, the persistence of sedation and amnesia into the postoperative period is undesirable. The use of a midazolam and propofol combination takes advantage of the rapid recovery from propofol, whereas the benzodiazepine reduces intraoperative recall and anxiety. Taylor et al. used a variable-rate propofol infusion (25–120 µg·kg⁻¹·min⁻¹) to provide sedation for outpatients undergoing operations with local anesthesia lasting 45–55 min. Before injection of the local anesthetic, patients received midazolam 2 mg intravenously or a similar volume of saline according to a randomized, double-blind protocol. The addition of midazolam resulted in a significant increase in the level of sedation, decreased intraoperative anxiety, and reduced recall of painful intraoperative events (e.g., infiltration of the local anesthetic solution). Importantly, when given at the outset, midazolam did not compromise the rapid recovery or favorable side effect profile after propofol sedation.

Propofol sedation can also be supplemented by opioid analgesics to provide sedation–analgesia for uncomfortable procedures performed without local anes-

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Fig. 5. Sedation visual analogue scores recorded by patients (A) and by a blinded observer (B) before (time 0), during (15, 30, 45, and 60 min), and after PACU sedation with propofol. Patients received propofol 0.2 mg·kg⁻¹ and 8 µg·kg⁻¹·min⁻¹ (group 1, solid squares); 0.4 mg·kg⁻¹ and 17 µg·kg⁻¹·min⁻¹ (group 2, open squares); 0.5 mg·kg⁻¹ and 35 µg·kg⁻¹·min⁻¹ (group 3, solid circles); and 0.7 mg·kg⁻¹ and 67 µg·kg⁻¹·min⁻¹ (group 4, open circles). Values represent mean ± SEM. *P < 0.05 compared with group 1; †P < 0.05 compared with 15-min value in same group. Reproduced from Smith et al., with permission.
PROPOFOL: AN UPDATE

Anesthesia. During extracorporeal shock wave lithotripsy, a combination of propofol and fentanyl produced comparable sedation and improved cardiorespiratory stability compared with an alfentanil–midazolam mixture, whereas both techniques decreased the anesthesia time and permitted a more rapid recovery than an epidural technique.97 Similarly, a mixture of alfentanil and propofol provided satisfactory conditions for transvaginal oocyte removal without clinically significant respiratory depression.99 In contrast, significant respiratory depression has been reported when midazolam–fentanyl or midazolam–alfentanil combinations are used.82,97

One of the advantages of propofol’s pharmacologic profile relates to the ease with which the resultant level of sedation can be altered. Several investigative groups have experimented with alternative methods for providing propofol sedation.100–105 The use of a computer-controlled infusion device to achieve a target plasma propofol concentration derived from population pharmacokinetics resulted in satisfactory levels of sedation during 88% of the total infusion time.100 However, a recent comparative study failed to find any clinically significant advantages of the pharmacokinetic-based delivery system compared with conventional manual bolus–infusion schemes.101

An alternative approach is to allow patients to self-administer sedative medications during monitored anesthesia care using a patient-controlled analgesia device. Using bolus doses of propofol 0.7 mg·kg⁻¹ with a lockout interval of 3 min, satisfactory sedation and a very high level of patient satisfaction was achieved during dental extractions102 and during procedures performed under regional anesthesia.103 In a comparison of patient-controlled sedation (PCS) by propofol and anesthesiologist-administered fentanyl–midazolam, the PCS group reported greater satisfaction and more rapid recovery of postoperative cognitive function.104 However, these differences were likely caused by the use of propofol versus midazolam, rather than being specifically related to the use of the PCS technique. Ghouri et al. compared propofol, midazolam, and alfentanil when administered using a patient-controlled analgesia device to supplement a basal infusion during operations performed under local anesthesia.105 Although all three drugs were associated with a high degree of patient satisfaction, propofol was associated with less postoperative nausea than alfentanil. Propofol produced more pain on injection, whereas midazolam was associated with decreased intraoperative recall.

Discharge times were similar with propofol and midazolam, but discharge was delayed after alfentanil, probably because of the higher incidence of nausea. Although PCS with propofol may be an acceptable method of intraoperative drug delivery, no controlled trial has yet compared PCS with conventional bolus–infusion administration of propofol by an anesthesiologist.

In summary, propofol is capable of producing easily controllable levels of sedation during a variety of procedures performed with or without supplemental local or regional anesthesia. Its mood-altering (e.g., euphorogenic) properties are felt to be “well-suited for conscious sedation procedures.”5 Low-dose infusions of propofol are associated with a predictably rapid recovery with few (if any) postoperative side effects. When amnesia and supplemental analgesia are needed, small doses of midazolam (2–3 mg) and fentanyl (50–75 µg) or alfentanil (0.5–1 mg) can be administered without affecting recovery times or increasing the incidence of perioperative side effects. Novel methods of propofol delivery (e.g., PCS) are associated with a high degree of patient acceptance. However, comparative trials are needed to determine whether these new modalities provide any additional benefit over conventional techniques for administering intravenous sedative medications during local anesthesia.

Neuroanesthesia

Considerable interest has been shown in the use of propofol for maintenance of neurosurgical anesthesia because a rapid recovery profile would facilitate an earlier postoperative assessment of central nervous system function. Propofol infusions can be used as an alternative to the volatile anesthetic agents, which all have the ability to cause cerebrovascular dilatation and thereby increase intracranial pressure (ICP). Analogous to the barbiturates, propofol can reduce ICP and intracranial pressure, decrease cerebral metabolic requirement for O₂ (CMRO₂), and may provide cerebral protection. In 1993, the Food and Drug Administration approved the use of propofol for neurosurgical procedures.

Propofol and the Cerebrovascular Circulation

In clinical practice, use of propofol has been associated with cerebral vasoconstriction, decreased cerebral blood flow (CBF), and reduced CMRO₂ (table
6) Propofol also reduces the cerebral consumption of metabolic substrates. In contrast, in vitro studies have suggested that propofol has direct cerebral arterial and venous dilating properties. In patients undergoing coronary artery bypass graft surgery, induction with propofol 2 mg·kg⁻¹ intravenously produced a 51% decrease in CBF, a 36% reduction of CMRO₂, and a 25% decrease in cerebral perfusion pressure (CPP). However, the relation between the cerebral effects and the systemic hypotensive effects after induction of anesthesia with propofol in neurological patients is unclear.

In patients with brain tumors undergoing ventriculostomy for intracranial hypertension, induction of anesthesia with propofol 2.5 mg·kg⁻¹ resulted in significant decreases in both mean arterial pressure (MAP) and CPP, while ICP remained unchanged. In patients with severe head injuries and normal ICP values, Pinaud et al. assessed regional CBF using a xenon-133 internal carotid artery injection technique. During a propofol-based anesthetic technique, these investigators found a 25% reduction in MAP, a 26% decrease in mean regional CBF and a similar decrease in CPP. Decreases in CBF have also been recorded even when blood pressure was maintained at baseline values using vasopressor drugs. Using a canine model, Artu et al. also found a significant reduction in CBF despite unchanged MAP values. These authors concluded that although the reductions in CBF and CMRO₂ (52% and 28%, respectively) were numerically different, they remained coupled. If propofol reduces CBF independently of changes in CPP, the mechanism of this action could be a reduction in cerebral metabolism. However, the decreases in CBF have not always been associated with equivalent reductions in CMRO₂.

Ramani et al. administered a progressively increasing propofol infusion to rats during a "basal" opioid-N₂O anesthetic. While maintaining the MAP constant with an angiotensin II infusion, these investigators reported a close relation between CBF and CMRO₂. At low concentrations of propofol, an increase in activity on the electroencephalogram (EEG) was noted. However, at higher concentrations of propofol, the EEG showed progressive suppression (with an apparent correlation between EEG power and CMRO₂). To achieve EEG burst suppression during clinical neuroanesthesia, blood

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Propofol Regimen</th>
<th>CBF (i)</th>
<th>CVR (f)</th>
<th>CMRO₂ (i)</th>
<th>ICP (i)</th>
<th>MAP (i)</th>
<th>CPP (i)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Stephan et al.</td>
<td>11 cardiac</td>
<td>2 mg·kg⁻¹</td>
<td>51%*</td>
<td>55%*</td>
<td>36%*</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Herregods et al.</td>
<td>6 head injury</td>
<td>2 mg·kg⁻¹</td>
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<td>NR</td>
<td>NR</td>
<td>56%*</td>
<td>34%*</td>
<td>46%*</td>
<td>Air/O₂ ICP &gt; 25 mmHg</td>
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<tr>
<td>Ravussin et al.</td>
<td>23 intracranial</td>
<td>1.5 mg·kg⁻¹</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>32%*</td>
<td>10%*</td>
<td>15%</td>
<td>100% O₂ ICP &gt; 15 mmHg</td>
</tr>
<tr>
<td>Vandeneeste et al.</td>
<td>13 vertebral disk</td>
<td>100-350 μg·kg⁻¹·min⁻¹</td>
<td>27%*</td>
<td>51%*</td>
<td>18%</td>
<td>NR</td>
<td>NR</td>
<td>5%</td>
<td>0.5% enflurane, 6% N₂O; phenylephrine</td>
</tr>
<tr>
<td>Van Hemelrijck et al.</td>
<td>7 treated</td>
<td>2.5 mg·kg⁻¹</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>45%*</td>
<td>49%*</td>
<td>100% O₂</td>
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<td>Pinaud et al.</td>
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<td>150 μg·kg⁻¹·min⁻¹</td>
<td>26%*</td>
<td>NR</td>
<td>NR</td>
<td>16%*</td>
<td>26%*</td>
<td>28%*</td>
<td>Air/O₂</td>
</tr>
<tr>
<td>Van Hemelrijck et al.</td>
<td>7 baboons</td>
<td>200 μg·kg⁻¹·min⁻¹</td>
<td>39%*</td>
<td>NR</td>
<td>NR</td>
<td>22%</td>
<td>NR</td>
<td>17%*</td>
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<tr>
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<td>6 dogs</td>
<td>400 μg·kg⁻¹·min⁻¹</td>
<td>52%*</td>
<td>155%*</td>
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<td>3%</td>
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<td>1.7-3.5 mg·kg⁻¹</td>
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<td>NR</td>
<td>45%*</td>
<td>45%*</td>
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<td>Raman et al.</td>
<td>9 rabbits</td>
<td>283-1100 μg·kg⁻¹·min⁻¹</td>
<td>38%*</td>
<td>43%*</td>
<td>NR</td>
<td>NR</td>
<td>10%*</td>
<td>N₂O-O₂</td>
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</tbody>
</table>

CBF = cerebral blood flow; CVR = cerebral vascular resistance; CMRO₂ = cerebral metabolic rate for oxygen; ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure; NR = not reported.

