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# Using Alcohol as a Standard to Assess the Degree of Impairment Induced by Sedative and Analgesic Drugs Used in Ambulatory Surgery

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***Background:*** **There is a need for a standard by which to compare the degree of subjective and behavioral impairment caused by anesthetic drugs, because anesthesiologists may not be able to gauge how extreme or important a statistically significant change in psychomotor functioning is. This study examined the psychomotor and subjective effects of alcohol at blood concentrations equal or greater than 0.10% as a standard with which to compare those effects caused by sedative and analgesic agents commonly used in ambulatory surgery.**

***Methods:*** **Twelve healthy human volunteers (11 men and 1 nonpregnant woman), with an average age of 28 yr (range 24–34 yr) and an average alcohol consumption of four drinks per week, were selected in this institutional review board-approved study. Each subject was exposed to five drug conditions (70 mg/70 kg propofol intravenously, 2 mg/70 kg midazolam intravenously, 50 μg/70 kg fentanyl intravenously, 0.8 g/kg alcohol orally, and placebo orally and intravenously) in a double-blind randomized fashion over five weekly sessions. Testing was done at baseline and at different intervals until 240 min after drug administration. Testing included psychomotor performance (Maddox Wing, eye-hand coordination, auditory reaction time test, and digit symbol substitution test), subjective effects (strength of drug effect scale, drug liking scale, and visual analog scale), and short-term memory. Psychomotor performance was used as an index of objective impairment, and mood was used as an index of subjective impairment.**

***Results:*** **After consumption of the alcoholic beverage, a blood alcohol level of 0.11 ± 0.003% (mean ± SE) was obtained at 15 min after injection. The study drugs not only produced statistically significant impairment (*i.e.*, impairment greater than that seen with placebo) but also, at one or more times after injection, produced impairment similar to that observed with alcohol at a blood alcohol concentration of 0.11%. Midazolam produced a similar degree of impairment to that of alcohol for a longer duration than did fentanyl and propofol.**

***Conclusions:*** **This study provides evidence that degree of impairment caused by sedative and analgesic drugs used in ambulatory surgery is similar to that obtained with a dose of alcohol that produces a blood alcohol concentration of 0.11%. We suggest that anesthesiologists can use alcohol as a standard by which to assess degree of impairment produced by drugs used for sedation/analgesia. (Key words: Alcohol. Analgesics, opioids: fentanyl. Anesthetics, intravenous: propofol. Recovery: memory; mood; psychomotor; subjective. Sedatives, benzodiazepines: midazolam.)**

DURING the past two decades, there has been a rapid growth in ambulatory surgery. More than 60% of all elective surgery, for example, is now performed on an outpatient basis.[1] Many studies have shown impairment in psychomotor and cognitive function after administration of different sedative and analgesic agents that are commonly used in anesthesia for ambulatory surgery, including benzodiazepines, such as midazolam; opioids, such as fentanyl; and the intravenous anesthetics, such as propofol.[2–5] Psychomotor tests used in these and other studies typically include such tests as simple and choice reaction time, divided attention, and/or eye-hand coordination. It is not clear sometimes, though, what the degree of impairment produced by these tests means. That is, if a drug, such as midazolam, 2 h after its administration produces impairment of reaction time amounting to an increase of 100 ms (relative to a drug-free baseline), what does this mean to the anesthesiologist engaged in day-case surgery?

One approach to addressing this issue is to follow the recommendations of the World Health Organization, which recommends that a psychoactive drug un-

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der investigation for behavioral toxicity be compared to alcohol.[6] Numerous studies have been done over the years on alcohol's impairing effects, and laws have been mandated that restrict people from operating a motor vehicle when their blood alcohol concentration exceeds a certain level (in most states in the United States, 0.08–0.10%).[7–10] Medical caregivers in our society may find it beneficial to use alcohol as a standard by which to compare impairment caused by other drugs.

