

Sleep Tendency as a Measure of Recovery after Drugs Used for Ambulatory Surgery

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Background: Although tests of psychomotor function indicate that drug effects after ambulatory anesthesia are short-lived, patients often feel washed out for long periods of time. Among the psychomotor tests that measure different motor and cognitive functions, none directly measures sleepiness or alertness. The authors hypothesized that sleepiness, measured by a sleep latency test, would be a more sensitive indicator of drug effect after an anesthetic than psychomotor tests. The second objective was to determine a sedation regimen that produced the least residual effect.

Methods: On four separate occasions, volunteers (N = 12) received an injection of propofol 2.5 mg/kg; propofol 2.0 mg/kg and fentanyl 2 µg/kg; propofol 2.0 mg/kg and midazolam 2 mg/70 kg; or midazolam 0.07 mg/kg and fentanyl 2 µg/kg. Dependent measures included the multiple sleep latency test (MSLT), Maddox Wing and digit symbol substitution tests, auditory and visual reaction times, and a divided attention task.

Results: The multiple sleep latency test demonstrated sleepiness up to 4 h after injection, and in some patients, sleepiness continued up to 8 h afterward. Psychomotor function was impaired only at 2 h after injection of the drug combination.

Conclusion: The multiple sleep latency test may be a more sensitive measure of a drug's effect than other tests of psychomotor function. For up to 8 h after an injection of midazolam and fentanyl, patients must consider driving or operating heavy machinery unsafe activities.

TODAY, many surgical procedures are performed in an outpatient setting, where patients receive conscious sedation. The goal of ambulatory anesthesia is to have a patient leave the clinic as soon as possible after a procedure to return to normal activities. During conscious sedation for endoscopic, cardiac, and ambulatory surgical procedures, medication is administered to provide amnesia and sedation, to reduce anxiety, and to control pain. The ideal agent or combination of agents would have a rapid onset of action and ensure analgesia, amnesia, and anxiety reduction during surgery with little or no residual effect on memory, attention, or coordination. Agents commonly used in outpatient centers are benzodiazepines for anxiety reduction, sedation, and amnesia, and opioids to control pain. Midazolam and fentanyl are

often used for conscious sedation because it is believed that they have little residual effect on attention or psychomotor performance after a patient is discharged. This impression is based on studies showing that psychomotor function is affected for only 2 h after this drug combination.¹

Although tests of psychomotor function indicate that the effects of anesthetics or sedatives after ambulatory anesthesia are fairly short-lived,²⁻⁷ some studies suggest that residual effects are not detected by routine clinical examination or psychomotor testing.^{1,8,9} In one study, tests of visualization, aiming, and perceptual speed taken by a patient 2 h after intravenous midazolam had returned to baseline; however, the patient's ability to stand steadily and walk a straight line had not.¹⁰ In another study of propofol and midazolam, psychomotor function was affected for 30 min and 2 h respectively, but free recall was impaired for 2 h and 24 h respectively.⁹

Patients often feel washed out for longer periods than psychomotor test results indicate. Furthermore, in our opinion, patients should wait for a longer period of time than psychomotor tests indicate, before engaging in activities that require their attention. Psychomotor or cognitive function tests do not measure sleepiness or alertness directly. A more sensitive test of this phenomenon may be one that requires passivity rather than activity. We hypothesized, therefore, that sleepiness, as measured using the sleep latency test, is a more sensitive indicator of impairment after an anesthetic. We also sought to determine a sedation regimen that produced the least residual effect.