* P < 0.05, significant change from baseline value.
† P < 0.01, significant change from baseline value.
‡ P < 0.001, significant change from baseline value.
§ ICP estimated from lumbar cerebrospinal fluid pressure.
1 Mean arterial pressure maintained at baseline values with vasopressors.
** P value not recorded.

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Fig. 6. Autoregulation of cerebral blood flow (measured by xenon-133 technique) during manipulation of mean arterial blood pressure with phenylephrine in humans anesthetized with a propofol infusion. Reproduced from Craen et al., with permission.

Propofol concentrations of 6.3 ± 1.4 μg·ml⁻¹ were required. Herrgods et al. studied patients with increased ICP (>25 mmHg) after severe head injury. They found that propofol 2 mg·kg⁻¹ resulted in a 34% decrease in MAP and a 56% decline in ICP. However, there was an associated 46% decrease in the CPP. Although most studies have found a reduction in ICP after induction of anesthesia with propofol, the associated decrease in MAP usually leads to a decreased CPP. Ravussin et al. studied patients undergoing craniotomy and found that an induction dose of propofol 1.5 mg·kg⁻¹ followed by a maintenance infusion of 100 μg·kg⁻¹·min⁻¹ resulted in 32% and 10% decreases in cerebrospinal fluid pressure and MAP values, respectively. Recent investigations have described reductions of ICP even when CPP was maintained during propofol anesthesia. For example, in patients with supratentorial mass lesions without intracranial hypertension, TIVA with propofol led to a decrease in lumbar cerebrospinal fluid pressure from 9.3 ± 3.9 (mean ± SD) to 5.1 ± 2.9 mmHg when arterial blood pressure was maintained with vasopressor drugs.

It appears that the autoregulatory capacity of the cerebral circulation remains intact during propofol anesthesia (fig. 6). In an animal model, Werner et al. demonstrated that cerebral autoregulation was preserved even after high doses of propofol. Several investigative groups have reported that the response of the cerebrovascular system to changes in CO₂ tension is also preserved during propofol anesthesia (fig. 7). Eng et al. studied CBF noninvasively using transcranial Doppler assessment of the velocity of middle cerebral artery blood flow during conditions of normocapnia, hypocapnia and hypercapnia in both the awake state and during propofol anesthesia. Reactivity to CO₂ was preserved; however, the slope of the CO₂-response curve was decreased in the presence of propofol. Furthermore, there was no detectable difference when N₂O was added, a finding since confirmed by Craen et al.

Propofol and Cerebral Protection

It has been suggested that propofol can reduce neuronal injury after incomplete ischemia by reducing CMRO₂. Using an hypoxic animal model, propofol was reported to improve tolerance of global cerebral ischemia. The improvement in survival was similar to that seen in a barbiturate control group. Using a hypotensive model of global ischemia, Weir

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et al. reported that the animals receiving an infusion of propofol showed higher postisult CBF, improved electrolyte homeostasis, and better recovery of EEG activity than control animals. However, histologic outcome was unchanged in the propofol-treated animals.

After incomplete focal ischemia produced by temporary right common carotid artery ligation and hemorrhage-induced hypotension, neurologic outcome was improved and neuronal damage reduced in animals receiving propofol titrated to produce EEG burst suppression compared with a group receiving fentanyl—N₂O. However, in another study of focal ischemia after temporary middle cerebral artery occlusion, administration of propofol resulted in no significant difference in outcome or infarct size, compared with halothane anesthesia. Of interest, the same model was able to demonstrate a reduction in infarct size when a barbiturate anesthetic was compared with halothane. In a different animal model of focal ischemia, Gelb et al. were also unable to demonstrate any significant reduction in the area of ischemia when propofol or thiopental were compared with halothane.

Ravussin and de Tribolet used a continuous infusion of propofol to provide anesthesia for cerebral aneurysm surgery. After induction with propofol 1.8 ± 0.1 mg·kg⁻¹, anesthesia was maintained with a propofol infusion of 87 ± 3 µg·kg⁻¹·min⁻¹. EEG burst suppression was achieved during the temporary clipping of the vessel by increasing the propofol infusion to 500 µg·kg⁻¹·min⁻¹. During this treatment period, volume loading and dopamine infusions were used to avoid hypotension and to provide moderate hypertension (MAP 100 mmHg) in an attempt to improve collateral blood flow. None of the patients who required a temporary clip (three of whom had the temporary clip applied for more than 20 min) showed signs of neurologic deterioration. As might be expected, the use of propofol to achieve EEG burst suppression is associated with a reduction in cardiac output and MAP. Propofol 1 mg·kg⁻¹ followed by an infusion of 333 µg·kg⁻¹·min⁻¹ for 30 min and then 250 µg·kg⁻¹·min⁻¹ was used to produce burst suppression. While maintaining the cardiac filling pressure at baseline levels with supplemental fluids, MAP, cardiac output, and left ventricular stroke work index decreased by 20%, 23%, and 26% respectively. These cardiovascular changes are similar to those reported with thiopental.

Propofol and Clinical Neuroanesthesia

Numerous studies have compared anesthetic techniques for neuroanesthesia. Recently, Todd et al. reported on the results of a randomized, prospective comparison of three neuroanesthetic regimens. All patients were undergoing elective craniotomy for supratentorial mass lesions and were randomized to receive one of the following: (1) a propofol–fentanyl–based anesthetic consisting of propofol 1–2 mg·kg⁻¹ followed by infusions of propofol 50–300 µg·kg⁻¹·min⁻¹ and fentanyl 0.03–0.05 µg·kg⁻¹·min⁻¹; (2) thiopental 4–6 mg·kg⁻¹ followed by isoflurane–N₂O anesthesia; or (3) thiopental followed by fentanyl–N₂O anesthesia with supplemental isoflurane as needed to maintain hemodynamic stability. The isoflurane–N₂O group resulted in higher heart rate (HR) values during induction of anesthesia and a lower MAP during the maintenance period than did the other anesthetic techniques. However, this treatment group had significantly more patients with an ICP greater than 24 mmHg. Overall, the fentanyl–N₂O group had the most rapid emergence, and isoflurane–N₂O was associated with the slowest emergence. The fentanyl–N₂O group had a higher incidence (17%) of vomiting on emergence than the propofol–fentanyl (2.5%) or isoflurane–N₂O (5%) groups. There were no differences between the three groups with respect to recovery milestones or neurologic outcome. These authors concluded that all three anesthetic regimens were equally acceptable.

Ravussin et al. compared a thiopental–isoflurane technique with a propofol-based anesthetic technique in patients undergoing elective neurosurgical procedures. They found that hemodynamic variables were similar in the two groups during induction. However, during application of the Mayfield head-holder, the propofol-based technique provided improved control of HR, MAP, and cerebrospinal fluid pressure. During the early recovery period, the propofol-treated patients had shorter recovery times and higher Glasgow coma scale scores compared with the thiopental–isoflurane group. Yet, the differences between the two groups were no longer significant after 30 min. Paillot et al. compared recovery after carotid endarterectomy surgery with either propofol or etomidate–isoflurane anesthesia. Although hemodynamic stability was similar with both techniques, subjective and cognitive functioning (as assessed using sedation scores and psychometric testing, respectively) recovered more rapidly in the propofol group.
PROPOFOL: AN UPDATE

Given the length of many neurosurgical procedures, the issue of cost-effectiveness of drugs like propofol has assumed greater importance. Todd et al. calculated the cost of the propofol–fentanyl anesthetic to be three times higher than the thiopental–isoflurane–N₂O techniques. In addition, the use of intravenous anesthetic and analgesic infusions will also require specialized equipment for drug administration (e.g., infusion pump, intravenous tubing sets). Aitken and Farling estimated that anesthetic for aneurysm clipping using propofol is twice as expensive as an isoflurane-based technique. However, the relative costs of anesthetic and analgesic drugs change over time. More importantly, the cost of the anesthetic drugs is only a small fraction of the total hospital costs for a neurosurgical procedure.

Propofol and the Electroencephalogram

One of the primary concerns when using propofol for neuroanesthesia relates to the reports of alleged seizure-like activity after propofol anesthesia. Yet, in animal models of status epilepticus, propofol suppressed seizures and possessed anticonvulsant properties similar to thiopental. For example, propofol increases the lidocaine seizure threshold in rats. However, subanesthetic doses of propofol have been shown to augment the proconvulsant activity of the excitatory amino acids kainic acid and quisqualic acid.

Propofol, in common with other intravenous sedative–hypnotic drugs, induces dose-dependent changes in the EEG. When propofol is infused at a low rate to provide sedation, the most commonly observed EEG change is an increase in beta activity. However, when given at a rate sufficient to produce unconsciousness, propofol produces an increase in delta activity. At even higher infusion rates, propofol can achieve EEG burst suppression. There is no evidence that propofol produces epileptiform activity in nonepileptic patients. Indeed, successful use of propofol to treat status epilepticus has been reported.

Propofol decreases the duration of seizures in patients receiving electroconvulsive therapy (ECT) when induction doses are compared with those of methohexital. However, the use of propofol in known epileptic patients remains controversial. Hodkinson et al. described three patients who developed increased epileptiform activity on EEG recordings when they received propofol 2 mg·kg⁻¹ as part of an anesthetic technique for seizure surgery. Areas of the brain which had not previously been shown to contain an epileptogenic focus displayed abnormal activity after propofol administration. The effect of propofol on the EEG activity of epileptic patients appears to be variable, with some patients showing increased spike activity and others displaying decreased EEG activity. Ebrahimi et al. found that epileptiform activity increased in only 1 of 13 patients with temporal lobe epilepsy after a 2-mg·kg⁻¹ bolus of propofol. The central nervous system depressant effects of propofol appear to be dose-dependent; low doses may increase the activity of an epileptic focus, and higher doses (>1 mg·kg⁻¹) lead to suppression of EEG activity. Of interest, in a study of 11 mentally retarded patients with pharmacologically controlled epilepsy, Oei-Lim et al. found that the use of a low-dose infusion of propofol to provide conscious sedation during dental surgery (92 ± 18 µg·kg⁻¹·min⁻¹, mean ± SD), did not increase interictal EEG activity.