A number of studies have used this approach of comparing a study drug with a large dose of alcohol.[11–14] In one study, for example, the degree of behavioral toxicity produced by two solvents, toluene and methyl ethyl ketone was examined, and alcohol at a dose producing a blood alcohol level of 0.08% (targeted) was used as a positive control.[11] Toluene at 100 ppm produced impairment, but it was less than that produced by alcohol. The other solvent had no effect on performance. Had not alcohol been included in this study, it would have been more difficult to interpret the degree of impairment found with toluene. By inclusion of one or more doses of alcohol (including doses of alcohol that are considered by law to produce impairment that contraindicates driving a motor vehicle), the results become more meaningful from a clinical standpoint. We believe that the same approach would provide a valuable service to anesthesiologists who are interested in the sedative and analgesic drugs they use and how impairment produced by these drugs compares to that of a drug with an "established reputation" of producing impairment. Therefore, in this preliminary study, we examined the effects of midazolam, fentanyl, and propofol on objective and subjective indexes of impairment and compared the degree of impairment at different times after injection to that seen with a dose of alcohol that produced blood alcohol concentrations of 0.11%.

## Materials and Methods

### *Subjects*

This study was approved by our local Institutional Review Board. Informed consent from each subject was obtained before initiating the study. Subjects were told that the drug(s) to be used were (1) commonly used in medical settings and (2) may come from one of five classes (*i.e.,* sedative/tranquilizer, opiate, general anesthetic at subanesthetic doses, alcohol, or placebo).

Twelve healthy volunteers (11 men and 1 woman; age range 24–34 yr, mean age 28 yr; weight range 60–101 kg, mean weight 80.3 kg) participated in the study. Their history of recreational drug and alcohol use was light-to-moderate: the subjects consumed an average of four drinks per week (range 1–10 drinks/week). Three subjects had a history of smoking marijuana at least once a month, and three subjects smoked fewer than three tobacco cigarettes daily. They were recruited from the local university community *via* newspaper and bulletin board advertisements. Before the first session, subjects were scheduled for a screening interview, at which point they completed the symptoms checklist (SCL-90; a questionnaire designed to assess psychiatric symptomatology)[15] and a locally developed health questionnaire (to determine their psychiatric and mental status). Candidates with any history of significant psychiatric disorders or substance use disorder were excluded.[16] An anesthesiologist performed a medical history and physical examination, and volunteers with any history of cardiac, pulmonary, neurologic, 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 hepatic function (as assessed by serum glutamate oxaloacetate transaminase, bilirubin, alkaline phosphatase, total protein tests) could be assured.

Subjects were instructed not to eat food or drink any nonclear liquids for 4 h, not to drink clear liquids for 2 h, and not to use any drugs (including alcohol, but excluding normal amounts of caffeine and nicotine) 24 h before sessions. Subjects were instructed 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, pseudodouble-blind (see Experimental Sessions), crossover trial was conducted. Subjects were exposed to each of five conditions in five sessions spaced approximately 1 week apart: placebo (placebo drink followed by saline or Intralipid injection intravenously), propofol (70 mg/70 kg), midazolam (2 mg/70 kg), fentanyl (50 μg/70 kg), and alcohol (56 g/70 kg alcoholic drink followed by saline or Intralipid injection). The dose of alcohol was served in 450 ml (per 70 kg) of a lime-flavored diet tonic water solution, was equivalent to four to five drinks, and has been shown to produce a blood alcohol concentration in a fasting

