Clinical Recovery and Psychomotor Function after Brief Anesthesia with Propofol or Thiopental

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Propofol, the new intravenous anesthetic agent, is generally used in outpatient anesthesia with expectations of fast recovery. We assessed recovery from anesthesia in a double-blind, crossover, controlled manner in 12 healthy volunteers using clinical tests during the first hour and several psychomotor tests 0.5, 1, 3, 5, and 7 h after brief anesthesia with propofol (2.5 mg/kg and 1.0 mg/kg 3 min later) or thiopental (5.0 mg/kg and 2.0 mg/kg 3 min later). Subjects were able to respond to command, sit, and stand steadily significantly faster (P < 0.05) after propofol (time until standing steadily 33 ± 7 min; mean ± SD) when compared to thiopental anesthesia (time until standing steadily 62 ± 29 min; mean ± SD). Psychomotor performance remained significantly worse (P < 0.05 to P < 0.001) compared to control for 1 h after propofol and for 5 h after thiopental anesthesia. We conclude that the rapid and complete recovery makes propofol a suitable anesthetic for patients undergoing brief ambulatory surgery. (Key words: Anesthesia; outpatient recovery. Anaesthetics, intravenous: propofol; thiopental. Monitoring: psychomotor function.)

PROPAPOL is commonly administered to patients undergoing ambulatory surgery because of the rapid and uncomplicated recovery after its administration.1-4 The purpose of this study was to examine the hypothesis that recovery of psychomotor function, using sensitive and novel computerized equipment, is faster after propofol anesthesia when compared to thiopental anesthesia. In this study, no other drugs were given or surgical interventions performed, and the differences in recovery can be directly attributed to the effects of the study drugs.

Materials and Methods

Subjects and Experimental Design

This study was approved by The University of Chicago Clinical Investigation Committee, and written informed consent was obtained from each participant. Twelve healthy male volunteers (22 ± 4.2 yr, 72 ± 12 kg, 176 ± 8.8 cm; mean ± SD) participated in the study. Subjects were excluded if they received regular medication or had a history of mental or neurologic illness. All were social drinkers who used alcohol moderately one to six times per month. Participants were instructed to abstain from any medication and drugs (including marijuana) during the entire trial and from alcohol for 3 days before tests. Subjects fasted from midnight the night before testing until the time of testing; all received a light standardized meal 5.5 h after drug injection. Subjects were told not to drive a car, operate heavy machinery, or work until the day after the study and were required to have an escort accompany them home after sessions.

The study was a double-blind, randomized, placebo-controlled, crossover trial. We studied recovery and residual effects of propofol (Diprivan®, Stuart Pharmaceuticals, Wilmington, DE), thiopental (Pentothal®, Abbott, Abbott Park, IL), and placebo (Intralipid®, Kabi, Sweden) on psychomotor skills in three successive test sessions, allowing a 1-week washout interval between treatments. Before entering the study, all subjects practiced using the psychomotor test apparatuses on several separate occasions to attain a stable level of performance. The purpose of this pretraining was to minimize the possibility of learning of tasks during the actual testing.

Each test morning the subjects received intravenously either placebo, propofol (2.5 mg/kg and 1.0 mg/kg 3 min later), or thiopental (5.0 mg/kg and 2.0 mg/kg 3 min later). Awakening and clinical recovery were assessed by an individual unaware of which drug had been administered. Psychomotor function was evaluated 1 h before injection (baseline) and 1, 3, 5, and 7 h after the drug injection. The digit symbol substitution test was also performed 30 min after drug administration. Individual tests were always repeated in the same order, and the entire test battery took 30 min to complete.

Assessment of Awakening and Clinical Recovery

The time from the beginning of the first injection until the subject responded to command was recorded. Sitting up without help for 10 s was attempted every 5 min after the subject regained consciousness. The ability to stand steadily was assessed by the Romberg test, which was attempted
every 5 min starting 10 min after the subject was able to maintain a sitting position without help.

**Computer-assisted Psychomotor Tests**

The psychomotor test battery that was used was developed in our laboratory and has been previously described.\(^5\) Body sway was measured using a strain-gauge platform (Kistler Instrumente AG, Winterthur, Switzerland) connected to a computer. Subjects stood on the platform for 90 s with eyes closed. The movement of the center point of gravity of their body in the anterior–posterior and lateral directions was measured. To establish multiple reaction time, subjects pressed specific keys of the keyboard after the occurrence of either a particular visual stimulus (the appearance of specific letters on specific sides of the computer screen), auditory stimulus (the presence or absence of a tone), or a combination of both visual and auditory stimuli. On each test occasion, a total of 40 stimuli were presented. Divided-attention mistakes and correct responses were measured by presenting the subjects with increasingly higher numbers from 0 to 9, delivered simultaneously at the rate of one number every 1–1.5 s, in each of the four quadrants of the computer screen. When the number 9 appeared, subjects had to note the quadrant and press the corresponding letter on the computer keyboard. Coordination accuracy and mistakes were measured by having the subjects use a "mouse" to track a randomly moving target on the computer screen for 120 s. "Accuracy" was the average distance (measured in pixels) between the center of the target and the location of the mouse. Coordination mistakes were the number of times the center of the target exceeded a fixed distance from the location of the mouse.