Methods

This study was approved by our Institutional Review Board, and informed written consent was obtained from subjects. Eight men and four women in good health volunteered for the study. Their mean age (\pm SD) was 26.3 ± 4.4 yr, mean height was 174 ± 13 cm, and mean weight was 74 ± 13 kg. Because the multiple sleep latency test (MSLT) is less reliable in insomniacs than in those with normal sleep habits,¹¹ potential subjects were screened by telephone to determine the regularity of their sleep habits. Candidates were excluded if they complained of difficulty initiating or maintaining sleep, varied usual bedtime or time of rising by more than 1 h, did not spend 7.5-8.5 h each night in bed, napped during the day, or had insomnia or narcolepsy. An anesthesiologist conducted a personal interview and a phys-

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ical examination to verify the health status of the subjects. Electrocardiography, complete blood count, and Chem-17 tests were performed. In addition to taking the patient's medical history, physical examination, and laboratory tests, additional exclusion criteria included an adverse experience with anesthesia, sedation, or analgesia; systemic disease; and pregnancy or the possibility of pregnancy during the study. On each day of testing, urine pregnancy tests were performed to ensure that subjects were not pregnant. Subjects were asked to avoid depressants including ethanol (confirmed by measuring exhaled ethanol), and stimulants including caffeine-containing foods (coffee, tea, cola, chocolate) for 24 h before study sessions.

Psychomotor performance was measured using the Maddox Wing test,¹² a digit symbol substitution test (DSST),¹³ auditory and visual reaction times, and a divided attention task.¹⁴ Subjects had three practice sessions with the psychomotor test apparatus to reduce learning of the tasks during the actual testing. The psychomotor tests take approximately 5 min to complete.

For the first (acclimation) period of study, volunteers were admitted to the General Clinical Research Center (GCRC) for screening of their nighttime sleep patterns and daytime sleep latency. They arrived by 2200 h and were monitored with an electroencephalogram or an activity monitor to ensure 8 h in bed and adequate sleep efficiency (sleep time > 75% of time in bed). The following day, psychomotor performance and sleep latency measured using the MSLT were tabulated at 1000, 1200, 1400, and 1600 h. Subjects were admitted to the study if average sleep latency was ≥ 10 min and they had no onsets of rapid eye movement (REM) sleep, which is indicative of narcolepsy.

Subjects returned to the laboratory on four other days. They were again monitored to ensure 8 h in bed and adequate sleep efficiency (sleep time > 75% of time in bed). To control for any day-of-the-week effects, three subjects were admitted to the GCRC on Sunday, three on Monday, three on Tuesday, and three on Wednesday. They were always admitted on the same day of the week for each of the 4 days of drug injection. They were in bed by 2230 and were awakened at 0630. At 0700 they were prepared for sedation and then received one of four injections, administered in random order: propofol 2.5 mg/kg; propofol 2.0 mg/kg and fentanyl 2 μ /kg; propofol 2.0 mg/kg and midazolam 2 mg/70 kg; or midazolam 0.07 mg/kg and fentanyl 2 μ /kg. Subjects and investigator were blinded to agents administered. Electrocardiogram, blood pressure, and oxygen saturation were monitored during the time of sedation.

At 2, 4, 6, and 8 h after drug injection (approximately 1000, 1200, 1400, and 1600 h), subjects were instructed to lie down on a bed in a dark, quiet room to try to fall asleep. A standard electroencephalogram technique (electro-oculogram, chin electromyograph, and C3, C4,

and O₂ electroencephalogram referenced to the ears) was used.¹⁵ The MSLT was conducted according to published guidelines.¹⁶ Latency tests were concluded (*i.e.*, subjects were awakened) at the first signs of stage-1 sleep (at least two consecutive 30-s epochs), the first epoch of stage-2 or REM sleep, or 20 min of wakefulness. Subjects were not allowed to lie down or fall asleep at other than scheduled times. Sleep latency was scored in minutes to the first epoch of nonwakefulness using published criteria.¹⁵ After each latency test, psychomotor performance was assessed with the tests described above. Subjects ate breakfast after the tests at 2 h after injection and ate lunch after tests at 4 h after injection.

Statistical Analysis. For each test (psychomotor performance and sleep latency), repeated-measures analysis of variance was used to compare the effects of the different drugs (present or absent), the change in effects with time, and the interaction of the effects, if any. The repeated measurements analyzed were the changes in test results from 2 to 8 h after drug injection for each test. For the psychomotor tests, learning effects were determined by using the week of testing as the grouping factor.

