Subjective and Psychomotor Effects of Subanesthetic Doses of Propofol in Healthy Volunteers

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Propofol is increasingly being used in medical and surgical procedures in which conscious sedation of the patient is desired. The mood-altering and psychomotor effects of subanesthetic concentrations of propofol have not been well characterized. Therefore, we examined the effects of intravenous infusions of different subanesthetic doses of propofol on mood and psychomotor/cognitive performance in healthy volunteers (n = 10). A prospective, randomized, placebo-controlled, double-blind, crossover design was used in which subjects first were administered an intravenous loading dose of propofol or placebo (Intralipid) and then were infused over a 20-min period with a given dose of propofol or placebo. Each subject received placebo (Intralipid loading dose and infusion), low-dose propofol (0.08 mg/kg loading dose and 0.5 mg·kg⁻¹·h⁻¹ infusion), moderate-dose propofol (0.16 mg/kg loading dose and 1.0 mg·kg⁻¹·h⁻¹ infusion), and high-dose propofol (0.32 mg/kg loading dose and 2.0 mg·kg⁻¹·h⁻¹ infusion) in four sessions spaced approximately 1 week apart. Propofol induced changes in mood in a dose-related fashion. Some of these mood-altering effects lingered for as long as 30 min after termination of the infusion, but, in general, mood had returned to baseline levels 1 h after termination of the infusion. Intralipid induced no changes in mood during the infusion period. Psychomotor functioning was impaired during, and anterograde amnesia was present after, the high-dose propofol infusion. These results suggest that propofol as a sedative has a spectrum of effects that are well-suited for ambulatory surgery (e.g., sedation, amnesia, and rapid and complete recovery). (Key words: Anesthetics, intravenous propofol. Brain, psychomotor performance; memory. Surgery: ambulatory.)

PROPOFOL (2,6-diisopropylphenol) is a short-acting, rapidly metabolized intravenous agent that has typically been used to induce or maintain anesthesia. However, several recent reports have examined its efficacy as a sedative.1-10 In general, recovery from an infusion of propofol is more rapid than recovery from such widely used agents as intravenous midazolam and diazepam, as assessed by either psychomotor performance or clinical observation by medical staff.1,2,4-6,9,10 Almost complete anterograde amnesia has been reported with this agent when used as a perioperative sedative.3,7 Infusion doses for sedation have varied across studies and have ranged from 1.7 to 5 mg·kg⁻¹·h⁻¹. Because propofol is associated with rapid psychomotor/cognitive recovery, induces amnesia of the surgical or medical event, and can easily be titrated to achieve different levels of sedation, this agent appears to be well suited for some ambulatory surgery procedures.

To date, no studies have fully characterized the effects of subanesthetic doses of propofol on mood. A sedative agent ideally should not induce unpleasant subjective effects (e.g., anxiety). In the present study, we examined the effects of propofol on mood, memory, and psychomotor performance to more fully characterize the spectrum of subjective and behavioral effects that could be expected from subanesthetic doses of propofol.

Materials and Methods

SUBJECTS

This study was approved by the Institutional Review Board of the University of Chicago Pritzker School of Medicine. Informed consent from each subject was obtained prior to initiating the study. Subjects were told that the drug(s) to be used were 1) commonly used in medical settings, 2) may come from one of five classes (i.e., sedative/tranquilizer, stimulant, opiate, or general anesthetic at subanesthetic dose[s], or placebo), and 3) would be clinically safe at the dose(s) used. Eight men and two women (mean age 25.3 ± 4.6 yr, mean weight 74.8 ± 9.8 kg) participated. Their history of recreational drug and alcohol use was relatively light: the subjects consumed, on average, 4.0 ± 2.1 drinks per week. No subjects currently smoked marijuana, and two subjects were light cigarette smokers (fewer than 8 cigarettes smoked daily).