Reports of adverse neurologic sequelae after propofol administration led the United Kingdom Committee on Safety of Medicines to report that "convulsions" and involuntary movements have been associated with the use of propofol. This committee subsequently advised that care should be taken when propofol is used in epileptic patients. The case reports include descriptions of convulsions and myoclonic movements with opisthotonos (hyperreflexia and arching of the back). These clinical signs can be associated with depressed levels of consciousness. Saunders and Harris reported four such cases and suggested that many of the reports of convulsions actually represent opisthotonos and an associated depression in consciousness level resulting from a drug-induced state of decerebrate rigidity. In three of the four cases, an EEG demonstrated a sleeplike EEG pattern consistent with cortical depression without any evidence of epileptiform activity. Other workers have confirmed the absence of seizure activity by EEG recording during involuntary

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movements with propofol\textsuperscript{150} and have suggested that these events result from preferential depression of subcortical areas.\textsuperscript{163} Excitatory events (e.g., myoclonus, tremor, and dystonic posturing) during induction of anesthesia appear to be less prominent with propofol than with etomidate, thiopental or methohexitone.\textsuperscript{164}

In summary, the use of propofol is associated with significant reductions in CBF, CMRO\textsubscript{2}, and ICP. Propofol appears to have a cerebral protective action similar to that of the barbiturates. Because changes in blood pressure after induction doses of propofol are frequently reflected by changes in CPP, propofol should be administered with caution to avoid acute hemodynamic changes in patients with reduced intracranial compliance, as well as in patients receiving diuretic therapy. Propofol was recently approved by the Food and Drug Administration for use in neuroanesthesia, although the package insert cautions against its use in patients with increased ICP or abnormal cerebral circulation. The use of propofol in patients with seizure disorders remains controversial. However, increasing evidence suggests that propofol possesses profound anticonvulsant activity (see Electroconvulsive Therapy, below).

Cardiac Anesthesia

The optimal anesthetic technique for cardiac surgery should provide (1) intraoperative hypnosis, amnesia, and analgesia; (2) hemodynamic stability with minimal direct myocardial depression; and (3) rapid recovery without the need for introtropic support. High-dose opioid techniques became popular because of the excellent hemodynamic stability associated with fentanyl and its newer analogues. However, opioid-based techniques may not provide an optimum degree of hemodynamic stability throughout the operation\textsuperscript{165} and are more likely to be associated with intraoperative awareness.\textsuperscript{166} Supplementation of an opioid-based anesthetic with volatile agents reduces the incidence of intraoperative awareness and improves hemodynamic stability, but may increase the potential for myocardial ischemia.\textsuperscript{167} The use of a high-dose opioid technique also prolongs the duration of postoperative mechanical ventilatory support.\textsuperscript{168} Prolonged stays in the ICU are expensive and may increase the risk of nosocomial infections.

Propofol's unique pharmacokinetic profile provides for a rapid recovery from its sedative and hypnotic effects.\textsuperscript{7} Propofol appears to have an advantage over existing anesthetic techniques with respect to emergence times,\textsuperscript{169,170} but its safety in patients with poor cardiac reserve has been the subject of considerable debate in the anesthesia literature.\textsuperscript{169-172} Most of the early clinical studies involving the use of propofol during cardiac surgery focused on its acute hemodynamic effects when used for induction of anesthesia in patients with good left ventricular function undergoing elective coronary artery bypass graft surgery. Only recently have investigators evaluated the use of propofol-based maintenance anesthetic techniques in both healthy patients and those with impaired left ventricular function.\textsuperscript{173} compared with thiopental or etomidate, propofol appears to possess greater direct negative inotropic effects on papillary muscle.\textsuperscript{174} Therefore, propofol should be used with caution in patients with preexisting cardiac disease.

Induction and the Prebypass Period

Use of propofol for induction of anesthesia in cardiac surgery patients can produce significant hypotension before laryngoscopy and tracheal intubation. For example, in patients with good left ventricular function scheduled for elective coronary artery bypass graft surgery, induction with propofol 1.5 mg·kg\textsuperscript{-1} intravenously resulted in decreases in systolic and diastolic arterial pressures of 28\% and 23\%, respectively.\textsuperscript{174} However, these patients had received diazepam 0.1 mg·kg\textsuperscript{-1} and fentanyl 8 μg·kg\textsuperscript{-1} before propofol administration. Although HR, cardiac output, and filling pressures were unchanged, decreases in systemic vascular resistance and left ventricular stroke work index of 25\% and 32\%, respectively, were reported. Anesthesia was maintained with a continuous propofol infusion adjusted to maintain hemodynamic stability (mean infusion rate of 86 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}). Tracheal intubation was associated with a transient increase in MAP in 50\% of patients, however, no MAP value exceeded the preoperative baseline value. Sternotomy resulted in a hypertensive reaction in only one patient.


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A more recent study using a similar protocol design confirmed these hemodynamic changes but failed to find any adverse effects on myocardial blood flow or deleterious changes in cardiac metabolism during the prebypass period.175 Use of a smaller dose of propofol (0.5 mg·kg⁻¹) in combination with alfentanil 50 μg·kg⁻¹ followed by infusions of propofol 50–85 μg·kg⁻¹·min⁻¹ and alfentanil 0.8 μg·kg⁻¹·min⁻¹ failed to prevent the initial decrease in arterial pressure after induction.176 Even without an opioid, induction with propofol 2 mg·kg⁻¹ followed by an infusion of 200 μg·kg⁻¹·min⁻¹ produced a similar postinduction decrease in MAP.177 Intubation was associated with an increase in MAP and HR, but the addition of fentanyl 10 μg·kg⁻¹ intravenously prevented the acute hemodynamic response to sternotomy. Another study involving patients undergoing cardiac surgery was prematurely terminated because two patients with three vessel coronary artery disease became hypotensive after propofol 1 mg·kg⁻¹ and fentanyl 6 μg·kg⁻¹.178 The hypotensive responses were attributable to the vasodilator effects of propofol, enhanced by its interaction with fentanyl, in patients with low initial pulmonary capillary wedge pressure values. However, no electrocardiographic evidence of myocardial ischemia was noted during the periods of hypotension. In comparison with alternative anesthetic induction agents, propofol produces a greater degree of hypotension as a result of decreased venous tone and reductions in total peripheral resistance. In addition, in common with other hypnotics, there is an interaction with opioid analgesics which exacerbates these hypotensive effects.

The desire to avoid hypotension on induction while maintaining hemodynamic stability during laryngoscopy, tracheal intubation, and sternotomy led to the use of benzodiazepine–opioid combinations for induction of anesthesia followed by a propofol infusion for maintenance of anesthesia. Mora et al. described a technique involving diazepam premedication followed by induction with fentanyl, 25 μg·kg⁻¹ intravenously, and maintenance with a propofol infusion (50–500 μg·kg⁻¹·min⁻¹) or enflurane 0.25–2% adjusted to maintain MAP within 15% of the postinduction values. These investigators found that both maintenance techniques resulted in comparable myocardial depression and control of hemodynamic variables. Russell et al. used a similar sedative–opioid induction (diazepam 0.1 mg·kg⁻¹ and fentanyl 25 μg·kg⁻¹) followed by a two-stage propofol infusion, consisting of 167 μg·kg⁻¹·min⁻¹ for 15–20 min and 50 μg·kg⁻¹·min⁻¹ after sternotomy. A steady-state propofol concentration of 4.85 μg·ml⁻¹ was achieved within 15 min, and was not associated with untoward hemodynamic responses to either intubation or sternotomy.179 Underwood et al. followed an opioid induction with either a two-stage propofol infusion or enflurane.180 Analogous to the findings of Mora et al., these investigators found similar hemodynamic changes in both groups, with fewer patients requiring vasodilator therapy in the propofol group. However, one patient receiving enflurane developed increased myocardial lactate production and electrocardiographic evidence of ischemia, and one propofol-treated patient developed lactate production without any electrocardiographic changes. In comparing cardiac patients with normal versus impaired left ventricular function (ejection fraction < 45% and left ventricular end-diastolic pressure values > 16 mm Hg), Phillips et al. found no significant differences in hemodynamic variables when propofol was used for maintenance of anesthesia in the prebypass period.181

In a prospective randomized trial, Hall et al. compared the safety of a propofol-based technique consisting of sufentanil 0.2 μg·kg⁻¹ and propofol 1–2 mg·kg⁻¹ and followed by a variable-rate propofol infusion (50–200 μg·kg⁻¹·min⁻¹), with an opioid–volatile anesthetic technique consisting of sufentanil 5 μg·kg⁻¹, supplemented with enflurane.182 Aside from an increased incidence of hypotension after induction in the propofol group, they found no significant differences between the anesthetic treatment groups with respect to hemodynamic stability, myocardial metabolic indices, or incidence of adverse effects before the start of cardiopulmonary bypass (CPB). In a more recent study, Hall et al. evaluated three anesthetic techniques in patients with decreased left ventricular function.173 In addition to the two treatment groups described above, these investigators added a third study group consisting of an opioid induction (sufentanil 5 μg·kg⁻¹) followed by a variable-rate propofol infusion (50–200 μg·kg⁻¹·min⁻¹) for maintenance of anesthesia. Although the overall control of hemodynamic variables was satisfactory in all three groups, propofol caused hypotension when used for induction with sufentanil, 0.2 μg·kg⁻¹. Patients in the opioid induction–propofol maintenance group tended to have decreased requirements for vasopressor medication and had less biochemical evidence of myocardial ischemia than the opioid–volatile anesthetic group.
Cardiopulmonary Bypass

Pharmacokinetic studies of propofol during CPB revealed the rapid onset of a transient decrease in propofol concentrations after the start of CPB as a result of acute hemodilution, followed by a gradual increase in the blood concentration during the hypothermic phase (fig. 8). These changes permitted the achievement of high propofol concentrations (5 μg·ml⁻¹) during sternotomy while still maintaining hypnotic drug concentrations during CPB without changing the propofol infusion rate. Rewarming on CPB led to a decrease in propofol concentration to prebypass levels, suggesting that the hypothermic state was associated with changes in both hepatic enzyme activity and regional blood flow. However, hypnotic levels were maintained throughout the operation. Mora et al. also investigated propofol levels during CPB and observed that higher propofol infusion rates were required during CPB to achieve propofol levels similar to those measured during the prebypass period. However, Massey et al. failed to find a significant change in the propofol blood concentration during CPB when a zero-order infusion of propofol 67 μg·kg⁻¹·min⁻¹ was administered during cardiac surgery. Differences in the sampling site and timing of sample collections may explain the differences between these kinetic studies. The propofol concentrations remained greater than 1 μg·ml⁻¹ throughout the operation in both studies. This is the concentration at which noncardiac patients awaken from propofol anesthesia. Not surprisingly, none of the patients experienced recall of intraoperative events.

Propofol has been found to be a vasodilator during CPB, and high-dose infusion regimens (5 mg·kg⁻¹ followed by 333 μg·kg⁻¹·min⁻¹) can further reduce O₂ consumption during hypothermic CPB. When using propofol, the combination of vasodilation and decreased O₂ consumption may confer additional protection against the adverse effects of CPB. In comparative cardiac studies involving propofol-based techniques and standard opioid–volatile balanced anesthetic techniques, no differences have been found in the need for inotropic support upon termination of CPB.

