David S. Warner, M.D., Editor

Propofol

Its Role in Changing the Practice of Anesthesia

*Paul F. White, Ph.D., M.D., F.A.N.Z.C.A.**

Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. By Audrey Shafer, Van A. Doze, Steven L. Shafer, and Paul F. White. ANESTHESIOLOGY 1988; 69:348–56. Reprinted with permission.

The pharmacokinetic and pharmacodynamic properties of propofol (Diprivan™) were studied in 50 elective surgical patients. Propofol was administered as a bolus dose, 2 mg/kg iv, followed by a variable-rate infusion, 0–20 mg/min, and intermittent supplemental boluses, 10–20 mg iv, as part of a general anesthetic technique that included nitrous oxide, meperidine, and muscle relaxants. For a majority of the patients (n = 30), the pharmacokinetics of propofol were best described by a two-compartment model. The propofol mean total body clearance rate was 2.09 ± 0.65 l/min (mean ± SD), the volume of distribution at steady state was 159 ± 57 l, and the elimination half-life was 116 ± 34 min. Elderly patients (patients older than 60 yr *vs.* those younger than 60 yr) had significantly decreased clearance rates (1.58 ± 0.42 *vs.* 2.19 ± 0.64 l/min), whereas women (*vs.* men) had greater clearance rates (33 ± 8 *vs.* 26 ± 7 ml • kg^{-1} • min $_{-1}$) and volumes of distribution (2.50 ± 0.81 *vs.* 2.05 ± 0.65 l/kg). Patients undergoing major (intraabdominal) surgery had longer elimination half-life values (136 ± 40 *vs.* 108 ± 29 min). Patients required an average blood propofol concentration of 4.05 ± 1.01 micrograms/ml for major surgery and 2.97 ± 1.07 micrograms/ml for non-major surgery. Blood propofol concentrations at which 50% of patients (EC_{50}) were awake and oriented after surgery were 1.07 and 0.95 microgram/ml, respectively. Psychomotor performance returned to baseline at blood propofol concentrations of 0.38–0.43 microgram/ml (EC_{50}). This clinical study demonstrates the feasibility of performing pharmacokinetic and pharmacodynamic analyses when complex infusion and bolus regimens are used for administering iv anesthetics.

IN the early 1980s, outpatient (ambulatory) surgery was just starting to become a widely accepted approach for elective surgery. As the volume and complexity of ambulatory surgery procedures increased, it became apparent that the traditional intravenous (*e.g.*, barbiturates [thiopental, methohexital]) and volatile (halothane, enflurane, isoflurane) anesthetics were associated with frequent side effects (*e.g.*, residual sedation, dizziness, confusion, fatigue, nausea and vomiting), which prolonged early recovery and delayed discharge home from both hospital-based and freestanding ambulatory surgery centers. Therefore, it was apparent to practitioners that a need existed for anesthetic drugs and techniques that could facilitate the early recovery process after elective surgical procedures.

As a young academic anesthesiologist and clinical pharmacologist working in the Department of Anesthesia at Stanford University Medical Center (Stanford, California), I was intrigued by the potential of propofol (Diprivan; Imperial Chemical Industries [ICI], Macclesfield, England, United Kingdom), a novel intravenous anesthetic, to facilitate the transition of surgical care from the inpatient to the outpatient setting. By developing a more in-depth understanding of propofol's pharmacokinetics and dynamics properties,[1] I believed that propofol could become a useful drug for both induction

Paul F. White, Ph.D., M.D., F.A.N.Z.C.A.

and maintenance of general anesthesia, as well as for sedation in operating rooms, diagnostic centers, and intensive care units.

The preliminary clinical experience with propofol (ICI 35 868) in Europe suggested that its use was associated with longer induction times and a higher incidence of pain on injection than other intravenous induction agents.[2,3] Although these early studies did not find clinically significant advantages of propofol over the popular barbiturates, thiopental and methohexital, with respect to speed of recovery from anesthesia, postoperative side effects were consistently less frequent in the propofol-treated patients.[4,5] Nevertheless, the early European investigators clearly recognized the potential benefits of propofol for day surgery (ambulatory) procedures.