Before the first session, subjects attended a screening interview, at which point they completed the Symptom Checklist (SCL-90)11 (a questionnaire designed to assess psychiatric symptomatology) and a health questionnaire in order to determine their psychiatric and medical status. A psychiatric interview was conducted by a psychiatric social worker. Candidates with any history of significant psychiatric disorders or substance use disorder (Diagnostic and Statistical Manual DSM-III-R criteria15), except for tobacco dependence, were excluded. An anesthesiologist took the role of the psychiatrist.
performed a medical history and physical examination, and volunteers with a history of neurologic, cardiac, pulmonary, hepatic, or renal disease, or any other medical contraindication were excluded from the study. A blood test was done on potential subjects so that normal liver (as assessed by serum glutamate oxaloacetate transaminase, bilirubin, alkaline phosphatase, total protein tests) and kidney (as assessed by blood urea nitrogen, creatinine, potassium, chloride, sodium, and carbon dioxide tests) functioning could be assured.

Subjects were instructed to refrain from using recreational drugs (including alcohol) for 24 h before sessions. Subjects were told not to drive a car, operate heavy machinery, or cook with a stove until the day after the study, and were transported home after sessions. Payment for the study was made during a debriefing session, held after completion of the study.

**Experimental Design**

A prospective, randomized, placebo-controlled, double-blind, crossover trial was conducted. Subjects were exposed to each of four conditions in four separate sessions spaced approximately 1 week apart: placebo (Intralipid loading dose and infusion), low-dose propofol (0.08 mg/kg loading dose and 0.5 mg·kg\(^{-1}\)·h\(^{-1}\) infusion), moderate-dose propofol (0.16 mg/kg loading dose and 1.0 mg·kg\(^{-1}\)·h\(^{-1}\) infusion), and high-dose propofol (0.32 mg/kg loading dose and 2.0 mg·kg\(^{-1}\)·h\(^{-1}\) infusion). We chose the loading doses to reach equilibrated blood levels during the infusion.\(^\text{13}\) Mood, physiologic status, and psychomotor performance were assessed before, during, and at periodic intervals after the 20-min infusion period in each of the four sessions of the experiment.

**Experimental Sessions**

The experiment took place in a laboratory located in the Department of Anesthesia and Critical Care. Each session was approximately 2 h in duration and took place in the morning. Subjects had been instructed not to eat food for 6 h and not to drink any liquids (including water) for 4 h before sessions. A negative urine test for pregnancy was required for female subjects before each session could start. Noninvasive measurements of the following physiologic variables were initiated at the beginning of the session: heart rate, ECG, peripheral oxygen saturation, and blood pressure. Subjects were in a semirecumbent position on a bed during the entire testing period. After noninvasive physiologic monitoring had begun, a catheter was inserted into one of the subject's forearm veins, and an infusion of normal saline was started. Subjects were told that during the baseline testing period, an inactive agent (i.e., placebo) would be infused into their forearm vein. At this time, subjects completed several mood forms and psychomotor tests.

Upon completion of baseline testing, the intravenous loading dose was administered over a 10-s interval. Immediately following the loading dose, the infusion was started using a calibrated infusion pump (model AS20GH, Baxter Healthcare Corp., Hookset, NH) and continued for 20 min. Loading doses and the infusion were administered through a stopcock at the catheter site. At this point, subjects were instructed that the substance being administered into their forearm vein may or may not contain drug. The drug (Intralipid or propofol) was drawn up by one anesthesiologist; a second anesthesiologist blind to the drug administered the drawn-up emulsion (Intralipid or propofol) in order to preserve the double-blind nature of the study. At periodic intervals during and after the infusion period (see below), mood, psychomotor performance, and physiologic status of the subject were assessed. The technicians obtaining these assessments were also blind to the study drug being injected or infused. Drinking water was permitted after the infusion period was terminated. When no tests were scheduled, subjects were free to engage in sedentary recreational activities such as reading, listening to the radio or to cassette tapes, and watching television, but studying was not permitted.