**Other Psychomotor Tests**

The digit symbol substitution test measured changes in sensory processing performance and the subjects' ability to concentrate.\(^6\) Subjects had to pair digits to symbols correctly for 2 min. The Maddox wing device was used to measure the balance of extraocular muscles. The amount of exophoria (deviation of the visual axis of one eye away from that of the other) was expressed as the power of the prism (in diopters) used to prevent deviation.\(^7\) Attention and coordination were evaluated by an action judgment tester (Lafayette Instrument Co., Lafayette, IN). In this test, the subject used a steering wheel to keep two pointers properly positioned on a moving track. Lateral nystagmus was measured by recording the angle between the two lateral directions of gaze at which the end-position nystagmus appeared.\(^8\) The integrative activity of the central nervous system was determined with a critical flicker fusion test\(^9\) (Lafayette), which measured the subject's ability to discriminate the fusion of flickering light. Finally, using 100-mm visual analog scales, participants subjectively estimated impairment of their overall performance and difficulties in concentration. Estimates could range from "not at all" to "extremely."

**Statistical Analyses**

Parameters of awakening and clinical recovery were compared between propofol and thiopental with Student's paired \(t\) test. For each psychomotor test, two-way analysis of variance (ANOVA) first was used to determine whether differences between various treatments in general were significant (interaction of time and treatment). Then, separately at each test time, one-way ANOVA (for repeated measures) was applied to detect differences between the three treatments. If results were significant, as a post hoc test, the Fisher protected least significant difference test was used to assess whether differences between individual pairs of treatments were significant. \(P < 0.05\) was considered significant.

**Results**

**Awakening and Clinical Recovery**

Subjects responded to command and were able to sit up and stand steadily significantly faster \((P < 0.05)\) after propofol than after thiopental anesthesia (table 1).

**Psychomotor Recovery**

For all psychomotor tests, two-way ANOVA (time \(\times\) treatment effects) showed that overall differences between the treatments were significant \((P < 0.05–0.001)\). No significant differences between test days regarding baseline performance were present. At 1, 3, and 5 h after injections, significant differences \((P < 0.05\) to 0.001) were evident between various treatments. In case of significance, statistical pairwise comparison between all treatment were made, and the results are shown in figures 1–3.

**Effects of Thiopental**

The greatest amount of impairment of performance was always apparent after thiopental. Thiopental significantly \((P < 0.05–0.001)\) impaired reactive skills (fig. 1),

<table>
<thead>
<tr>
<th>Table 1. Times (minutes) to Respond to Command, Sit, and Stand after Brief Anesthesia with Propofol (2.5 + 1.0 mg/kg) or Thiopental (5.0 + 2.0 mg/kg)</th>
</tr>
</thead>
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<tr>
<td>Parameter</td>
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<tr>
<td>Response to command</td>
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<tr>
<td>Able to sit</td>
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<td>Able to stand</td>
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Values are mean ± SD.

* \(P < 0.05\) versus thiopental.
attention (fig. 1), and flicker fusion (fig. 3) for as long as
1 h; body sway (fig. 1), coordinative skills (fig. 1), Maddox
wing (fig. 2) and action judgment (fig. 2) for as long as 3
h; and digit symbol substitution (fig. 2) and nystagmus
(fig. 2) for as long as 5 h after anesthesia when compared
to placebo control. Figure 3 shows that subjects subjec-
tively felt their performance and concentration to be im-
paired only for as long as 1 h after thiopental anesthesia.
Seven hours after injection no impairment compared to
baseline or placebo control was seen.

Effects of Propofol

Impairment in the digit symbol substitution test (fig.
2) was significant ($P < 0.001$) as long as 30 min after
injection. Coordinative skills (fig. 1) were impaired for as
long as 1 h after propofol anesthesia. No other psycho-
motor test or subjective assessment showed evidence of
impairment for more than 1 h after propofol anesthesia.