Based on these preliminary reports from Europe, I proposed to study the use of propofol for induction and maintenance of general anesthesia as an alternative to methohexital for short ambulatory surgical procedures at Stanford University Medical Center.[6] When the company that developed the emulsion formulation of propofol, namely ICI, learned about the details of my study proposal (which involved the use of a variable-rate continuous infusion of propofol using a very crude infusion system [*i.e.*, a simple gravity-dependent volutrol drip chamber]), I was contacted by the medical director of ICI's American partner, Stuart Pharmaceuticals (Wilmington, DE), and was advised to immediately discontinue my comparative study. According to the decision makers at ICI, the use of this type of drug delivery system would compromise the efficacy of propofol because of the potential for varying amounts of the propofol emul-

sion to adhere to the drip chamber and intravenous tubing during the maintenance infusion. It was also apparent that ICI was primarily interested in developing propofol as an induction agent by intravenous bolus administration in North America because of the dominant position of volatile anesthetics during the maintenance period. According to the medical director of Stuart Pharmaceuticals, ICI was concerned that by including the maintenance infusion arm in our study, we might be compromising the US Food and Drug Administration approval process. After explaining that I had already enrolled six patients in the propofol arm of the study protocol without any untoward effects, I was able to convince the "powers that be" at ICI (and Stuart Pharmaceuticals) to let us continue my comparative study by arguing that these were very short surgical procedures and the propofol maintenance infusion could also be viewed as a "slow bolus" injection of the drug over 15–20 min.

The surgeons and anesthesiologists at Stanford were initially extremely skeptical about using this unusual, milky-appearing intravenous substance for producing general anesthesia. However, the impressive recovery profile of propofol, which was characterized by a rapid emergence, with the ability to ambulate very soon after surgery, and an extremely low incidence of postoperative nausea and vomiting,[6] quickly convinced them that this drug could be a useful addition to our armamentarium. This early experience with propofol convinced me and my colleagues that this unique compound had the potential for markedly facilitating recovery after both ambulatory and inpatient surgery.

The postanesthesia care unit nurses also observed that patients receiving propofol seemed to be more alert and "clearheaded" after surgery. The nurses also commented that these patients frequently displayed mood elevating (*e.g.*, euphorigenic) effects in the postanesthesia care unit. After its approval by the Food and Drug Administration in 1986, propofol rapidly became the intravenous anesthetic of choice for ambulatory surgery. Even when compared with the newer, less-soluble volatile anesthetics (*e.g.*, sevoflurane), use of propofol for induction and maintenance of anesthesia was associated with an earlier discharge from the postanesthesia care unit and the ambulatory surgery facility, as well as a reduced incidence of postoperative nausea and vomiting and higher patient satisfaction with their anesthetic experience.[7]

As a pharmacology graduate student working with Professors Edmond I Eger II, M.D., Walter L. Way, M.D., and Anthony J. Trevor, Ph.D., at the University of California, San Francisco, I had written my Ph.D. dissertation on the pharmacokinetics and dynamics of ketamine and its optical isomers.[8,9] To optimize the administration of propofol during surgery, it was obviously important to understand its basic pharmacokinetic and pharmacodynamic properties. Therefore, my clinical research group
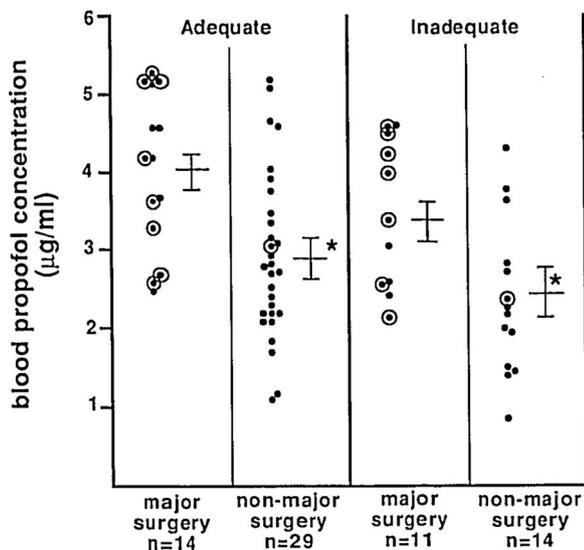
Fig. 1. Blood propofol concentration (μg/ml) in relation to type of surgical procedure at times of absence of autonomic response (adequate) or presence of autonomic response (inadequate) to surgical stimulation. Individual and mean ± SEM values are shown. *Encircled dots* represent values for patients who received supplemental opioid analgesic medication during the operation. * Significant differences between groups (major *vs.* nonmajor surgery), $P < 0.05$. From Shafer *et al.*[1]