Results

The drug effect was apparent with some psychomotor tests 2 h after drug injection. Auditory reaction time was greater in the four drug groups combined (mean \pm SD 0.31 ± 0.06 s) compared with reaction time during the acclimation session (0.27 ± 0.05 s) ($P < 0.05$) (Fig. 1). No one drug affected reaction times more than another. Correct responses on the divided attention test were fewer after the combination of fentanyl and midazolam (86 ± 16 responses) than after the other drugs (94 ± 5 responses) ($P < 0.01$) (Fig. 2). Correct responses on the digit symbol substitution test were fewer in the two groups that received midazolam (47 ± 8 responses) than in the other two groups (51 ± 7 responses) ($P < 0.05$) (Fig. 3). No effect was noted with the Maddox Wing, divided attention reaction time, or visual reaction time. Four hours after drug injection, no effect was noted on any of the psychomotor tests.

Sleep latency reflected increased sleepiness up to 4 h after drug administration (Fig. 4). Sleep latency was longer in the propofol and propofol with fentanyl groups combined (2 h 9.41 ± 4.6 min; 4 h 10.2 ± 6.4 min) than in the midazolam with propofol or midazolam with fentanyl groups combined (2 h 5.6 ± 3.6 min; 4 h 6.4 ± 4.2 min) at 2 h ($P < 0.0025$) and 4 h ($P < 0.025$) after injection. The two propofol groups combined (results stated previously) had shorter sleep latency times 2 h after drug administration than at the same time during the acclimation session (14.3 ± 4.3 min) ($P = 0.001$). When the midazolam with fentanyl treatment

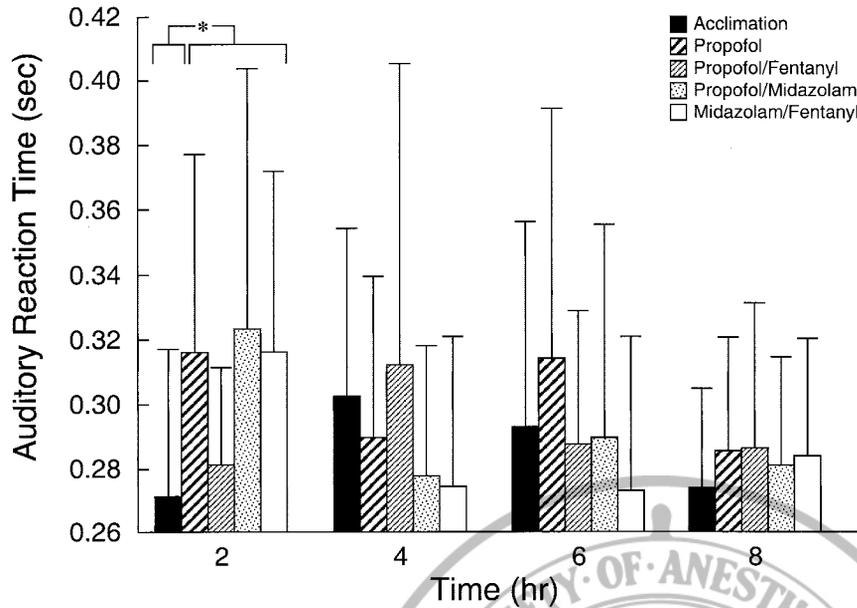


Fig. 1. Results of the auditory reaction time test from 2–8 h after drug injection. The solid bars indicate the average response time; whiskers indicate SD. Two hours after drug administration, auditory reaction time was greater in the four drug groups than in the placebo group (* $P < 0.05$).

