

Comparison of a Lower-lipid Propofol Emulsion with the Standard Emulsion for Sedation during Monitored Anesthesia Care

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Background: **The currently used emulsion formulations of 1% propofol contain 10% soybean oil. However, a new emulsion of 1% propofol (Ampofol) containing 50% less lipid has recently become available for clinical investigation. This study was designed to compare the pharmacodynamic properties of Ampofol with those of a standard formulation (Diprivan) when administered for intraoperative sedation.**

Methods: **Sixty healthy outpatients undergoing minor operations with local anesthesia were randomly assigned to receive either Ampofol (n = 31) or Diprivan (n = 29) for intravenous sedation. The sedation was initiated with an intravenous loading dose of propofol, 0.75 mg/kg, followed by an initial infusion rate of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to achieve an Observer's Assessment of Alertness/Sedation score of 3. The targeted level of sedation was maintained with a variable-rate propofol infusion during the operation. The onset times to achieving a sedation score of 3, the severity of pain on injection of the loading dose, intraoperative hemodynamic variables, and electroencephalographic Bispectral Index values were recorded. In addition, recovery times, postoperative pain and nausea, and patient satisfaction with the sedative medication were assessed.**

Results: **There were no significant differences between Ampofol and Diprivan with respect to onset times, dosage requirements, Bispectral Index values, hemodynamic variables, recovery times, or patient satisfaction scores. The incidence of moderate pain on injection was higher in the Ampofol group (26% *vs.* 7% with Diprivan; $P < 0.05$).**

Conclusions: **Ampofol was equipotent to Diprivan with respect to its sedative properties during monitored anesthesia care. Although both groups received pretreatment with intravenous lidocaine, Ampofol was associated with more pain on injection.**

PROPOFOL has become an increasingly popular intravenous sedative during operations performed under local anesthesia as a part of a monitored anesthesia care technique.[1] Although propofol infusions have been used for sedation both in the operating room (OR)[2] and in the intensive care unit,[3] long-term sedative infusions have been associated with hypertriglyceridemia.[4,5]

Ampofol (Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, CA) is a new lower-lipid emulsion of propofol that contains 50% less soybean oil (5%) and egg lecithin (0.6%) than the current formulations, namely Diprivan (AstraZeneca, Wilmington, DE) and generic propofol (Gensia Sicor, Irvine, CA). Based on an animal study in which propofol was administered in a lipid-free vehicle,[6] we hypothesized that this new lower-lipid emulsion formulation would alter the pharmacodynamic (sedative) profile of propofol by prolonging its onset time.

Therefore, we designed a randomized, double-blind study to evaluate the efficacy of Ampofol and Diprivan when used to provide intravenous sedation during monitored anesthesia care. In addition to assessing the induction time, intraoperative hemodynamic variables, electroencephalographic Bispectral Index (BIS) values, recovery times, and postoperative side effects were evaluated.

Materials and Methods

After obtaining institutional review board approval (University of Texas Southwestern Medical Center at Dallas, Dallas, Texas) and written informed consent, 63 outpatients with American Society of Anesthesiologists physical status class I or II who were undergoing breast biopsy or Lifeport (Hurlzen Medical Products, Manchester, GA) placement procedures under local anesthesia were assigned to receive either Ampofol or Diprivan according to a computer-generated random number table. Patients with neurologic, cardiovascular, or metabolic diseases; impaired renal or hepatic function; or a positive pregnancy test and those who were breast feeding at the time of surgery, as well as patients with a history of drug abuse, egg lecithin, or soybean oil allergies, were excluded from participating in this study.

All patients were premedicated in the preoperative holding area with rofecoxib, 50 mg oral, and midazolam, 20 μg/kg intravenous, at 30–45 min and 5–10 min, respectively, before entering the OR. On arrival in the OR, routine monitors were applied for recording heart rate, mean arterial pressure, and oxygen saturation values. In addition, a one-channel BIS® monitor (Model 1050, Rev 3.12 U; Aspect Medical System, Natick, MA) was used for recording intraoperative BIS values. All patients were given supplemental oxygen through a nasal cannula with a carbon dioxide sampling port to monitor the respiratory rate.