Fig. 2. Concentration–response curves for awakening and orientation as a function of blood propofol level (μg/ml). The cumulative percent of patients who awoke or were oriented at various blood propofol levels are shown. From Shafer *et al.*[1]

at Stanford University performed a study that used propofol for induction and maintenance of general anesthetic as part of a "balanced" anesthetic technique.[1] In this classic pharmacokinetic–pharmacodynamic study, propofol's pharmacokinetic variables, namely the volume of distribution (159 l), clearance (2.1 l/min), and elimination half-life (116 min), were defined. We also examined the effect of age and sex on the drug's pharmacokinetic profile. Patients younger than 60 yr and women had a greater hepatic clearance rates. These data suggested that lower maintenance infusion rates would be required during surgery in older patients. On the other hand, women would require higher maintenance infusion rates of propofol. These data further suggested that women might experience a more rapid recovery from propofol's central depressant effects, a finding later confirmed in a study published by Hoymork and Raeder.[10]

Our early pharmacokinetic–pharmacodynamic studies with propofol also provided important information about the effect of the type of surgery on the maintenance requirement for propofol.[1,11] Although it was not surprising to learn that major surgery required higher blood concentrations than minor surgery (fig. 1), the elimination half-life of propofol was found to be prolonged in patients undergoing intraabdominal surgery because of a reduction in the drug's clearance rate. In addition to defining the blood levels of propofol required during both major and minor operations, we determined the propofol blood concentrations associated with recovery of consciousness (fig. 2) and return of cognitive and psychomotor functioning (fig. 3).
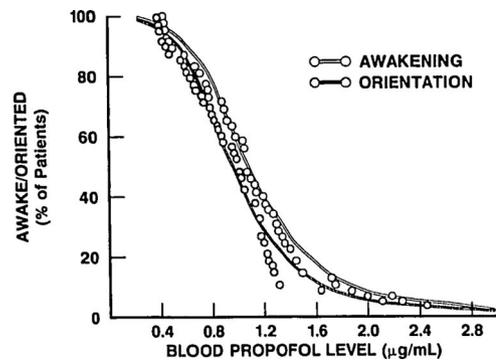
Our pharmacokinetic–pharmacodynamic analysis revealed the "steep" nature of the dose–response relation between propofol's concentrations in the blood and recovery from its sedative–hypnotic depressant effects on the central nervous system (figs. 2 and 3). Importantly, when patients awoke from the hypnotic effect of propofol, they were almost immediately oriented to person, place, and time (fig. 2). However, recovery of cognitive and psychomotor function occurred at significantly lower propofol concentrations (fig. 3). Interestingly, the recovery of cognitive skills closely paralleled the recovery from the sedative effects of propofol. Propofol's pharmacokinetic–pharmacodynamic variables have subsequently been incorporated into a variety of mathematical models for improving the delivery of propofol during surgical procedures performed during both general anesthesia and intravenous sedation (as part of monitored anesthesia care techniques).[12]

Knowledge of propofol's pharmacokinetic and pharmacodynamic profile has lead to the development of improved drug delivery systems involving computer-assisted continuous infusion and target-controlled infusion of propofol.[13–15] Using a monitor of the hypnotic effects of propofol on the brain (*e.g.*, electroencephalographic Bispectral Index [BIS®] monitor; Aspect Medical Systems, Norwood, MA), it is possible to create a closed-loop delivery system for improving the titration of propofol during both general anesthesia and monitored anesthesia care.[16] In a more "in-depth" evaluation of closed-loop controlled administration of propofol using the BIS® monitor as an alternative to "standard clinical practice" for titrating propofol during intravenous anesthesia, Struys *et al.*[17] reported that the use of the closed-loop technique was associated with less cardiovascular depression and a faster recovery from propofol anesthesia.