group (2 h 3.8 ± 1.6 min; 4 h 4.9 ± 2.0 min) was compared with the other three medication groups combined (2 h 8.7 ± 4.5 min; 4 h 9.4 ± 6.1 min), sleep latency was shorter at 2 h ($P = 0.001$) and at 4 h ($P < 0.025$). At 2 and at 4 h after injection, every subject fell asleep more quickly after receiving midazolam and fentanyl than after the acclimation session; the average decrease in sleep latency (\pm SD) was $10.5 (\pm 3.8)$ min and $7.4 (\pm 4.8)$ min, respectively. Even 6 h after injection, 6 of 12 subjects who received midazolam and fentanyl fell asleep sooner than they did after the acclimation session. No practice effects were significant.

Discussion

The first objective was to compare sleep latency with psychomotor function testing to determine which test was more sensitive in detecting drug effect. The second objective was to determine which sedation regimen produced the least residual effect. We found that the MSLT was a more sensitive instrument for detecting drug effect after different anesthetic regimens. Midazolam combined with fentanyl shortened sleep latency even 4 h after drug administration. Sleep latency times were greater after propofol and propofol with fentanyl than

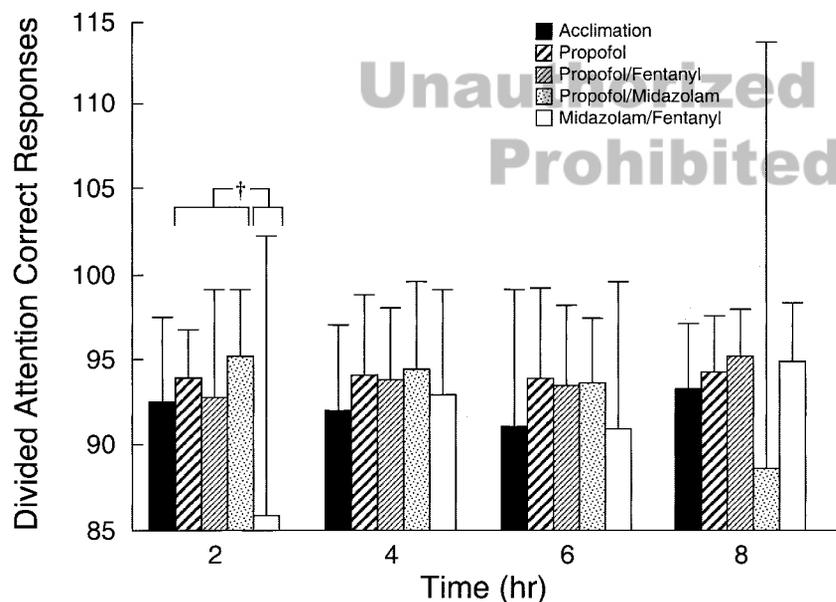


Fig. 2. Correct responses for the divided attention task from 2–8 h after drug injection. The solid bars indicate the average number of responses; whiskers indicate SD. Two hours after drug administration, correct responses were fewer after fentanyl and midazolam than after the other drug groups ($\dagger P < 0.01$).