Recovery Phase

Mora et al. reported that in cardiac surgery patients receiving fentanyl, 25–50 μg·kg⁻¹ for induction of anesthesia, use of a propofol maintenance infusion (50–500 μg·kg⁻¹·min⁻¹) was associated with a more rapid emergence from anesthesia than similar patients maintained with either fentanyl (0.15–0.45 μg·kg⁻¹·min⁻¹) or thiopental infusions (0.05–1.0 mg·kg⁻¹·min⁻¹). Propofol also permitted earlier extubation compared with high-dose fentanyl. Chong studied 198 consecutive patients undergoing a variety of cardiac procedures using a standard anesthetic technique involving a propofol infusion (67–100 μg·kg⁻¹·min⁻¹) at the start of CPB. If patients were hemodynamically stable and bleeding was not excessive in the postanesthesia care unit, separation from ventilatory support was attempted on return of consciousness. The median time to extubation was 2 h; by 24 h, only 2.5% of the patients required continuing ventilatory and inotropic support. In the propofol group, five patients, four of whom had undergone a repeat coronary artery bypass graft procedure, required reintubation. A retrospective comparison with a comparable group of patients anesthetized with an opioid-based technique demonstrated a median time to extubation of 7 h. However, these data are in conflict with the results of Hall et al. and Mora et al., who found no significant differences in the time to extubation between opioid–propofol and opioid–volatile anesthetic techniques. In the recent series by Hall et al., a significantly longer time to extubation was noted in patients in whom an opioid induction was followed by a propofol infusion. However, these investigators suggested that the larger cumulative doses of morphine
required for postoperative analgesia in the propofol induction–maintenance group contributed to prolonging their time to extubation.

In summary, induction of anesthesia with an opioid–benzodiazepine combination followed by a maintenance infusion of propofol, supplemented with an inhalational agent or opioid analgesic or both as needed to control blood pressure and HR, appears to provide acceptable anesthetic conditions for patients undergoing routine cardiac surgery and is associated with a rapid emergence and early extubation. The use of a titrated infusion of propofol for maintenance of anesthesia is not associated with an increased requirement for inotropic support after cardiac surgery.

Pediatric Anesthesia

The use of propofol in children was initially described in 1985. Although intravenous induction techniques are generally considered to be less popular in infants and children because of difficulty in obtaining vascular access, the availability of eutectic mixture of local anesthetics (EMLA) cream and propofol have renewed interest in the use of intravenous techniques in this patient population. With the increased use of the laryngeal mask airway (LMA), particularly for pediatric ambulatory surgery and for diagnostic procedures outside the operating room, propofol has advantages over other intravenous induction drugs.

Dosage Requirements

The pharmacokinetics of propofol in children are optimally described by a standard three-compartment model, as summarized in table 1. Using a computer controlled infusion device similar to the one described by White and Kenny in adults to maintain propofol anesthesia in children, Marsh et al. found, as expected, that the pharmacokinetic-based infusion system systematically overpredicted the measured blood propofol concentrations when adult parameters were used for children aged 1–12 yr. When pharmacokinetic data derived from children were used to program the kinetic-based infusion pump, the device more accurately achieved predicted plasma propofol concentrations. Compared with the dose for adults, the initial dose of propofol should be increased by 50% in children, and at equilibrium, the maintenance infusion should be increased by 25–50%. Browne et al. reported that the propofol infusion rate needed to suppress movement in 95% of children (ED95) was 175 μg · kg⁻¹ · min⁻¹, twice the ED95 for adults. Early studies involving the use of propofol for induction of anesthesia in children have reported that the propofol dose required for loss of the eyelash reflex in 90% of children was 2.8 mg · kg⁻¹ in nonpremedicated children, and 2.0 mg · kg⁻¹ in children premedicated with trimethazine 3.0 mg · kg⁻¹. However, another study suggested that premedication with meperidine 1 mg · kg⁻¹ intramuscularly or trimethazine 2 mg · kg⁻¹ orally had no effect on the propofol induction dose requirement (2.9 mg · kg⁻¹). In 90 nonpremedicated children aged 3–12 yr, Hannonallah et al. found the ED50 for loss of the eyelash reflex to be 2.0 mg · kg⁻¹, and the ED95 for subsequent acceptance of the face mask without disruptive movements to be 2.3 mg · kg⁻¹.

When comparing a computerized, target-controlled propofol infusion with intermittent bolus dosing in 40 children aged 1–12 yr, no difference was found in the induction dose requirement. The median effective dose was found to be higher in infants aged 1–6 months than children aged 10–16 yr (3.0 mg · kg⁻¹ vs. 2.4 mg · kg⁻¹). Using an incremental dosing technique, propofol 2.5 mg · kg⁻¹ produced loss of consciousness in 95% of children aged 3–15 yr who had been pretreated with alfentanil 5 μg · kg⁻¹. When using a smaller induction dose of propofol (1.5 mg · kg⁻¹ intravenously), significantly more older children (10–15 yr) lost consciousness than in the younger group.

Cardiorespiratory Effects of Propofol

Several studies have suggested that induction of anesthesia with propofol decreases HR by 10–20% in children. Irrespective of whether an induction dose of propofol is followed by an inhalation agent or a propofol infusion, the HR response was similar. However, the HR decrease associated with propofol is significantly greater in toddlers than in older children. During strabismus surgery, the incidence of bradycardia resulting from the oculocardiac reflex has been found to be higher in children receiving propofol infusions compared with an inhalation technique.

In children, a 10–25% decrease in MAP usually occurs immediately after induction with propofol. Hannallah et al. found that 48% of children had a 20% or greater decrease in MAP during the first 10 min after an induction dose of propofol. However, a majority of these "hypotensive" episodes occurred while

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breathing 1–3% halothane and all returned to within 20% of baseline MAP values after decreasing the inspired halothane concentration. Induction doses of propofol (1.6–2.6 mg·kg⁻¹) followed by a mixture of halothane, 0.5%, and 30% N₂O in O₂ in spontaneously breathing children, resulted in a 15% decrease in MAP at 1 min and a 50% decrease at 5 min after injection of propofol.¹⁹⁷ These investigators reported that the magnitude of the hemodynamic change was not related to the size of the induction dose of propofol. In a study involving 40 children aged 1–13 yr, Doyle et al. found no differences in intraoperative MAP values between children maintained with a computer-controlled propofol infusion pump (range of infusion rates 300–600 μg·kg⁻¹·min⁻¹) or halothane 0.5–2%, in combination with N₂O, 67%, in O₂.¹⁹⁴

Using pulsed Doppler echocardiography, Aun et al. compared the hemodynamic effects of propofol 2.5 mg·kg⁻¹ and thiopental 5 mg·kg⁻¹ for induction of anesthesia in toddlers (<2 yr) and older children (2–12 yr).¹⁹⁷ The decrease in MAP was greater after propofol (28–31%) than thiopental (14–21%) in both age groups. The decrease in systemic vascular resistance was similar (15%) in toddlers after thiopental or propofol, but in older children the decrease in systemic vascular resistance was almost three times greater with propofol (19% vs. 7%). Cardiac index decreased by 10–15% with both anesthetic agents. In pre-school-aged children ventilated with 60% N₂O in O₂ during a maintenance infusion of propofol 400 μg·kg⁻¹·min⁻¹, investigators found a 25% decrease in MAP and a 23% decrease in stroke volume.¹⁹⁸ Administration of atropine, 20 μg·kg⁻¹ intravenously, increased HR and MAP but did not influence propofol’s effect on the stroke volume.

Propofol appears to suppress the pharyngeal and laryngeal reflexes more effectively than thiopental.²⁰² Propofol has been used to facilitate tracheal intubation without muscle relaxants after an inhalational induction in children undergoing outpatient surgery,²⁰³ reportedly producing intubating conditions similar to succinylcholine. However, in children aged 2–7 yr, Rodney et al. found intubating conditions to be poor when using propofol 3.5 mg·kg⁻¹ as the sole agent for tracheal intubation.²⁰⁴ The addition of alfentanil, 20 μg·kg⁻¹, improved intubating conditions and effectively attenuated the pressor response to tracheal intubation compared with propofol alone or to a thiopental–succinylcholine combination. The 20% incidence of apnea (lasting >20 s) after induction with propofol 2.5 mg·kg⁻¹ is similar to that observed with thiopental.²⁰⁵ However, premedication with opioids or benzodiazepines will increase the incidence of apnea.²⁰⁵ Mantsch et al. reported age and dose-related increases in the incidence of apnea in children (<12% at 3–5 yr vs. 38% at 10–15 yr; 3% with propofol 2.0 mg·kg⁻¹ vs. 28% with propofol 2.5 mg·kg⁻¹).¹⁹⁶ Martin et al. found a greater incidence of airway obstruction before tracheal intubation when anesthesia was induced in children with halothane (34%) than with propofol (10%), but the ability to more rapidly establish intravenous access and administer muscle relaxant drugs may have facilitated airway management in the propofol group.