After 0.5 μg/kg fentanyl and 0.5 mg/kg lidocaine were

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administered, patients were given a loading dose of propofol, 0.75 mg/kg (injected over 15–18 s through an 18-gauge catheter placed in a small vein on the dorsum of the hand). The 1% propofol solution (either Diprivan or Ampofol) was prepared by the OR pharmacist in unlabeled syringes according to the randomization table provided by the study sponsor. In addition to the patients, the anesthesiologists and the investigators were unaware of the propofol formulation. After the propofol loading dose, a continuous infusion of propofol was started at an initial rate of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to achieve a patient Observer's Assessment of Alertness/Sedation's (OAA/S)[7] score of 3. This level of sedation was maintained by varying the propofol infusion between 25 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the surgical procedure. A local anesthetic solution, consisting of 0.25% bupivacaine and/or 1% lidocaine, was injected at the surgical site by the operating surgeon before the skin incision for intraoperative analgesia. Supplemental fentanyl, 25- to 50-μg intravenous boluses, was administered to treat pain not responding to additional local anesthetic solution. On closure of the skin incision, the propofol infusion was discontinued.

The mean arterial pressure, heart rate and BIS values were recorded at 1, 3, and 5 min after the initial bolus injection of propofol and then at 5-min intervals until 5 min after discontinuation of the propofol infusion. Pain on injection of propofol was assessed using a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) every 5–10 s until the patient achieved an OAA/S score of 3. The induction time was determined as the time from the initial injection of propofol until the patient achieved an OAA/S score of 3. Recovery times were assessed at 1- to 5-min intervals from the time the propofol infusion was discontinued until the patients opened their eyes on command; were orientated to person, date, and place; ambulated; and were judged to be "home ready." In addition, the maximal postoperative pain and nausea scores (on an 11-point verbal rating scale [0 = none, 10 = worst imaginable]), the patients' quality of recovery score[8] (on a scale from 0 to 18), and recall of pain on injection of propofol were assessed at the time the patient was discharged home from the day-surgery unit. A follow-up telephone call was performed at 24 h after surgery to assess the patients' maximal pain and nausea scores in the postdischarge period (on the 11-point verbal rating scale), as well as their overall satisfaction with the intraoperative sedation on a 100-point verbal rating scale (1 = highly dissatisfied, 100 = highly satisfied).

Statistical Analyses

Before initiating the study, a power analysis was performed to estimate the sample size. The calculation was based on the mean times to achieve an OAA/S score of 3 for the two study groups. Assuming an induction time in the Diprivan group of 58 s with an SD of 20 s, a sample size of 29 patients for each group was necessary to detect a 15-s prolongation in the time from injection of propofol until the patients achieved an OAA/S score of 3, with $\alpha = 0.05$ and $\beta = 0.2$, using the software nQuery Advisor (Statistical Solutions, Saugus, MA). A two-sample *t* test was used for comparison of all continuous variables between the groups. The Kruskal-Wallis test and the chi-square test were used for analysis of all nonparametric variables, as appropriate. Data are expressed as mean (± SD) or median (and interquartile range), and *P* values less than 0.05 were considered statistically significant.

Table 1. Demographics, duration of Anesthesia, and Intraoperative Medications and Fluid in the Two Treatment Groups

	Diprivan	Ampofol
No.	29	31
Age, yr	51 ± 12	52 ± 15
Weight, kg	73 ± 20	75 ± 28
Height, cm	168 ± 8	165 ± 8
Sex (M/F)	5/24	2/29
Type of operation, No. (%)		
Breast biopsy	16 (55)	22 (71)
Lifeport placement	13 (45)	9 (29)
Duration of anesthesia, min	39 ± 17	44 ± 19
Duration of surgery, min	30 ± 13	34 ± 15
Propofol bolus, mg	52 ± 12	52 ± 10
Propofol infusion, mg	272 ± 145	336 ± 209
Average propofol infusion rate, $\mu g \cdot kg^{-1} \cdot min^{-1}$	98 ± 29	101 ± 28
Midazolam, mg	1.4 ± 0.3	1.5 ± 0.3
Induction fentanyl, μg	35 ± 7	34 ± 7
Maintenance fentanyl, μg	36 ± 36	32 ± 41
Intravenous fluids, ml	818 ± 269	852 ± 375

Values are expressed as number or mean ± SD. There were no significant differences between the two study groups.