**Subjective Effects Measures**

1. The Addiction Research Center Inventory is a true–false questionnaire designed to differentiate among classes of psychoactive drugs.\(^\text{14}\) A computerized short form of the Addiction Research Center Inventory was used.\(^\text{15}\) This included 49 items and yielded scores for five different scales: Pentobarbital-Chlorpromazine-Alcohol Group (a measure of sedation), Benzedrine Group (a measure of intellectual efficiency and energy), Amphetamine (a measure specific for dose-related effects of amphetamine), Lysergic Acid (a measure of somatic and dysphoric effects), and Morphine-Benzedrine Group (a measure of euphoria). The Addiction Research Center Inventory was administered before the injection, approximately 10 min after the infusion had started, and approximately 15 and 60 min after the infusion period had ended.

2. A Drug Adjective Checklist commonly used to assess psychoactive drug effects was included in the tests of subjective effects.\(^\text{16}\) The checklist consists of 17 items that the subject rated on a 5-point scale from 0 ("not at all") to 4 ("extremely"). The items in the adjective list were as follows: "flushing," "skin itchy," "sweating," "turning of stomach," "nodding," "relaxed," "coasting or spaced out," "talkative," "heavy or sluggish feeling," "dry mouth," "drive," "sleepy," "carefree," "drunken," "good mood," "tingling," and "energetic." The Drug Adjective Checklist was filled out before the injection, approximately 10 min after the infusion had started, and
approximately 15 and 60 min after the infusion period had ended.

3. The Visual Analogue Scale (VAS) consisted of 11 100-mm lines, labeled with the following adjectives: "stimulated," "happy," "sick," "high," "anxious," "sedated," "down," "hungry," "nauseous," "dizzy," and "lightheaded." Subjects were instructed to place a mark on each line indicating how they felt at the moment, ranging from "not at all" to "extremely." The VAS was filled out before the injection, approximately 5, 10, and 20 min after the infusion had started, and approximately 5, 15, 30, and 60 min after the infusion period had ended.

4. The Drug Effects/Liking questionnaire assessed the extent to which subjects currently felt a drug effect on a scale of 1 to 5 (1 = "I feel no effect from it at all"; 5 = "I feel a very strong effect") and assessed the extent to which subjects liked the drug effect on a 100-mm line (0 = disliked a lot; 50 = neutral; 100 = liked a lot). The Drug Effects/Liking questionnaire was filled out before the injection, approximately 5, 10, and 20 min after the infusion had started, and approximately 5, 15, 30, and 60 min after the infusion period had ended.

**Memory**

Ten minutes after the infusion had started (when propofol was presumably at steady-state levels in the blood), subjects were shown 20 words from preselected norms sequentially on a computer screen; each word was presented for 2 s with an interword interval of 1 s. To assess immediate recall, for 2 min after the last word was presented, subjects were instructed to write down as many words as they could remember from the list, in any order. To assess delayed recall, 60 min after the infusion period had ended, subjects were instructed to write down as many words as they could remember from the original list. Different lists of words, equivalent in their level of usage, were used across sessions.

**Psychomotor Performance**

Subjects completed two psychomotor tests: eye-hand coordination\(^{18}\) and the Digit Symbol Substitution Test.\(^{19}\) To measure eye-hand coordination skills, the subject traced a randomly moving target on the computer screen with a small cross for 2 min. The cross was controlled by the computer mouse, operated by the dominant hand. The dependent measures derived from this test were seconds outside of a 1-cm circle surrounding the randomly-moving circle, mean distance (expressed in pixels) from the center of the randomly moving circle, and number of times the cross exceeded the 1-cm circle (defined as "coordination mistakes"). The eye-hand coordination and Digit Symbol Substitution Test tests were completed before the injection, 10 min after the infusion had started, and 15 and 60 min after the infusion period had ended.