Recovery Profile

Mirakhur reported a significantly shorter time to awakening in children who received propofol for induction of general anesthesia (11–14 min) compared with thiopental (16–22 min).²⁰⁸ They also noted a significantly lower incidence of nausea with propofol. A more recent study comparing induction with propofol 3 mg·kg⁻¹ to thiopental 5 mg·kg⁻¹ reported that the time required for children over 5 yr of age to give their name and to be discharged from the hospital was significantly shorter in the propofol group.²⁰⁹ In children aged 1–5 yr, propofol only reduced the time to eye opening. Puttick and Rosen compared a propofol–N₂O technique with thiopental–N₂O–halothane in 38 children undergoing outpatient dental extractions and found that the times to spontaneous eye opening and discharge were significantly shorter with propofol (8 ± 3 and 36 ± 7 min, respectively) than thiopental–halothane (11 ± 6 and 44 ± 13 min, respectively).²⁰⁸ Times to extubation and discharge from the postanesthesia care unit have been also been shown to be significantly shorter in a study of 40 children aged 3–8 yr undergoing minor otorhinolaryngologic operations when propofol was used for induction followed by a propofol maintenance infusion of 100 μg·kg⁻¹·min⁻¹ compared with a thiopental–halothane technique.²⁰⁶

In a more recent study comparing inhalational induction and maintenance with halothane to intravenous induction and maintenance with propofol (3 mg·kg⁻¹, followed by 150 μg·kg⁻¹·min⁻¹) in infants aged 2–12 months, investigators reported significantly shorter times to spontaneous movement, extubation and sucking response in the propofol group.²⁰⁷ Watcha et al. found a significant decrease in times to ambulation and discharge, as well as a lower incidence of postoperative...
emesis, after strabismus surgery when anesthesia was maintained with a propofol infusion, 160 mg·kg⁻¹·min⁻¹, as part of a TIVA technique compared with either a balanced or inhalation technique.²⁰⁶ Similarly, Weir et al. found a significant decrease in the incidence of vomiting during the first 24 h after strabismus surgery with propofol 150–300 µg·kg⁻¹·min⁻¹ compared with halothane 0.5–1% (41% vs. 64%).²⁰₈ In a subgroup of children who did not require postoperative opioid analgesics, an even greater difference was found (24% vs. 71%). Of interest, Tramèr et al. failed to find any significant difference in the incidence of postoperative vomiting between propofol and isoflurane when N₂O was avoided.²⁰⁹ In the strabismus population, the adjunctive use of ondansetron 5 mg·m⁻² was ineffective in reducing the incidence of nausea and vomiting after either propofol or isoflurane anesthesia.²⁰⁹

In a study involving 40 children aged 1–12 yr undergoing general surgical procedures while spontaneously breathing N₂O 67% in O₂ through an LMA,¹⁹⁴ the investigators failed to find a significant difference in the time to spontaneous eye-opening between a group maintained with a propofol infusion and a group maintained with halothane. The major difference between this investigation and the earlier studies may relate to the shorter duration of anesthesia,¹⁹ adjunctive use of N₂O,²⁰⁰ and the spontaneous breathing of these children.²⁰⁶

**Propofol for Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) sequence images can be difficult to obtain in awake children because they are extremely sensitive to motion artifacts. In the noisy environment of the magnetic resonance imaging scanner, children are often unable to remain immobile long enough for a successful scan to be performed. Concerns about maintenance of airway patency has led some clinicians to secure the airway with a tracheal tube while maintaining anesthesia with a propofol infusion.²¹⁰ Other investigators have used infusions of propofol for sedation of spontaneously breathing children and found it to be a safe technique which provides superior scanning conditions to thiopental or methohexitheinel, with no repeat scans being required in children receiving propofol compared with 75% of those children receiving barbiturates for sedation.²¹¹ The peak CO₂ values measured at the oral or nasal cannulae can be used to monitor the respiratory rate and the pattern of ventilation,²¹² and these values have been shown to correlate with arterial CO₂ tension measurements.²¹³

During computerized axial tomographic (CAT) scanning, the minimum effective infusion rate after induction of anesthesia with propofol was 25 µg·kg⁻¹·min⁻¹. However, higher infusion rates and/or supplemental boluses were required to prevent a motor response to subsequent head positioning.²¹⁴ Tracheal intubation may also be avoided by maintaining a patent airway using an LMA. When using an LMA in the computerized tomographic scanner, the recommended doses of propofol are 2.5 mg·kg⁻¹, followed by an infusion of 85 µg·kg⁻¹·min⁻¹.²¹⁵ Sedation with propofol also avoids the concerns associated with repeat exposures to halothane. With short-term administration, tolerance to propofol does not appear to develop in children after repeated exposures.²¹⁶ However, the apparent safety of propofol infusion techniques for sedation in spontaneously breathing children is not a valid reason to dispense with the services of the anesthesiologist.²¹⁷,²¹⁸

In summary, propofol is being used with increasing frequency in children of all ages. On a per-kilogram body weight basis, the induction and maintenance dosage requirements for propofol are higher in neonates and children than in adults. Propofol's pharmacokinetic profile, recovery characteristics and apparent antiemetic activity make it a particularly useful agent for pediatric outpatient anesthesia and for sedation during radiologic procedures.

**Sedation in the Intensive Care Unit**

The primary objectives of sedation in the ICU are to enhance patient comfort, to reduce anxiety, to facilitate sleep, and to minimize resistance to mechanical ventilation. The ideal sedative agent for critically ill patients in the ICU would have minimal depressant effects on the respiratory and cardiovascular systems, would not influence the biodegradation of other drugs, and would be eliminated by pathways which are independent of renal, hepatic, or pulmonary function, resulting in a short elimination half-life without active metabolites.²¹⁶ The most commonly used sedative–analgesic agents (namely, midazolam and morphine) lack many of these properties. Although lacking some of the properties of an ideal sedative, propofol was approved by the Food and Drug Administration for ICU sedation in 1993.

The first clinical report describing the use of propofol for sedation in the ICU was published in 1987.²²⁰ Ten patients who required mechanical ventilation were se-
dated with an infusion of propofol for 8 h at a mean infusion rate of 32 \( \mu g \cdot kg^{-1} \cdot min^{-1} \). Patients were maintained at a level of sedation where they appeared comfortable and were asleep when left undisturbed, but were easily arousable with verbal or light tactile stimulation. Two of the three patients who received an initial bolus dose of propofol 1 mg \( \cdot kg^{-1} \) experienced 40% and 53% decreases in MAP, respectively. In addition, the mean and diastolic blood pressure values for the study group were significantly lower than baseline values throughout the study period. The range of blood propofol concentrations during the infusion was 0.1–1.9 \( \mu g \cdot ml^{-1} \). These blood levels are similar to the propofol concentrations reported by Barr et al. during light sedation of patients in the ICU.\(^{221}\) In the latter study, recovery was so rapid that eight of the ten ICU patients required resedation within 45 min after the propofol infusion had been discontinued.

*Pharmacokinetics of Propofol in the Intensive Care Unit*

Early pharmacokinetic studies involving rapid bolus injections or short-term infusions suggested that propofol was rapidly eliminated from the body. Although limited clinical significance, studies evaluating the pharmacokinetics of propofol after prolonged infusion in critically ill patients have suggested the presence of a very long elimination half-life.\(^{222}\) Beller et al. performed an extensive pharmacokinetic study in 14 general surgical ICU patients sedated with propofol over a 4-day period.\(^{225}\) A constant-rate propofol infusion was discontinued every 24 h for assessment of elimination kinetics and clinical recovery. The awakening times were similar after the 24, 48, 72 and 96 h study periods. Furthermore, propofol concentrations before the infusion was discontinued were similar and the slopes of the plasma propofol decay curves did not change over the 4-day study period. There was no evidence of a change in receptor sensitivity or drug accumulation despite the duration of the propofol infusion.

Albanese et al. also studied the pharmacokinetics of a constant rate infusion of propofol (50 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)) in ICU patients.\(^{222}\) They found a prolonged elimination half-life of 726–3,000 min (1,878 ± 672 min, mean ± SD), a total-body clearance of 0.95–2.58 \( l \cdot min^{-1} \) (1.57 ± 0.56 \( l \cdot min^{-1} \)), and a very large volume of distribution of 415–2,836 \( l \) (1,666 ± 756 \( l \)), suggesting that propofol was extensively redistributed from the blood and other well-perfused tissues into the less-well perfused (“deep”) tissue compartments. These variables are similar to those reported by Morgan et al. in their study involving propofol infusion during general anesthesia lasting as long as 9 h.\(^ {11}\) Baillie et al. calculated clearance values ranging from 1.1 to 40.1 \( l \cdot min^{-1} \), with a median total body clearance of 2.1 \( l \cdot min^{-1} \) and a mean (\( \pm SD \)) elimination half-life value of 1,411 ± 586 min.\(^ {224}\) Surprisingly, blood concentrations of propofol decreased by 50% in the first 10 min after terminating the propofol infusion (fig. 9). Because this decline was more rapid than would be predicted from the clearance rate, the authors concluded that redistribution of propofol between blood and the peripheral tissue compartments occurred even after the cessation of an 86-h infusion. The long “terminal” elimination half-life of propofol after prolonged administration appears to represent drug elimination from a “shallow” tissue compartment and the residual levels produce no clinically significant effects.

In comparing propofol with midazolam, propofol is typically associated with a more rapid recovery from its clinical and EEG effects.\(^{225–227}\) Carrasco et al. studied 88 critically ill patients who were allocated to receive either propofol or midazolam for short-term (<24 h), medium-term (24 h to 7 days), or long-term (>7 days) sedation.\(^ {225}\) The mean doses of propofol and midazolam were 38 and 2.8 \( \mu g \cdot kg^{-1} \cdot min^{-1} \), respectively. Patients in the propofol treatment group were adequately sedated for a higher proportion of the study period than those receiving midazolam. Propofol was also associated with a significantly shorter time to tracheal extubation than midazolam after discontinuing short,

![Fig. 9. Decrease in blood concentration of propofol after discontinuation of infusion in 12 patients in the intensive care unit. Mean duration of infusion was 95.6 h, mean rate of infusion 43 \( \mu g \cdot kg^{-1} \cdot min^{-1} \), and mean elimination half-life 23.5 h. Reproduced from Baillie et al.,\(^ {224}\) with permission.](https://anesthesiology.pubs.asahq.org)
medium and long-term infusions. In each treatment
group, the time to extubation correlated with the
duration of the sedative infusion. On the basis of estimated
costs (including drug costs and additional nursing care), the more rapid recovery from propofol sedation in the short-term subgroup was associated with significant cost savings compared with midazolam. However, this advantage was not evident in the medium- or long-term subgroups. These data suggest that propofol is more cost-effective than midazolam for short-term sedation in the ICU.

In a large multicenter study, Aitkenhead et al. compared propofol and midazolam infusions in 101 critically ill patients.228 Patients received either propofol 30 μg·kg⁻¹·min⁻¹ or midazolam 1.7 μg·kg⁻¹·min⁻¹ for 24 h. The infusion rates were adjusted to maintain a “light” level of sedation and most patients in both treatment groups were able to obey simple commands immediately after discontinuing the sedative infusions. Of the patients not responding immediately after discontinuing the propofol infusion, all but one of the propofol-treated patients responded within 20 min. However, only six of the remaining 15 midazolam-treated patients responded within 20 min. In a subgroup of 39 patients who were judged to be fit for discontinuation from ventilatory support, this was achieved in a mean of 5 min (range 0–13 min) in the patients receiving propofol compared with 148 min (range 17–555 min) in the midazolam group (P < 0.001).

Combinations of opioids and benzodiazepines are commonly used for sedation. Comparisons between opioid–benzodiazepine and opioid–propofol combinations have revealed similar clinical conditions in the ICU.229,230 Carrasco et al. also confirmed that recovery was more rapid after propofol alone than after either midazolam or an opioid–benzodiazepine combination.230 Interest in speed of recovery has led to investigations of the use of volatile agents for ICU sedation. Isoflurane has been shown to be superior to midazolam for short-term sedation in patients who require mechanical ventilation, with a faster recovery and a better quality of sedation.231 Recently, Millane et al. studied the quality of sedation and the time to recovery between isoflurane (median inspired concentration of 0.35%) and propofol (median infusion rate of 25 μg·kg⁻¹·min⁻¹) in 24 patients requiring mechanical ventilation.232 There were no significant differences with respect to cardiovascular variables, analgesic requirements, sedation scores, or the quality of sedation as assessed by the ICU nurses. Although the results suggested a more rapid recovery after long-term sedation with isoflurane, analysis of the results is difficult because only seven of the 24 patients actually completed the entire study.