individual of close to 0.10%. Doses of the sedative/analgesic drugs were to represent the doses that might be given in ambulatory surgery—in retrospect, we realize we chose doses of propofol and fentanyl that were rather low (*i.e.*, the fentanyl and propofol doses chosen fell on the low end of the conscious sedation dosage continuum). Mood, psychomotor performance, and physiologic status were assessed before and at intervals after the injection(s) in each of the five 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 4.5 h in duration, and most sessions were conducted from 10:00 AM to 3:30 PM. At arrival for each session, subjects were given a breath alcohol test with a breath alcohol analyzer (ALCO-SENSOR III, Intoximeters, St. Louis, MO) to rule out the presence of alcohol in their system. Subjects then completed several subjective effect forms and psychomotor tests, and monitoring of respiratory rate, noninvasive arterial hemoglobin oxygen saturation, heart rate, and blood pressure commenced. Subjects lay on a bed and fentanyl, midazolam, propofol, or saline or Intralipid was injected by an anesthesiologist unaware of the drug being injected.

In the alcohol and placebo conditions, before injection, subjects consumed the liquid over 20 min. In the alcohol condition, subjects first drank the alcoholic beverage, and then either physiologic saline or Intralipid was injected. In the placebo condition, subjects were given an alcohol-free beverage followed by injection of physiologic saline or Intralipid. Therefore, in all five conditions, subjects received an intravenous injection but, in only two of the conditions, consumed a drink before the injection. Because of the need for subjects to be NPO in three of the other five conditions, we did not have subjects consume a placebo beverage before the midazolam, fentanyl, and propofol injection (a drink before injection in all five conditions would have been a true "double-blind" procedure).

*Physiologic Measures*

Four physiologic measures were assessed: heart rate, blood pressure, respiratory rate, and noninvasive arterial oxygen saturation. During the peri-injection period, systolic and diastolic blood pressure, heart rate, respiration rate, and arterial hemoglobin oxygen saturation were assessed at specific times. Values were within normal ranges and were not subjected to statistical analysis. Subjects remained in a recumbent or semirecumbent position for at least 3 h after the injection, after which they could get up if they so desired. At intervals after the injection (see below), mood, psychomotor performance, and physiologic status of the subject were assessed. On the day of beverage consumption, blood alcohol concentrations were measured by a breath alcohol analyzer at baseline and 15, 60, 120, 180, and 240 min after the injection. 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.

*Psychomotor Performance*

Subjects completed four psychomotor/cognitive tests: Maddox Wing (MW), auditory reaction time (ART), eye-hand coordination, and the digit symbol substitution test (DSST). The MW test measures relative position of the eyes in prism diopters.[17] In the ART test, subjects were instructed to press the space bar on a computer keyboard when they first detected an auditory stimulus; mean auditory reaction time was determined after ten trials.[18] To measure eye-hand coordination skills, the subject tracked a randomly moving target on the computer screen, with a small cross, for 1 min. The cross was controlled by a computer "mouse" operated by the dominant hand.[18] The number of seconds that the cross deviated from the circle by more than 1 cm (seconds outside the circle) was measured. In the DSST, subjects replaced a number with a corresponding symbol; the paper-and-pencil test was timed for 1 min, and the dependent measure was the number of symbols correctly matched by the subject.[19] These psychomotor tests were completed before injection and 15, 60, 120, 180, and 240 min after injection. The DSST also was completed 5, 30, 45, 90, 105, 150, and 210 min after injection. The above tests have been found to be sensitive to the effects of a number of psychoactive drugs including opioids,[4] alcohol,[18] barbiturates,[5] and benzodiazepines.[2] Although learning or practice effects on the psychomotor tests may have occurred during this study, the randomized design should have controlled for this potentially confounding variable.

*Memory*

Immediate free recall was tested by presenting 15 words from preselected norms for 2 s each with a

between-word interval of 1 s.[20] Immediately after the last word was presented, the subjects were asked to write in any order as many of the words as they could remember. Individual separate word lists were presented at baseline and 15, 120, and 240 min after injection.