Results

Of the 63 outpatients enrolled in the study, 3 withdrew before the study medication was administered. The two treatment groups were comparable with respect to demographic characteristics (table 1). Similarly, no differences were found in the duration of sedation, in the dosages of adjunctive anesthetic and analgesic medications, or in the amount of intravenous fluid administered (table 1).

There was no difference between the two groups with respect to induction time. Although the overall incidence of pain on injection was higher in the Ampofol group compared with the Diprivan group, this difference did not achieve statistical significance. However, the incidence of moderate pain on injection was significantly higher in the Ampofol (*vs.* Diprivan) group (table 2). Among the eight patients in the Ampofol group who experienced moderate pain on injection, only two had recall of the pain when questioned at the time they were discharged home.

Table 2. Results in the Two Treatment Groups

	Diprivan	Ampofol
Induction time,* s	67 ± 36	65 ± 17
Pain on injection, No. (%)	8 (28)	16 (52)
Mild pain	6 (21)	8 (26)
Moderate pain	2 (7)	8 (26)†
Severe pain	0	0
Recall of pain	0	2 (7)
Awakening time, min	4 ± 2	3 ± 6
Orientation time, min	7 ± 3	8 ± 4
Home readiness time, min	52 ± 21	53 ± 24
Maximal pain score at discharge	0 (0–0)	1 (0–1)
Maximal nausea score at discharge	0 (0–0)	0 (0–0)
Quality of recovery score (0–18)	16 (16–16)	16 (16–16)
Maximal pain score at 24 h, No.	2 (0–2)	1 (0–2)
Maximal nausea score at 24 h, No.	0 (0–0)	0 (0–0)
Satisfaction score at 24 h, No.	100 (100–100)	100 (100–100)

Values are expressed as mean ± SD, median and interquartile range, or number and percentage.

* From injection of propofol to achievement of Observer's Assessment of Alertness/Sedation score of 3. † $P < 0.05$ compared with Diprivan group.

Intraoperative mean arterial pressure and BIS values were similar in the two study groups (table 3). In addition, there were no significant differences between the two study groups with respect to recovery times, postoperative pain and nausea scores, quality of recovery scores, or patient satisfaction with their intraoperative sedation (table 2). There were also no differences in postdischarge side effects at the 24 h follow-up evaluation.

Table 3. Intraoperative Changes of Electroencephalogram BIS Values and MAP Values in the Two Treatment Groups

	Diprivan	Ampofol
Baseline BIS	96 ± 4	96 ± 4
Maintenance BIS		
At 1 min	66 ± 18	64 ± 17
At 3 min	58 ± 17	56 ± 16
At 5 min	66 ± 13	61 ± 14
At 10 min	69 ± 12	62 ± 14
At 15 min	63 ± 12	55 ± 11
At 30 min	61 ± 13	58 ± 13
BIS at end of propofol infusion	66 ± 10	64 ± 15
BIS at 5 min after discontinuation	78 ± 8	70 ± 15
Baseline MAP, mmHg	96 ± 13	102 ± 11
Maintenance MAP		
At 1 min	92 ± 15	94 ± 15
At 3 min	85 ± 14	91 ± 14
At 5 min	82 ± 9	83 ± 19
At 10 min	81 ± 12	80 ± 12
At 15 min	75 ± 15	76 ± 12
At 30 min	71 ± 14	75 ± 17
MAP at end of propofol infusion	71 ± 13	74 ± 13
MAP at 5 min after discontinuation	74 ± 13	78 ± 15

Values are expressed as mean ± SD. There were no significant differences between the two study groups.