**Sedation after Head Injury**

The use of propofol was studied in 10 patients with severe head injuries requiring sedation during controlled mechanical ventilation.233 The rate of propofol infusion was adjusted to maintain ICP at less than 10 mmHg and CPP at greater than 60 mmHg. After 24 h, the propofol was stopped and the patients were allowed to recover from the sedative medication. The mean rate of propofol infusion was 48 μg·kg⁻¹·min⁻¹ (range 30–83). There were no significant changes in MAP; however, mean CPP tended to increase during the study. The quality of sedation was judged to be “good” in nine of the ten patients. In a comparison of propofol with a combination of morphine and pentobarbital, Pearson et al. found no significant difference in cardiovascular stability, ICP, or outcome between the two groups.234

**Sedation after Cardiac Surgery**

Several publications in the anesthesia literature have described the use of propofol infusions for sedation in the ICU after cardiac surgery. Many of these studies have demonstrated more rapid recovery after the use of propofol compared with midazolam (table 7). Grounds et al. randomized patients to receive either an infusion of propofol or intermittent bolus doses of midazolam to maintain a stable level of sedation.235 Sedation was discontinued when predetermined criteria were met and the patient was then discontinued from ventilatory support. The average doses of the sedative drugs were propofol 13 μg·kg⁻¹·min⁻¹ and midazolam 0.27 μg·kg⁻¹·min⁻¹. Propofol permitted patients to be maintained at the desired sedation level for a significantly higher percentage of time (90–96%) compared with midazolam (80–89%). In this study235 and a similar one by McMurray et al.,236 the requirements for analgesic medications were greater in the midazolam-sedated patients, suggesting that less ideal sedative conditions existed in the latter group. To maintain a more profound level of sedation, higher mean infusion rates of propofol (45 μg·kg⁻¹·min⁻¹) and midazolam (1.5 μg·kg⁻¹·min⁻¹) were required.238

For cardiac surgery patients who require sedation and mechanical ventilation for a short period followed by

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SMITH ET AL.

Table 7. Comparative Recovery Times after Sedation with Propofol or Midazolam after Coronary Artery Bypass Surgery

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Infusion Regimen (µg·kg⁻¹·min⁻¹)</th>
<th>Time to Responsiveness (min)</th>
<th>Time to Spontaneous Ventilation (min)</th>
<th>Time to Tracheal Exubation (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grounds et al.²³⁵</td>
<td>80</td>
<td>Propofol, 13</td>
<td>NR</td>
<td>13.6 (2.68)†</td>
<td>24.9 (2.97)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midazolam, 0.27*</td>
<td>NR</td>
<td>198 (22.5)†</td>
<td>226 (22.8)†</td>
</tr>
<tr>
<td>McMurray et al.²³⁶</td>
<td>100</td>
<td>Propofol, 19.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midazolam, 0.57*</td>
<td>NR</td>
<td>11.9 (2.9)†</td>
<td>11.9 (2.9)†</td>
</tr>
<tr>
<td>Snellen et al.²³⁷</td>
<td>40</td>
<td>Propofol, 15.2</td>
<td>NR</td>
<td>24 (7)‡</td>
<td>154 (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midazolam, 0.63</td>
<td>NR</td>
<td>66 (16)‡</td>
<td>243 (44)</td>
</tr>
<tr>
<td>Roekaerts et al.²³⁸</td>
<td>30</td>
<td>Propofol, 45.2</td>
<td>11 (8)†</td>
<td>52 (32)†</td>
<td>250 (135)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midazolam, 1.5</td>
<td>72 (70)†</td>
<td>195 (119)†</td>
<td>391 (128)</td>
</tr>
</tbody>
</table>

Times are mean (± SEM), except Roekaerts et al. [mean (± SD)], recorded from the cessation of the study drug. NR = not recorded.

† P < 0.001.
‡ P < 0.05.

rapid weaning from ventilatory support, propofol appears to be a more suitable agent. However, concerns regarding cardiovascular stability may limit the usefulness of propofol in this setting.²³⁹ A 15–20% decrease in MAP has been reported after a loading dose of propofol of 0.24–1.0 mg·kg⁻¹ after cardiac surgery.²³⁷,²³⁸,²⁴⁰ Roekaerts et al.²³⁸ reported that the pressure started to return toward the presedation values approximately 15 min after the start of the propofol infusion. However, the MAP value remained below baseline levels throughout the 10 h study period. This decrease in MAP was felt to be clinically acceptable in this patient population with an ejection fraction of ≥40% before surgery. McMurray et al. reported MAP values being "significantly lower" than awake values during propofol infusions lasting 9–12 h at a mean infusion rate of 12.7 µg·kg⁻¹·min⁻¹.²⁴⁰ Of importance, there were no reports of increased use of inotropes or signs of myocardial ischemia during the propofol infusion. Roekaerts et al. found that the use of propofol infusions for sedation was associated with lower HRs than was use of midazolam.²³⁸ This difference may have been caused by the effects of propofol on the baroreflex response, resulting in lower HR values despite decreased MAP values.²⁴¹ In patients "at risk" of developing myocardial ischemia, the lower HR values may be of benefit.²⁴² However, the effect of propofol on baroreflex activity during long-term infusions has not been studied.

Sedation of Children in the Intensive Care Unit

The use of propofol for sedation of children in the ICU has resulted in reports of neurologic sequelae after withdrawal of propofol, and the occurrence of metabolic acidosis during propofol infusions in the presence of upper respiratory tract infections. Thus, controversy surrounds the use of propofol for sedating neonates and young children in the ICU.

In 1992, Trotter and Serpell described neurologic sequelae in two children (aged 2.5 and 4 yr) sedated with propofol infusions after tracheal intubation for stridor caused by presumed viral infections.²³⁸ The children were sedated with high doses of propofol (as large as 300 µg·kg⁻¹·min⁻¹) and both developed abnormal movements, particularly fine twitching of the extremities after the propofol was stopped. However, both children made a full recovery. Lanigan et al. described a case of a 23-month child requiring sedation after tracheal intubation for stridor. Although the child had received several sedative regimens including high-dose propofol,²⁴³ jerky twitching and functional blindness occurred after the withdrawal of propofol. Imray and Hay described similar clinical signs in an 18-month-old girl who received propofol for sedation for 2 weeks after severe burns.²⁴⁵

Parke et al. described five children (ages 4 weeks to 6 yr) who required propofol infusions after intubation for upper respiratory tract infections.²⁴⁶ The average rate of infusion of propofol was high (125–167 µg·kg⁻¹·min⁻¹), and in all five children lipemic serum and metabolic acidosis developed, and bradycardia and fatal myocardial failure occurred. In view of the presence of lipemic serum and the lack of evidence for another cause of death, the authors suggested that the propofol emulsion (containing a lipid mixture of glycerol, egg phosphatide, and soybean oil) could have been a contributing factor.
A review of a large database of preterm infants who had received large doses of intravenous lipids as part of parenteral nutrition found that those who required ventilation for respiratory disease were not at risk of developing metabolic acidosis. Other possible causes of the reported metabolic disturbances included adrenocortical suppression, and an unexplained association between viral infections, high-dose propofol infusions and metabolic acidosis. The manufacturers of propofol have emphasized that the drug is not licensed for sedation of critically ill children (Diprivan package insert).

Hyperlipidemia and Propofol Sedation
Gottardis et al. studied changes in serum lipid concentrations in 10 patients receiving propofol (approximately 33 \( \mu \)g·kg\(^{-1} \)·min\(^{-1} \)) over a 3-day period. In this study, there was no significant rise in triglyceride or cholesterol. In contrast, 10 of 22 patients sedated with a propofol infusion (mean infusion rate of 39 \( \mu \)g·kg\(^{-1} \)·min\(^{-1} \)), experienced a doubling of their triglyceride levels after 3 days. Cook and Palma also found a progressive rise in lipid levels in patients sedated with propofol for 2 or 3 days at a mean infusion rate of 38.5 \( \mu \)g·kg\(^{-1} \)·min\(^{-1} \). After 1 week, the triglyceride levels were more than three times normal. The patients with elevated lipid levels appeared to have a slower return of higher mental functions. This finding is consistent with the effects of hypertriglyceridemia on cerebral function. Boyle et al. studied lipid levels in 22 patients receiving propofol sedation for periods as long as 14 days. The maintenance infusion rates of propofol ranged from 10 to 230 \( \mu \)g·kg\(^{-1} \)·min\(^{-1} \). Lipid levels were not altered in those patients receiving low rates of infusion of propofol (<33 \( \mu \)g·kg\(^{-1} \)·min\(^{-1} \)); however, serum triglyceride levels were markedly increased in the two patients who received infusion rates in excess of 100 \( \mu \)g·kg\(^{-1} \)·min\(^{-1} \) (6 mg·kg\(^{-1} \)·h\(^{-1} \)) over a 2-week period (fig. 10).

Other Pharmacologic Actions of Propofol
Adrenal Cortex. The potency of etomidate in inhibiting adrenal steroidogenesis is 1,500 times greater than that of propofol. Two studies have looked at cortisol secretion during propofol sedation in ICU patients and both concluded that although cortisol levels tend to decrease during the infusion period, there was no evidence of a clinically significant impairment of adrenal steroidogenesis.

Tetanus. Borget et al. have demonstrated reduced electrical muscular activity as measured by an EMG device in a patient with tetanus who was given propofol. Although the site of action was not determined, a central site appears likely.

Bronchodilatation. Pedersen reported two patients who developed severe bronchospasm after aortic valve replacement, and that the wheezing decreased after the administration of propofol. A reduction in peak inspiratory pressure and airway resistance, and an increase in dynamic compliance in patients with chronic obstructive pulmonary disease who were undergoing mechanical ventilation, also has been reported after a 2-mg·kg\(^{-1} \) bolus dose of propofol. The mechanism of the apparent bronchodilating action is not known but may be related to a direct effect of propofol on the bronchial smooth muscle (analogous to propofol's relaxant effects on vascular smooth muscle). Alternatively, the sedative effects of propofol may have simply decreased the stimulation from the tracheal tube.