*Subjective Effects Measures*

1. The visual analog scale (VAS) consisted of 20 100-mm lines, each labelled with the adjectives, "stimulated," "elated," "tingling," "high," "anxious," "sedated," "down," "hungry," "nauseous," "dizzy," "drunk," "in control of thoughts," "in control of body," "coasting or spaced out," "having pleasant thoughts," "having unpleasant thoughts," "having pleasant body sensations," "having unpleasant body sensations," "confused," and "carefree." 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 completed before injection and 5, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 min after injection.

2. 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"; 2 = "I think I feel a mild effect, but I'm not sure"; 3 = "I feel an effect, but it is not real strong"; 4 = "I feel a strong effect"; and 5 = "I feel a very strong effect") and assessed the extent to which subjects currently liked the drug effect on a 100-mm line (0 = dislike a lot; 50 = neutral; 100 = like a lot). The drug effects/liking questionnaire was completed before injection and 5, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 min after injection.

*Data Analysis*

Repeated measures analysis of variance was used for statistical treatment of the data. Factors were drug (alcohol, propofol, fentanyl, midazolam, and placebo) and time. 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 will be limited to drug or drug × time interactions; main effects of time will not be reported. When significant ($P < 0.05$) drug or drug × time interactions were obtained, Tukey's *post hoc* tests were done, comparing saline responses *versus* drug responses at a given time in a session. As our means of interpreting the degree of impairment produced by the study drugs, we chose to compare different drug responses to that observed 15 min after the consumption of alcohol, when blood alcohol concentrations were at ≥0.10%. Comparisons were done with Tukey's *post hoc* tests.

## Results

*Blood Alcohol Concentration*

Fifteen minutes after consumption of the alcohol drink, blood alcohol concentration (mean ± SE) was 0.11 ± 0.03%. Blood alcohol concentrations at 60, 120, 180, and 240 min after the drink were 0.09 ± 0.02%, 0.07 ± 0.02%, 0.05 ± 0.02%, and 0.03 ± 0.02%, respectively.

*Psychomotor Performance*

Table 1 shows the duration of statistically significant impairment of the three sedative drugs, *i.e.,* impairment significantly greater than placebo. When compared to placebo, midazolam and propofol produced statistically significant impairment on the DSST for 45 and 15 min, respectively, and fentanyl did not produce any significant impairment of this test (fig. 1, top). No statistically significant effects were seen with fentanyl on the MW, eye-hand coordination, and ART tests. Midazolam also produced no significant effects on the MW and ART tests but produced statistically significant impairment (lasting 15 min after injection) of eye-hand coordination. Propofol produced no significant impairment on the MW and eye-hand coordination tests but produced statistically significant impairment (lasting 15 min after injection) on the ART test.

**Table 1. Duration (min) of Statistically Significant Impairment ($t_{ss}$) (Impairment Greater Than That Seen with Placebo) and Impairment ($t_{alc}$) Similar to That Seen with Alcohol at a Blood Alcohol Concentration of 0.11%, of the Various Psychomotor Tests and the Short-Term Memory Test Caused by Fentanyl, Midazolam, and Propofol**

| | Fentanyl | | Midazolam | | Propofol | |
|---|---|---|---|---|---|---|
| | $t_{ss}$ | $t_{alc}$ | $t_{ss}$ | $t_{alc}$ | $t_{ss}$ | $t_{alc}$ |
| DSST | NS | NS | 45 | 45 | 15 | 15 |
| Eye hand (SOC) | NS | NS | 15 | 15 | NS | NS |
| Maddox wing | NS | NS | NS | NS | NS | NS |
| ART | NS | NS | NS | NS | 15 | 15 |
| Short-term memory | NS | NS | 15 | 15 | NS | NS |

NS = no significant effect; DSST = digit symbol substitution test; SOC = seconds outside circle; ART = auditory reaction time.