Discussion

Recovery in patients after or due to specific drugs is
difficult to study because of the effects of other drugs as
well as pain. Because propofol has been recommended
for anesthesia for ambulatory surgery, we studied recov-
ery and psychomotor skills after propofol compared to
thiopental anesthesia in volunteers to see what effects
these two drugs alone have on recovery. Furthermore,
recovery after propofol anesthesia has been evaluated previously with methods unlikely to detect subtle psychomotor effects.\(^4\,7\,10\)

Brief anesthesia induced subjective residual effects for as long as 1 h after thiopental anesthesia and impaired objective performance for 1 h and 5 h after propofol and thiopental, respectively. With the doses tested, the most profound impairment in psychomotor function was seen at the 1-h test after injection of thiopental. Recovery was distinctly faster after propofol than after thiopental. Statistically significant impairment after thiopental was still detectable at 5 h after anesthesia, whereas propofol-induced impairment was not detectable at 3 h or later after anesthesia. The ratio of equipotent doses of propofol and thiopental used was based on the literature, and these doses are equally adequate to provide anesthesia, such as that required for brief gynecologic procedures lasting as long as 10 min.\(^1\,4\,11\)

In accordance with results from our laboratory measuring the psychomotor effects of alcohol,\(^5\) midazolam and alcohol,\(^12\) and midazolam/fentanyl alcohol,\(^13\) the new series of computerized tests also proved sensitive to the effects of propofol and thiopental. Baseline values remained constant throughout the experiment, and performance measured after placebo control also remained constant. Therefore, pretraining to avoid learning during
FIG. 3. Mean flicker fusion threshold and participants' subjective estimate of worsened overall performance and difficulty to concentrate before and after intravenous injection of propofol 2.5 + 1.0 mg/kg (diamonds), thiopental 5.0 + 2.0 mg/kg (filled squares), and control (open squares) in 12 healthy volunteers. **P < 0.01 and ***P < 0.001 versus control. *P < 0.05; **P < 0.01; and ***P < 0.001 versus propofol.

actual testing was adequate, and the deviations found after drug injection were real, treatment-related effects. Sampson et al.14 and Johnston et al.2 compared recovery after brief propofol anesthesia with recovery after thiopental anesthesia in patients undergoing minor gynecologic surgery. In both studies, awakening and orientation occurred faster after propofol, but there was no major difference in time to discharge from the hospital. In practice, discharge of patients from the hospital after ambulatory surgery is based on clinical criteria, which include walking unaided.15,16 After propofol anesthesia, patients have met criteria for discharge faster than after, for example, methohexitol or isoflurane anesthesia.10,17,18 Our results with volunteers indicate that if discharge is attempted as early as 1 h after brief anesthesia, impairment of psychomotor skills will be present, even though patients will meet clinical criteria for discharge. Furthermore, at the time of discharge, during transportation, and at home, the patient's cognitive performance is likely to be superior after propofol anesthesia when compared to that after thiopental anesthesia.

Immediate recovery, e.g., awakening after a single injection of an intravenous anesthetic, depends largely on the distribution half-life of the agent administered. Awakening and clinical recovery occurs when the central nervous system concentration decreases to less than threshold level because of the redistribution of the drug to inert tissues, largely muscle.19 This could be one ex-
plation why recovery after propofol is faster when compared to that after thiopental. Residual psychomotor effects, in contrast, are more dependent on elimination. Intravenously administered propofol has been reported to have a distribution half-life of close to 5 min and a half-life of elimination of approximately 2 h;\textsuperscript{20} in contrast, thiopental has been reported to have an initial distribution half-life of 86 min and an elimination half-life of 12 h.\textsuperscript{21} However, Shafer and Stanski recently reported that distribution clearances are similar for both propofol and thiopental and that the elimination half-lives of propofol and thiopental are 6.3 and 12.7 h, respectively. They concede that due to very rapid hepatic and possibly extrapulmonary clearance of propofol relative to thiopental, propofol plasma concentration declines faster than the thiopental concentration, resulting in faster recovery with propofol. When studies are designed to measure recovery from the newer inhaled anesthetics, e.g., sevoflurane or desflurane, propofol is a preferable induction agent for such studies because thiopental has long-lasting residual effects that may modify recovery from the inhaled agents themselves.

We have previously studied recovery, residual effects, and driving skills after several premedications, intravenous anesthetics and inhaled anesthetics in healthy volunteers,\textsuperscript{22–25} and our present results with thiopental agree with our previous studies, which indicated that driving skills and psychomotor skills\textsuperscript{24,25} are impaired for as long as at least 8 h after brief thiopental and methohexitol anesthesia. The magnitude and duration of impairment of psychomotor performance after propofol anesthesia is distinctly less than after drugs such as thiopental, methohexitol, alphadione, diazepam, halothane, or enflurane. The fast and complete recovery of psychomotor performance after propofol indicates that it is well suited for anesthesia for brief ambulatory surgery.

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References