Antioxidant Activity. Propofol has been demonstrated to possess antioxidant properties similar to those of vitamin E. These properties make propofol a free radical scavenger and suggests that it may be useful in...
conditions such as multiorgan failure and acute respiratory distress syndrome.

**Status Epilepticus.** Propofol has been successfully used in the ICU for the management of status epilepticus, severe generalized myoclonus, and severe delirium tremens. However, propofol has also been implicated as the cause of agitation and grand mal convulsions after the withdrawal of sedative infusions. One patient experienced a generalized tonic-clonic seizure 6 days after propofol withdrawal. This phenomena may be similar to the “withdrawal syndrome” reported earlier in children.

In summary, propofol provides a quality of sedation comparable to that provided by other sedative-hypnotic drugs in the ICU. Compared with the benzodiazepines and barbiturates, recovery is more rapid after sedation with propofol, leading to a more rapid recovery of patient responsiveness, spontaneous ventilation, and tracheal extubation. As a result of its favorable recovery profile, propofol may reduce overall costs when used for short-term sedation. However, the use of propofol for long-term sedation in the ICU is expensive and may result in hyperlipidemia and abnormal motor activity. Therefore, improvements in recovery may not offset the increased cost of propofol compared with other available sedative agents.

**Miscellaneous Uses for Propofol**

**Obstetric Anesthesia**

The first reports describing the use of propofol for induction of general anesthesia in patients undergoing elective cesarean section were published in 1989. In a randomized comparison, anesthesia was induced with thiopental 4.5 ± 0.3 mg · kg⁻¹ or propofol 2.2 ± 0.3 mg · kg⁻¹ and subsequently maintained with isoflurane–N₂O. Because Apgar scores recorded in both groups were similar, propofol does not appear to adversely affect fetal outcome. Furthermore, it had no adverse effects on uterine contractility or intraoperative blood loss. In this study, maternal recovery was not significantly modified by the use of propofol; however, other investigators reported more rapid recovery when propofol was used in a similar protocol. In the latter investigation, patients received either propofol 2.5 mg · kg⁻¹ or thiopental 5 mg · kg⁻¹, followed by isoflurane–N₂O for the remainder of the operation, which lasted approximately 45 min. Propofol was associated with a significantly shorter time to orientation than thiopental (1.0 ± 0.9 vs. 2.3 ± 1.0 min), and improved performance on the Maddox wing test during the 1st h of recovery. However, when propofol was administered by infusion to maintain anesthesia, maternal recovery was not significantly faster compared with that in patients receiving thiopental–enflurane–N₂O.

After induction of anesthesia with propofol, maternal blood pressure values were found to be significantly lower than when thiopental was used. Compared with thiopental, propofol has also been reported to be more effective in attenuating the hypertensive response (and associated catecholamine rise) after tracheal intubation. Like other intravenous anesthetic agents, propofol readily crosses the placenta and reaches the fetal circulation. However, the concentrations reached in the neonate are comparable to those achieved with other anesthetic agents and unlikely to be of clinical significance under normal circumstances. However, neonatal depression may occur when propofol is infused for a prolonged period of time before delivery or when higher rates of propofol infusion (e.g., >150 μg · kg⁻¹ · min⁻¹) are used for maintenance of anesthesia. Propofol is also present in the breast milk of the mothers who received propofol for induction of anesthesia before cesarean delivery. However, the propofol concentrations are very low when compared with the placental transfer of propofol.

In summary, propofol can reduce the response to tracheal intubation in obstetric patients, a population in whom the use of opioid analgesics may be undesirable. Propofol readily crosses the placenta, but the usual induction doses do not appear to depress the neonate. Despite its rapid clearance in pregnant subjects, propofol does not appear to produce a clinically significant advantage with respect to maternal recovery. However, propofol represents an acceptable alternative for obstetric patients in whom barbiturates are contraindicated.

**Laryngeal Mask Airway**

The LMA has recently become available in the United States and is increasing in popularity. Preliminary experience suggested that the use of propofol for induction of anesthesia produces more acceptable conditions for LMA insertion than other intravenous agents (e.g., thiopental). An early, noncomparative clinical trial demonstrated that LMA insertion was possible within 20 s of a bolus dose of propofol 2.5 mg · kg⁻¹. Of the 100 patients studied, 6 coughed and 2 demon-
strated a mild "laryngeal reaction" to insertion of the LMA. In a dose-ranging study, LMA insertion was equally successful after propofol 2.0, 2.5, or 2.8 mg · kg⁻¹ but was unsatisfactory after 1.5 mg · kg⁻¹. In young children undergoing magnetic resonance imaging, insertion of an LMA was found to be successful on the first attempt in 84% of cases after propofol 2.5 mg · kg⁻¹.

Brown et al. compared propofol and thiopental for LMA insertion. Eighty patients received equihypnotic doses of propofol 2.5 mg · kg⁻¹ or thiopental 4 mg · kg⁻¹ for induction of anesthesia and the incidence of gagging was found to be significantly higher with thiopental compared with propofol. However, this effect could be overcome by the use of larger doses of thiopental. "Deepening" anesthesia with a volatile agent before LMA insertion has also been recommended when thiopental is used for anesthetic induction.

During maintenance of anesthesia with the LMA, a wide variety of anesthetic techniques are available. Supplementation of a propofol infusion with N₂O has been demonstrated to provide satisfactory conditions for the use of the LMA during both spontaneous and controlled ventilation. TIVA techniques using infusions of propofol and alfentanil have also been administered using the LMA to maintain the airway.

**Antiemetic Activity**

There is an increasing body of literature suggesting that propofol possesses antiemetic activity. Antagonism of the dopamine D₂ receptor by propofol has recently been suggested as a possible mechanism for this effect. Compared with the use of volatile agents, the use of propofol for general anesthesia was associated with less postoperative nausea and vomiting, and/or decreased requirements for antiemetic medication. Similar findings have been found when using propofol as an alternative to other intravenous induction or maintenance agents. More recently, propofol has been administered in subhypnotic doses to treat nausea and vomiting, suggesting that propofol possesses direct antiemetic properties. If postoperative nausea or vomiting occurred in the recovery room, propofol 10–20 mg intravenously was successful in 81% of patients (compared with 35% of those given a lipid emulsion). However, 6 of the 21 patients in the propofol group experienced a relapse within 30 min after receiving the propofol. It appears that the antiemetic effect of propofol is not attributable to the lipid emulsion (10% Intralipid) used to solubilize the drug. Unfortunately, the rapid clearance of intravenous propofol limits its clinical usefulness as a therapeutic antiemetic drug, unless a continuous infusion technique is used.

Propofol infusions have also been used successfully to treat refractory nausea and vomiting in patients receiving chemotherapy. Borgeat et al. used a subhypnotic infusion of propofol (16.7 μg · kg⁻¹ · min⁻¹ or 1 mg · kg⁻¹ · h⁻¹) in 14 patients with emetic symptoms refractory to ondansetron and dexamethasone. All patients experienced complete resolution of their symptoms during the infusion period, and 12 reported improved appetite. These patients also manifested slight euphoria and no evidence of sedation.

**Cardioversion**

Cardioversion is often performed as a day-case procedure. In these cases, anesthetic agents with a short recovery profile and good cardiorespiratory stability would be useful. Propofol has been compared with other available intravenous anesthetics, including etomidate, methohexitol, thiopental, and midazolam. Propofol produced a greater depression of blood pressure than etomidate, but recovery times were similar. However, pain on injection and myoclonus are frequently seen during induction of anesthesia with etomidate, and the myoclonus may be severe enough to interfere with the electrocardiogram interpretation. Methohexitol and propofol produce similar conditions for cardioversion, although use of propofol may be associated with a more rapid emergence from the hypnotic state. Two studies report similar 16–29% decreases in systolic blood pressure during cardioversion with thiopental 3.0–3.5 mg · kg⁻¹ or propofol 1.5–2.1 mg · kg⁻¹. However, Gupta et al. used larger mean doses (±SD) of both thiopental (5.2 ± 1.0 mg · kg⁻¹) and propofol (2.2 ± 0.3 mg · kg⁻¹) and found that a decrease in blood pressure was only seen in the propofol group.

Data on recovery when thiopental or propofol were used for cardioversion are conflicting. However, the discrepancies resulted from the use of different endpoints. Valtosen et al. demonstrated more rapid recovery after propofol using psychometric tests for assessment, whereas Sterrlo and Hägerdal found a prolongation of the time to awakening after propofol. Although midazolam remains a popular drug for providing sedation during cardioversion, recovery after midazolam is significantly longer than when propofol is used for cardioversion. Although the overall
success rate for cardioversion is similar with all intravenous anesthetic agents, propofol may increase the energy required for successful cardioversion.\textsuperscript{594}

\textit{Electroconvulsive Therapy}

In the published comparisons of propofol and methohexital for ECT, propofol is consistently associated with a shortened duration of seizure activity.\textsuperscript{151,295-297} Propofol also decreases the duration of seizures compared with thiopental.\textsuperscript{298} The effect of propofol on seizure duration is dose-related and the minimally effective dose (0.75–1.25 mg·kg\textsuperscript{-1}) should be used for ECT.\textsuperscript{155} Although it has been suggested that the efficiency of ECT is related to the duration of the motor seizure (e.g., >30 s),\textsuperscript{299} Malsch \textit{et al.} have found that the efficacy of ECT was similar in patients anesthetized with either propofol or methohexital, despite shortened seizure duration in the propofol group.\textsuperscript{300} In addition, propofol was more effective than methohexital in attenuating the rise in blood pressure and HR immediately after ECT.\textsuperscript{151,155,296,297,301} There is a surprisingly high incidence of myocardial infarction after ECT.\textsuperscript{302} Thus, the ability of propofol to attenuate the sympathetic response to ECT may offer additional protection against this potentially serious complication of the treatment. Overall, recovery from ECT appears to be similar after the use of either propofol or methohexital.\textsuperscript{151,155,303}

\textit{Malignant Hyperthermia}

Propofol-based anesthetics have been used for providing anesthesia to patients susceptible to malignant hyperthermia (MH).\textsuperscript{304} Animal studies using the swine MH model have reported no evidence of MH during propofol anesthesia.\textsuperscript{305,306} Propofol infusions have also been used to provide anesthesia to patients being tested for MH susceptibility.\textsuperscript{304,307} McKenzie \textit{et al.} have shown that not only can propofol be used successfully in MH-susceptible patients, but that propofol does not affect the sensitivity of \textit{in vitro} contracture testing.\textsuperscript{307} Hence, propofol appears to be safe in MH-susceptible patients and can be used during muscle biopsy procedures in patients whose susceptibility has not as yet been established.