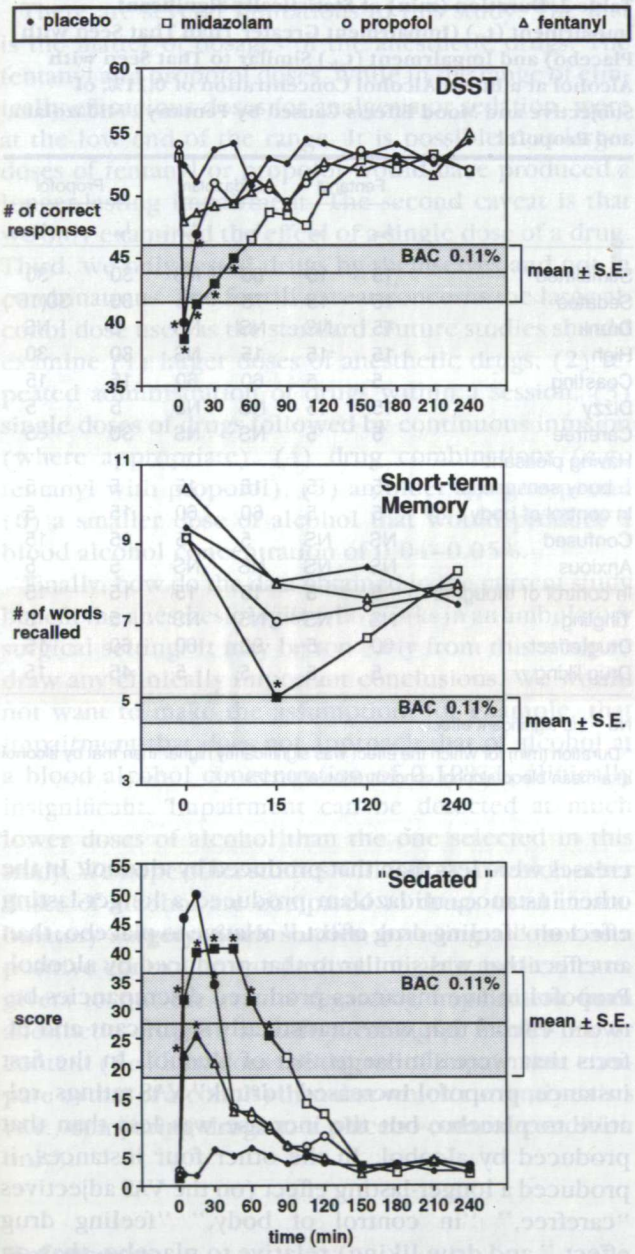


**Fig. 1. Effects of 2 mg/70 kg midazolam (square), 70 mg/70 kg propofol (circle), and 50 μg/70 kg fentanyl (triangle) on DSST performance (*top*), short-term memory (*middle*), and VAS "sedated" ratings (*bottom*) relative to placebo (diamond) and 56 g/70 kg alcohol that produced a mean blood alcohol concentration of 0.11% (*i.e.*, 15 min after injection). The alcohol effects are denoted by the shaded area in each of the graphs, with the mean being the center line and the outermost lines representing ±1 SEM. Closed symbols represent statistically significant differences from placebo at a given time. Asterisks represent drug effects that are both statistically significant from placebo and do not differ significantly from the alcohol effects that were associated with a blood alcohol concentration (BAC) of 0.11%.**

Table 1 also shows the duration of impairment of the three drugs relative to impairment produced by a dose of alcohol that produced a blood alcohol concentration of 0.11%. When compared to the impairment of the DSST caused by alcohol at a blood alcohol concentration of 0.11%, midazolam and propofol produced the same degree of impairment for 45 and 15 min after injection, respectively (fig. 1, top). Midazolam produced impairment for 15 min after injection on eye-hand coordination similar in degree to that of alcohol. Propofol produced impairment for 15 min after injection on the ART similar in degree to that of alcohol.

*Short-term Memory*

Fentanyl and propofol produced no significant impairment of short-term memory. Midazolam at 15 min after injection caused a significant decrease in short-term memory relative to placebo. This decrease was of a magnitude similar to that of alcohol at a blood alcohol concentration of 0.11% (fig. 1, middle).