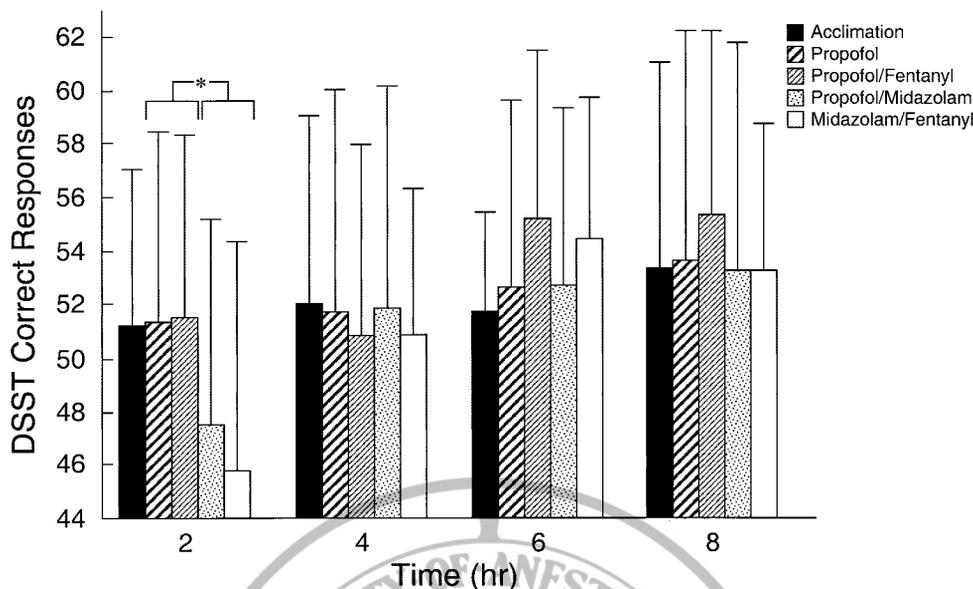


Fig. 3. Correct responses for the digit symbol substitution (DSST) task from 2–8 h after drug injection. The solid bars indicate the average number of responses; whiskers indicate SD. The number of correct responses were fewer after midazolam and propofol or fentanyl 2 h after drug administration compared with the number of responses in the other two drug groups ($*P < 0.05$).

after midazolam with propofol or midazolam with fentanyl 4 h after drug administration. Propofol with or without fentanyl had distinct effects 2 h after drug administration. Psychomotor function tests demonstrated an effect for only 2 h after a drug was administered. Differences between drugs were not found with any of the psychomotor tests. As measured with the MSLT,

drug effect was detectable for twice as long as with psychomotor testing, and individual drug differences were apparent. Propofol and propofol with fentanyl decreased sleep latency the least of the four drug combinations tested.

Psychomotor tests measure responses while a patient is in an attentive state after having been aroused to