BIS = Bispectral Index; MAP = mean blood pressure.

Discussion

Propofol, a highly lipophilic anesthetic, is commercially formulated as a lipid emulsion for intravenous use. The proprietary formulation, containing 10% soybean oil and 1.2% egg lecithin, is characterized by a rapid onset and offset of its sedative–hypnotic effects after administration.[9] Compared with the standard emulsion formulation, a previous study in rats[6] found that propofol administered in a lipid-free vehicle resulted in a longer time to onset of its hypnotic effect, with a trend toward a delayed recovery. Therefore, it was suggested that the nature of the formulation of propofol could influence its clinical characteristics by modifying its pharmacokinetic or pharmacodynamic properties or both.[10]

The current study showed that significantly reducing the lipid content of the propofol emulsion (up to 50%) did not alter the central nervous system pharmacodynamic profile of propofol when compared with the standard emulsion formulation. Using the same targeted level of sedation (*i.e.*, OAA/S score of 3), the average Ampofol infusion rate was not different from that of Diprivan. No differences could be found between the two formulations with respect to the induction or recovery times, intraoperative hemodynamics and BIS index values, or postoperative side effects. These data confirm a preliminary study comparing Ampofol and Diprivan when used for induction and maintenance of general anesthesia.[11]

A potential clinical advantage of Ampofol over the current formulations of propofol is in situations in which patients require large dosages of the drug for sedation in the OR or the intensive care unit. For example, Kimura *et al.*[5] reported that serum triglyceride concentration increased significantly postoperatively after an intraoperative propofol infusion at a rate of 4–9 $mg \cdot kg^{-1} \cdot h^{-1}$ (approximately 65–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$) using the currently available formulations of propofol, which contain 10% soybean oil. In a long-term intensive care unit sedation study involving Diprivan 1%, Boyle *et al.* found significant increase in lipid concentrations over time, necessitating discontinuation of the propofol infusion in some cases (W. A. Boyle, M.D., J. M. Shear, M.D., P. F. White, M.D., D. Schuller, M.D., unpublished data, September 1990). It is likely that in the presence of similar infusion rates of propofol, the Ampofol formulation would be associated with a reduced plasma triglyceride concentration compared with the standard emulsion formulations. Although the use of a 2% propofol formulation may result in a similar reduction in lipid concentrations at comparable levels of sedation to those produced by Ampofol, the 2% formulation of propofol is not approved for clinical use in the United States.

Induction of intraoperative sedation with a bolus dose of Ampofol was associated with a significantly higher incidence of moderate pain on injection when compared with Diprivan. Although 1% lidocaine, 0.5 mg/kg, was

administered before the injection of both formulations, 26% of the patients in the Ampofol group (*vs.* only 7% in the Diprivan group) reported moderate pain on injection. Of interest, only two of the eight patients in the Ampofol group who reported moderate pain recalled the pain when questioned postoperatively. The finding regarding the relative incidence and severity of pain on injection of these two propofol formulations also supports our previous study[11] and observations that suggest that the pain on injection of propofol is related to the free fraction of propofol.[12,13] Doenicke *et al.*[13] reported that a lower concentration of propofol in the aqueous phase of the emulsion reduced its pain on injection. These investigators suggested that the addition of a greater amount of lipid emulsion results in a higher percentage of propofol being absorbed by the fat particles. The 50% reduction in lipid content in the Ampofol formulation would be expected to double the "free" concentration of propofol in the aqueous phase and thereby contribute to more pain on injection. However, the observed increased pain on injection of Ampofol (*vs.* Diprivan) in this study does not support the recent theory that propofol's pain on injection was related to lipid-induced bradykinin release from the endothelium of peripheral veins.[14]

In summary, the Ampofol formulation of propofol is equipotent to Diprivan with respect to their pharmacodynamic profiles when used for intraoperative sedation during monitored anesthesia care. However, injection of Ampofol into a small peripheral vein was associated with more pain on injection than was Diprivan.

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