**Physiologic Measures**

Pulse, systolic and diastolic blood pressures, and hemoglobin oxygen saturation were measured noninvasively (model 54, Hewlett-Packard, Waltham, MA). These measures were assessed before the injection, 5, 10 and 20 min after the infusion had started, and 5, 15, 30, and 60 min after the infusion period had ended.

**Data Analysis**

Repeated-measures analysis of variance (ANOVA) was used for statistical treatment of the data. Factors typically used in the ANOVAs were dose (four levels) and time (four to eight levels). F values were considered significant for P < 0.05 with adjustments of within-factors degrees.
of freedom (Huynh-Feldt) to protect against violations of symmetry. Values reported in this paper are limited to dose or dose × time interactions; for brevity, main effects of time are not reported. Also for brevity, when a dose × time interaction is obtained, main effects of dose are not reported. When appropriate (when significant or near-significant \( P \leq 0.10 \) dose × time interactions were obtained), planned comparisons were made, comparing Intralipid responses to drug responses at a given time point in a session.

Results

Subjective Effects

Addiction Research Center Inventory

Significant or near-significant dose or dose × time effects were obtained on the Pentobarbital-Chlorpromazine-Alcohol Group (dose × time effect: \( F(9,81) = 3.1, P < 0.01 \), and Benzedrine Group (dose effect: \( F(3,27) = 3.7, P = 0.06 \)) scales (fig. 1). Pentobarbital-Chlorpromazine-Alcohol Group scores increased during the propofol infusion, and Benzedrine Group scores decreased; the change in scores and duration of effect were generally dose-related. Intralipid had no effect on scores from the Addiction Research Center Inventory scales.

Visual Analogue Scales

On the VAS, significant dose × time effects were obtained on the “high” (\( F(21,189) = 4.5, P < 0.001 \)) “sedated” (\( F(21,189) = 2.4, P < 0.05 \)) “dizzy” (\( F(21,189) = 4.1, P < 0.005 \)) and “lightheaded” (\( F(21,189) = 4.3, P < 0.005 \)) scales (fig. 2). These ratings all increased when first measured after propofol administration and remained at significantly elevated levels for as long as 15–30 min after the infusion had terminated. Magnitude of drug effects, i.e., peak and duration of effects, were generally dose-related. Intralipid had no effect on ratings from the VAS.

Drug Adjective Checklist

Ratings on 3 of the 17 adjectives increased significantly during the propofol infusion: “heavy or sluggish feeling” (dose × time: \( F(9,63) = 2.3, P < 0.05 \)) “coasting or spaced out” (dose × time: \( F(9,63) = 4.6, P < 0.01 \)), and “drunk” (dose × time: \( F(9,63) = 3.2, P < 0.05 \)). In general, ratings were dose-related, tended to peak during the infusion period, and had returned to baseline levels by 1-h post-infusion. Intralipid had no effect on ratings from the Drug Adjective Checklist.
Drug Effects / Liking Questionnaire

There was a clear dose-related increase in subjects' ratings of to what degree they felt a drug effect (fig. 3, top) (dose x time: F(21,189) = 6.3, P < 0.001). Drug liking, when averaged across subjects, was not significantly affected by propofol (fig. 3, bottom). However, inspection of each subject’s response to propofol revealed some variability on this measure (fig. 4). Figure 4 shows liking change scores—10-min infusion rating minus baseline (predrug) rating—for each of the four dosing conditions. The degree of liking or disliking was increased in a dose-related fashion. That is, subjects tended neither to like nor to dislike the effects of Intralipid, but in the high-dose propofol condition, five of the ten subjects liked the drug effects and three of the ten disliked the drug effects.

Memory

Immediate recall was not affected by propofol dose. An average of 8.7 words was remembered from the word list (collapsed across drug conditions). However, a significant main effect of dose was obtained when the words were recalled at the end of the postinfusion period (F(3,27) = 7.5, P < 0.001); in other words, there was impairment in delayed recall of events that took place during the infusion period. Planned comparisons revealed that significantly fewer words were recalled in the high-dose condition (2.4 words) as opposed to the other three conditions (6.8, 6.0, and 6.1 words in the placebo, low-dose, and moderate-dose conditions, respectively).