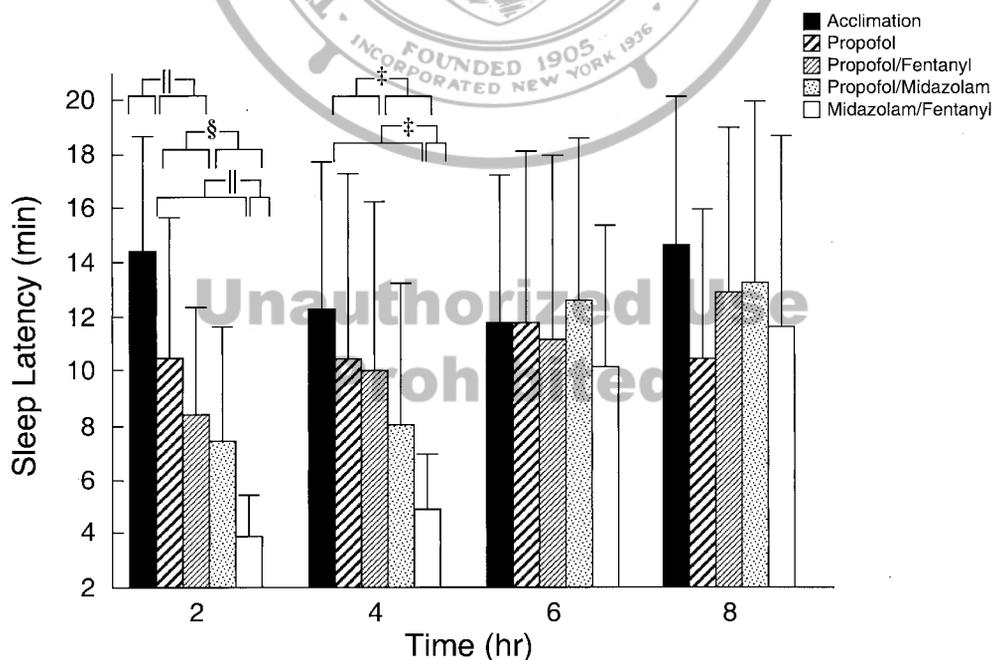


Fig. 4. Results of the multiple sleep latency test from 2–8 h after drug injection. The solid bars indicate the average time to fall asleep; whiskers indicate SD. Significant drug differences were present up to 4 h after drug administration. Sleep latency was longer in the propofol and propofol with fentanyl groups combined than in the midazolam with propofol or midazolam with fentanyl groups combined at 2 h ($\$P < 0.0025$) and at 4 h ($\ddagger P < 0.025$) after injection. The two propofol groups also had shorter sleep latency 2 h after injection compared with the same time during the acclimation session ($\|P = 0.001$). Sleep latency was shorter in the midazolam with fentanyl treatment group compared with the other three treatment groups at 2 h ($\|P = 0.001$) and at 4 h ($\ddagger P < 0.025$).

answer questions. In the DSST, for example, the subject is given 60 s to write a predetermined symbol below a predetermined digit in a series of numbers. Simple auditory and visual reaction times are determined by measuring the time the subject takes to press a button after hearing a sound or seeing a letter on the computer screen. In the divided attention task, several stimuli are presented simultaneously in different sectors of a computer screen. The subject is asked to press the appropriate key when a target stimulus appears in a background of false stimuli. After an ambulatory surgical procedure, a patient may fall asleep easily while driving but respond quickly when a horn is honked. Polysomnographic measures of sedation can detect effects of sedatives not detected on subjective assessment and performance measures.^{17,18} The MSLT produces a highly reliable measure of sleepiness.¹⁹ Healthy adults who have not received a drug have an average sleep latency of 10 min or more.¹⁶ Central nervous system depressants such as ethanol and stimulants such as caffeine significantly alter MSLT results.²⁰ Sleep latency is also shortened by hypnotics long after they have been administered.^{21,22,23} Hypnotic potency has been measured using the MSLT with daytime administration of triazolam,²⁴ antihistamines,²⁵ and alcohol.²⁶ Sleep latency was not different from baseline 8.5 h after midazolam 0.1 mg/kg with or without flumazenil.²⁷ Sleep latency increased, however, 8 h after 1 h of propofol anesthesia.²⁸ After ethanol, sleep latency decreased even when ethanol was no longer detectable in breath.^{29,30,31} In one study of simulated driving in patients with narcolepsy or sleep apnea, the relation between MSLT results and simulated driving performance was weak.³² In a similar study of patients with obstructive sleep apnea, driving performance improvement was correlated with an improvement in sleepiness (change in MSLT times).³³

Although psychomotor function tests indicated no effect 2 h after drug injection in the study, the shorter sleep latency times up to 4 h after injection of anesthetic drugs may affect tasks such as driving. A clear relation exists between fatigue and the risk of traffic accidents,³⁴ even though exact sleep latency times have not been correlated with absolute values for risk of accidents. Several other caveats are in order with regard to our findings. Many procedures in ambulatory care facilities are performed on patients who have concomitant disease, *e.g.*, chronic obstructive pulmonary disease and sleep apnea. Our results may not be applicable to these patients. These results may not be generalized because certain other variables were not manipulated. We did not vary the dose of either midazolam or fentanyl but chose clinically relevant doses. Patients may experience pain because of their procedure, and our volunteers did not.

In conclusion, our study suggests that sleep latency is a more sensitive indicator of drug effect after sedation

than are tests of psychomotor performance. Furthermore, propofol and propofol with fentanyl decreased sleep latency the least of the four drug combinations tested. When investigators wish to use indicators that are not dependent on active responses from patients, the measurement of the tendency to fall asleep, *i.e.*, sleep latency, can be a sensitive indicator of drug effect. Before receiving midazolam and fentanyl for sedation, patients must be warned to avoid activities that require attention (*e.g.*, driving) for at least 8 h after the drugs are administered.

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