*Subjective Effects*

**Visual Analog Scale.** Table 2 shows the duration of statistically significant effects of the three sedative drugs, *i.e.*, effect significantly greater than placebo. Statistical significance was obtained on 13 adjectives with one or more of the sedative drugs. When compared to placebo, fentanyl produced significant effects for 5–15 min after injection on 10 of the 13 adjectives. Midazolam produced significant effects lasting 5–75 min after injection on 8 of the 13 adjectives. Propofol produced significant effects lasting 5–30 min after injection on all 13 adjectives.

Table 2 also shows the duration of effects of the three drugs relative to impairment produced by a dose of alcohol that produced a blood alcohol concentration of 0.11%. When compared to the impairment in VAS adjectives caused by alcohol at a blood alcohol concentration of 0.11%, fentanyl produced similar effects on 9 of the 13 adjectives for 5–15 min after injection. Midazolam produced effects for 5–75 min after injection on 6 of the 13 adjectives similar in degree to that of alcohol. Propofol produced effects on 12 of the 13 adjectives for 5–30 min after injection similar in degree to that of alcohol. In addition, "sedated" ratings were significantly higher than that of alcohol at 5 and 15 min after administration (fig. 1, bottom).

**Drug Effects and Drug Liking.** When compared to placebo, fentanyl and propofol produced statistically significant effects on the "feeling drug effect" ratings

for 60 min, whereas midazolam produced a significant effect for 90 min after injection. On the drug liking scale, fentanyl, midazolam, and propofol produced statistically significant increases for 5, 5, and 45 min, respectively.

When compared to alcohol at a blood alcohol concentration of 0.11%, fentanyl, midazolam, and propofol produced similar effects on the "feeling drug effect" ratings for 5, 60, and 15 min, respectively. On the drug liking scale, fentanyl, midazolam, and propofol produced similar increases to that of alcohol at a blood alcohol concentration of 0.11%, for 5, 5, and 15 min, respectively.

## Discussion

Results of the study show that there were statistically significant changes in objective and subjective indexes of impairment. Overall, subjective indexes were impaired for a longer period than objective indexes. Midazolam tended to produce a longer duration of impairment than the other two study drugs. However, more importantly, this study was designed to compare drug-induced impairment to that caused by alcohol that produced a blood alcohol concentration of >0.10%. The degree of impairment at this blood alcohol concentration was used as a standard by which to compare the changes in mood and psychomotor performance after administration of drugs commonly used in ambulatory surgery. Results indicated that the study drugs produced subjective and/or objective impairment at one or more times after injection that were similar to that of alcohol at a blood alcohol concentration of 0.11%. Conversely, statistically significant impairment was obtained at one or more time points after injection that did not match that observed with alcohol.

Fentanyl in two instances produced discrepancies between effects that were statistically significant and effects that were similar to that of alcohol. In the first instance, fentanyl increased "drunk" VAS ratings, relative to placebo, but the increase was less than that produced by alcohol. In the second instance, fentanyl produced a longer-lasting effect on the adjective "feeling drug effect," relative to placebo, than an effect that was similar to that produced by alcohol. Midazolam in three instances also produced discrepancies between effects that were statistically significant and effects that were similar to that of alcohol. In two instances, midazolam increased VAS ratings (on adjectives "stimulated" and "high") relative to placebo, but the increases were less than that produced by alcohol. In the other instance, midazolam produced a longer-lasting effect on "feeling drug effect," relative to placebo, than an effect that was similar to that produced by alcohol. Propofol in five instances produced discrepancies between effects that were statistically significant and effects that were similar to that of alcohol. In the first instance, propofol increased "drunk" VAS ratings, relative to placebo, but the increase was less than that produced by alcohol. In the other four instances, it produced a longer-lasting effect (on the VAS adjectives "carefree," "in control of body," "feeling drug effect," and drug liking) relative to placebo, than an effect that was similar to that produced by alcohol. In summary, we have shown that with these often used anesthetic drugs, there are instances when there are statistically significant effects that approach the magnitude of effects seen with a large dose of alcohol. Second, subjective indexes of impairment moreso than objective indexes were more likely to show a discrepancy between effects that were statistically significant and effects that were similar to that of alcohol.