My proposal for studying the use of propofol for intravenous sedation during surgical procedures performed during local anesthesia was initially rejected by the decision makers at ICI/Zeneca (Wilmington, DE). After obtaining Food and Drug Administration approval for an investigator-sponsored investigational new drug applica-
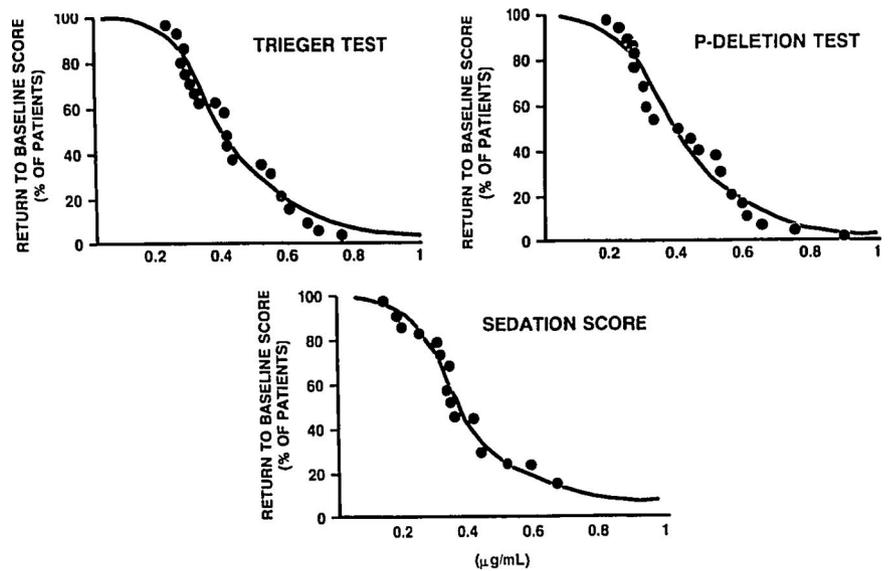
Fig. 3. Concentration–response curves for the return to baseline (preoperative) test scores as a function of blood propofol level (μg/ml). Each graph depicts the cumulative percent of patients who returned to baseline function for the Trieger test, p-deletion test, and sedation analog scales. From Shafer *et al.*[1]

tion to study propofol for intravenous sedation, the manufacturer agreed to supply me with the drug (and awarded us a small educational grant) for the purpose of performing a comparative study involving the use of propofol as an alternative to midazolam for sedation during local and regional anesthesia.[18] At the Diprivan (propofol) launch meeting held in Naples, Florida, in 1988, I predicted that by the end of the century, more propofol would be sold for intravenous sedation than general anesthesia, a suggestion that the company officials in attendance found very amusing. Some 10 years later, half of the propofol sold in the United States was used for intravenous sedation. Currently, more than 70% of propofol sold worldwide is administered for intravenous sedation in operating rooms, diagnostic centers, and intensive care units. In addition to propofol's important role in ambulatory surgery facilities, propofol has become increasingly popular in diagnostic centers for sedation during gastroenterology and pulmonary medicine procedures, as well as in critical care areas for sedation of ventilator-dependent patients as an alternative to benzodiazepines and/or opioid analgesics.

Summary

Propofol (Diprivan) was initially developed as an alternative to thiopental (Pentothal) and methohexital (Brevital) for induction of general anesthesia. Although the primary advantage of propofol over the popular barbiturates was initially alleged to be reduced somnolence and fatigue ("hangover" effect) in the early postoperative period, it has subsequently become apparent that the drug also allows for a more rapid recovery of cognitive and psychomotor skills, and its use was consistently associated with lower incidences of postoperative side effects such as postoperative nausea and vomiting and cognitive impairment. Subsequently, the benefits of us-

ing propofol for maintenance of general anesthesia as part of a "balanced" or total intravenous anesthetic technique have become apparent to anesthesia practitioners around the world.[19–21] However, the largest area of growth in propofol usage has been for intravenous sedation in operating rooms (*e.g.*, monitored anesthesia care techniques) and diagnostic centers (*e.g.*, a part of endoscopic procedures), as well as in the intensive care unit.

In preparing this article, it is important to acknowledge those who have assisted me with my studies involving propofol and many other new anesthetics, analgesics, and muscle relaxant drugs. I have been very fortunate to have worked under outstanding mentors at the University of California, San Francisco, and with highly supportive colleagues at Stanford University, Washington University, Cedars Sinai Medical Center, and the University of Texas. However, my greatest pleasure in academic medicine has come from my association with an amazing group of bright, hardworking medical students and clinical research fellows (see figure, Supplemental Digital Content 1, which shows Dr. and Mrs. Paul F. White with medical students and clinical research fellows at University of Texas Southwestern Medical Center, http://links.lww.com/A564). All of the coauthors' on my early articles describing the pharmacologic properties of propofol were medical students at Stanford University, namely Van Doze, Lynn Westphal, Steve Shafer, and Audrey Shafer (who was also my first clinical research fellow). It is to these outstanding individuals, and the more than 150 medical students and clinical research fellows who followed in their footsteps, that I dedicate this Classic Papers Revisited article.

In conclusion, I believe that propofol has truly had a revolutionary impact on the practice of anesthesia and perioperative medicine over the past 20+ years because of its ability to allow more complex surgical procedures

to be performed in higher-risk patients on an outpatient basis by facilitating the fast-track recovery process.[22]

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