Psychomotor Performance

Significant or near-significant dose x time effects were obtained on all three dependent measures derived from the eye-hand coordination test: seconds outside of the circle (F(9,81) = 3.4, P = 0.06), mean distance from the center of the circle (F(9,81) = 2.7, P < 0.05), and number of mistakes (F(9,81) = 2.5, P = 0.06). The high dose of propofol impaired eye-hand coordination (fig. 5), but the impairment was limited to the infusion period. Likewise, performance on the Digit Symbol Substitution Test was adversely affected by the high-dose of propofol (F(9,81) = 5.0, P < 0.001), but, again, the effects had dissipated by the 15-min postinfusion time point (fig. 5).

Physiologic Measures

Systolic and diastolic blood pressure, pulse, and hemoglobin oxygen saturation were not altered by the propofol regimen.

Discussion

This study shows relatively benign subjective effects from sedative doses of propofol in healthy volunteers, consistent with recent clinical studies4-6,8-10 that have used less rigorous and fewer mood inventories. Our study suggests that propofol does not induce dysphoria, in that the standardized Addiction Research Center Inventory did
not reflect increased Lysergic Acid scores (a measure that reflects dysphoria and somatic effects) during or after the propofol injection/infusion regimen. Furthermore, subjects reported no ill effects on either the VAS or the Drug Adjective Checklist. Effects that were reported, such as increased sedation and lightheadness, dissipated within 30 min postinfusion. Psychomotor performance was impaired during the high-dose propofol infusion, but this is not important from a clinical standpoint; what is important is that the psychomotor impairment had dissipated within 15 min after the infusion was terminated. Rapid recovery has been documented in clinical studies as well.1,2,5,9 Delayed recall was substantially impaired in the high-dose propofol condition. All of the aforementioned attributes of propofol, assessed in a controlled laboratory setting in which a placebo control was included, provides strong and convincing evidence that propofol is a suitable drug for ambulatory surgery and medical procedures in which sedation is needed.

Larger doses of propofol could have been used in order to extend the generality of the results obtained from this study to clinical situations in which infusion doses are as great as 5 mg·kg⁻¹·h⁻¹. However, because such doses of propofol are associated with more profound sedation and loss of consciousness, it is probable that completion of our battery of tests would not have been possible. Future studies can be conducted using larger loading and infusion doses, and measuring subjective effects after the infusion period is terminated in order to determine if such doses induce the same qualitative changes in mood as were noticed in the present study.

There was a side effect of propofol that some of our subjects reported, either by written comments on the mood forms or during the debriefing session: pain during propofol injection and/or infusion, which has been a common complaint in clinical studies.20-25 In the placebo condition, no subjects reported burning or stinging in the arm during the injection and/or infusion, but two, four and five subjects reported this adverse effect in the low-, moderate-, and high-dose conditions, respectively. A binomial test revealed that there was a significantly greater number of subjects reporting burning or stinging in each of the drug conditions than in the placebo condition.

In summary, the results of our laboratory study corroborate and extend those findings already cited in the clinical literature: propofol induces a change in mood that is well-suited for conscious sedation procedures. Furthermore, because the impairment produced by propofol is short-lived, it may be a more suitable drug for conscious sedation procedures than drugs that currently are being used, such as the benzodiazepines. Indeed, recent studies comparing recovery after propofol sedation to that of benzodiazepine sedation appear to substantiate this claim.1,2,4-6,9,10
Fig. 5. Time course of the effects of placebo (small circle, thin line), low-dose propofol (square), moderate-dose propofol (triangle), and high-dose propofol (large circle, thick line) on eye-hand coordination (mean distance from the center of a randomly moving circle [MDFC]) (left) and performance on the Digit Symbol Substitution Test (DSST) (bottom). See figure 1 for further details.

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References