Propofol has also been used successfully in two patients with acute intermittent porphyria; however, further work is required before declaring propofol safe in this patient population.\textsuperscript{308,309}

In summary, propofol can be used successfully for both ECT and cardioversion. However, the minimally effective dose should be used to avoid the need to increase the energy requirements for successful treatments. Propofol also appears to be a useful agent in patients who are MH susceptible and those with acute intermittent porphyria. Finally, propofol has a distinctive antiemetic action and its use during surgery can decrease emetic sequelae after general anesthesia.

\textit{Pain on Intravenous Injection}

Pain after injection of propofol occurs in 28–90% of patients.\textsuperscript{192,310,311} Even when low-dose propofol infusions are administered for sedation, the incidence of pain can be 33–50%.\textsuperscript{86,312} Although the mechanism responsible for the propofol-induced venous pain is unknown, it has been suggested that it results from activation of the kinin cascade system.\textsuperscript{313} The original diluent, Cremophor EL, was initially thought to be the causative agent. However, there was no measurable reduction in pain after the change to the current lipid emulsion formulation.\textsuperscript{314} Klement and Arndt have demonstrated that the pain is a function of the drug itself, rather than the formulation.\textsuperscript{315}

The use of small veins on the dorsum of the hand is associated with a greater incidence of pain compared with large veins in the antecubital fossa.\textsuperscript{193,195,310,313,314} Scott and colleagues found that decreasing the speed of injection, or injecting propofol into a fast flowing intravenous infusion in the dorsum of the hand, was of little benefit in reducing the incidence of pain.\textsuperscript{315} However, dilution of propofol with either 5% glucose solution or 10% Intralipid resulted in a significant reduction in the incidence of pain.\textsuperscript{315,316}

The use of local anesthetics (e.g., lidocaine 1–2%) reduces the pain resulting from propofol injection. King \textit{et al.} found that the reduction in pain from the addition of lidocaine to the propofol formulation was dose-related.\textsuperscript{317} However, 6% of patients still reported severe pain when lidocaine, 20 mg (1 ml), was mixed with 190 mg (19 ml) of propofol. Gehan \textit{et al.} found that lidocaine, 0.1 mg·kg\textsuperscript{-1} significantly reduced the incidence of pain, and that there was no additional benefit from increasing the dose to 0.4 mg·kg\textsuperscript{-1}.\textsuperscript{318} In children, lidocaine 0.2 mg·kg\textsuperscript{-1} was reported to prevent pain from propofol injection completely.\textsuperscript{319} However, other investigators have reported pain in 6\%\textsuperscript{29} and 27%\textsuperscript{191} of children receiving as much as 0.5 mg·kg\textsuperscript{-1} lidocaine. Johnson and colleagues found 40 mg of lidocaine to be highly effective and better than 20 mg.\textsuperscript{320} This dose of lidocaine was equally effective.
when mixed with the propofol or when given as a "pretreatment" dose with simultaneous occlusion of the venous drainage of the forearm 20 s before the injection of propofol. Some investigators have suggested that venous occlusion with a tourniquet increases the effectiveness of lidocaine pretreatment. However, the addition of lidocaine to propofol was more effective than pretreatment without venous occlusion. When a mixture is used, the lidocaine and propofol should be freshly mixed, and used within 30 min, otherwise a significant fraction of the lidocaine will have entered the lipid phase and resulted in a decline in the effective "free" concentration.

Manschot et al. reported a 4% incidence of pain when alfentanil 5 μg·kg⁻¹ was administered to children 30 s before an induction dose of propofol via a vein on the dorsum of the hand. However, in another investigation, alfentanil 15 μg·kg⁻¹ intravenously failed to prevent propofol injection pain in 55% of the children studied. In adults, several investigators have demonstrated that alfentanil 10–50 μg·kg⁻¹ administered 1–2 min before propofol infusion significantly reduced pain on injection. Pethidine, 100 μg, may be equally effective. Finally, cooling propofol to 4°C or the injection of cold saline at 4°C into the intravenous cannula immediately before administering propofol are apparently as effective as the addition of lidocaine, 10 mg, to 19 ml of the propofol emulsion.

Summary and Recommendations

In reviewing the numerous studies which have been published over the past 4 yr, it is obvious that propofol has become an extremely valuable adjuvant for a wide variety of diagnostic and therapeutic procedures. Although propofol was initially viewed as an "outpatient" anesthetic, it is becoming more widely used during pediatric, neurosurgical and cardiovascular anesthesia, as well as for sedation in the ICU. The cardiovascular depressant effects of propofol are well tolerated in healthy outpatients, but these effects may be more problematic in high-risk patient populations with intrinsic cardiac disease, as well as those with multiorgan system disease. In hypovolemic patients and those with limited cardiac reserve, even small induction doses of propofol (0.75–1.5 mg·kg⁻¹) can produce profound hypotension. Therefore, use of a carefully titrated loading (priming) infusion will minimize the cardiovascular depression which is commonly associated with bolus (loading) doses of propofol in the OR and ICU environments.

In higher-risk patient populations, a two-stage infusion (i.e., rapid "loading" infusion followed by a slower "maintenance" infusion) will improve hemodynamic stability. In premedicated patients receiving an opioid–propofol combination for induction of anesthesia, an initial propofol dose of 0.5–1 mg·kg⁻¹ may be adequate. When smaller induction doses of propofol are administered, a higher initial maintenance infusion rate will be required. To avoid untoward cardiovascular depression, a variable-rate maintenance infusion should be used as part of a balanced or TIVA technique, as well as for sedation during the peroperative period.

The use of propofol for maintenance of general anesthesia has not been widely accepted in the United States. Although propofol has proven to be a valuable adjuvant during short ambulatory procedures, its use for more prolonged operations (e.g., >2 h) has been questioned because of the increased cost and marginal differences in recovery times compared with those of standard inhalation or balanced anesthetic techniques. When propofol is used for maintenance of anesthesia in combination with an opioid infusion, the practitioner is confronted with the dilemma of whether to vary the hypnotic (propofol) or the opioid analgesic. A preliminary study suggests that the outcome is similar whichever component is altered. The availability of computer-controlled intravenous drug delivery systems may improve the ability of anesthesiologists to titrate drugs like propofol and, therefore, to use intravenous anesthetic techniques more effectively in their clinical practices.

Judging the "depth of anesthesia" remains a challenge when using intravenous anesthetic techniques. The use of the EMG, EEG and lower esophageal contractility devices as depth of anesthesia monitors during surgery has proven disappointing. There is a very poor correlation between the changes in EEG and lower esophageal contractility variables and hemodynamic responsiveness during propofol anesthesia. Future studies involving newer approaches to cerebral function monitoring (e.g., EEG–bispectral analysis, brainstem evoked potentials) may prove that these modalities are of greater clinical benefit. A simple, reliable and noninvasive monitor of anesthetic depth would clearly enhance the ability of practitioners to titrate centrally active drugs like propofol. Until a reliable cerebral function monitor is available, adjunctive use of mida-
zolam and \( \text{N}_2\text{O} \) with propofol will decrease the likelihood of intraoperative recall.

With the increasing popularity of low-dose propofol infusions (e.g., 25–100 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) for sedation, questions have been raised regarding the appropriateness of nonanesthesiologists using propofol infusions outside the operating room (e.g., in the radiology suite, for radiation therapy, or in the ICU). According to the manufacturer, when propofol is used for general anesthesia or monitored anesthesia sedation it should be “administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical or diagnostic procedure. Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and \( \text{O}_2 \) enrichment and circulatory resuscitation must be immediately available. For sedation of intubated, mechanically ventilated adult patients in the ICU, propofol should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management.” It could be extremely dangerous for nonanesthesiologists to administer propofol infusions for diagnostic and therapeutic procedures outside the OR.\(^{351}\)

To minimize the well-known side effects associated with propofol, it is recommended that (1) patients be adequately hydrated before administering a bolus dose or a rapid infusion of propofol, (2) when infused into small veins, previous administration of 1% lidocaine, 1–2 mI intravenously, will decrease the pain on injection, (3) use of a rapid loading infusion over 30–60 s (vs. bolus injection over 10–15 s) for induction and a variable-rate infusion for maintenance of hypnosis or sedation will decrease propofol’s acute cardiovascular and respiratory depressant effects, (4) when administered in combination with benzodiazepines (as part of a coinduction technique) or opioid analgesics as part of a balanced technique, the propofol induction dose requirement should be decreased in both adults and children, (5) in elderly and debilitated patients, both the induction and maintenance dose requirements should be reduced by 25–50%, (6) The dose of propofol should always be carefully titrated against the needs and responses of the individual patient, as there is considerable interpatient variability in anesthetic requirements, (7) adjunctive use of local anesthetics, nonsteroidal antiinflammatory drugs and opioids to provide postoperative analgesia will improve the quality of emergence after propofol anesthesia and sedation, and (8) strict aseptic techniques must always be maintained during the handling of propofol, as the lipid emulsion contains no antimicrobial preservatives and is capable of supporting rapid growth of microorganisms.\(^{352}\)

Controversy surrounds the appropriate handling of propofol. The manufacturer has recommended that the solution be prepared for use “just before initiation of each individual procedure.” Based on an \textit{in vitro} study of questionable clinical relevance,\(^{353}\) it is recommended that “the ampule neck surface or vial rubber stopper should be disinfected using 70% isopropyl alcohol. Administration should commence promptly and be completed within 6 h after the ampules or vials have been opened.” According to the manufacturers, any unused portions of propofol must be discarded at the end of the anesthetic (or sedative) procedure or at 6 h (whichever occurs sooner). In the ICU, the tubing and any unused portion of propofol must be discarded after 12 h. Given the cost of the drug, many practitioners have questioned the appropriateness of discarding all unused drug at the end of every case. In the ambulatory setting, this practice is cost-ineffective, and may lead to reluctance to use this otherwise useful drug for short outpatient procedures. The incidence of clinical infection caused by bacterial contamination of propofol is very low.\(^{354,355}\) Most of these cases involved propofol which had been drawn up a day before its administration. However, a recent report suggested that when propofol is aseptically drawn into an uncapped syringe, it will remain sterile at room temperature for several days.\(^{356}\) Further studies are clearly needed to determine the most cost-effective manner to use propofol in clinical practice.\(^{357}\)

In conclusion, propofol has become a widely used intravenous anesthetic for induction and maintenance of general anesthesia and sedation. The favorable recovery profile associated with propofol offers advantages over traditional anesthetic and sedative medications in clinical situations where a rapid recovery is important. However, more rapid recovery will only reduce overall costs if it permits a reduction in staffing or use of equipment. Although many questions still remain to be answered regarding this unique sedative–hypnotic drug, it is obvious that

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propofol has indeed provided a “new awakening” in anesthesia.338

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