**Table 2. Duration (min) of Statistically Significant Impairment ($t_{ss}$) (Impairment Greater Than That Seen with Placebo) and Impairment ($t_{alc}$) Similar to That Seen with Alcohol at a Blood Alcohol Concentration of 0.11%, of Subjective and Mood Effects Caused by Fentanyl, Midazolam, and Propofol**

| | Fentanyl | | Midazolam | | Propofol | |
|---|---|---|---|---|---|---|
| | $t_{ss}$ | $t_{alc}$ | $t_{ss}$ | $t_{alc}$ | $t_{ss}$ | $t_{alc}$ |
| Stimulated | 15 | 15 | 60 | NS | 30 | 30 |
| Sedated | 15 | 15 | 75 | 75 | 30 | 30(15*) |
| Drunk | 15 | NS | NS | NS | 5 | NS |
| High | 15 | 15 | 15 | NS | 30 | 30 |
| Coasting | 5 | 5 | 60 | 60 | 15 | 15 |
| Dizzy | 15 | 15 | NS | NS | 5 | 5 |
| Carefree | 5 | 5 | NS | NS | 30 | 5 |
| Having pleasant body sensations | 15 | 15 | 15 | 15 | 5 | 5 |
| In control of body | 5 | 5 | 60 | 60 | 15 | 5 |
| Confused | NS | NS | 5 | 5 | 15 | 15 |
| Anxious | NS | NS | NS | NS | 5 | 5 |
| In control of thoughts | 5 | 5 | 15 | 15 | 15 | 15 |
| Tingling | NS | NS | NS | NS | 5 | 5 |
| Drug effect | 60 | 5 | 90 | 60 | 60 | 15 |
| Drug liking | 5 | 5 | 5 | 5 | 45 | 15 |

NS = no significant effect.

* Duration (min) for which the effect was significantly higher than that by alcohol at a mean blood alcohol concentration of 0.11%.

There are several limitations to this study. The first is the matter of dosages of the anesthetic drugs. The fentanyl and propofol doses, while in the range of clinically efficacious doses for analgesia or sedation, were at the low end of the range. It is possible that larger doses of fentanyl or propofol would have produced a longer-lasting impairment. The second caveat is that we only examined the effect of a single dose of a drug. Third, we only tested drugs by themselves and not in combinations. The fourth caveat concerns the large alcohol dose used as the standard. Future studies should examine (1) larger doses of anesthetic drugs, (2) repeated administration of drugs within a session, (3) single doses of drugs followed by continuous infusion (where appropriate), (4) drug combinations (*e.g.,* fentanyl with propofol), (5) an older age group, and (6) a smaller dose of alcohol that would produce a blood alcohol concentration of 0.04–0.05%.

Finally, how do the data obtained in the current study benefit the anesthesiologist who works in an ambulatory surgical setting? It may be too early from this study to draw any clinically important conclusions. We would not want to make the assumption, for example, that impairment that does not approach that of alcohol at a blood alcohol concentration of 0.10% is clinically insignificant. Impairment can be detected at much lower doses of alcohol than the one selected in this study. We hope other studies will follow in which other doses of alcohol are compared to drugs used in ambulatory surgery. Such studies, by using alcohol as a positive control or standard will enable medical caregivers to put the results regarding impairment from anesthetic drugs in a more meaningful framework or context (*i.e.,* how does the degree of impairment compare to that of alcohol?) than that which currently exists (*i.e.,* comparing drugs to a placebo-control condition only).

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