Anesthesiology
1997; 87:1082-8

Subjective, Psychomotor, Cognitive, and Analgesic Effects of Subanesthetic Concentrations of Sevoflurane and Nitrous Oxide

Jeffrey L. Galinkin, M.D., Debra Janiszewski, B.A.,† Christopher J. Young, M.D.,‡ Jerome M. Klafta, M.D.,‡ P. Allan Klock, M.D.,‡ Dennis W. Coalson, M.D.,‡ Jeffrey L. Apfelbaum, M.D.,§ James P. Zacny, Ph.D. ‡*

Background: **Sevoflurane is a volatile general anesthetic that differs in chemical nature from the gaseous anesthetic nitrous oxide. In a controlled laboratory setting, the authors characterized the subjective, psychomotor, and analgesic effects of sevoflurane and nitrous oxide at two equal minimum alveolar subanesthetic concentrations.**

Methods: **A crossover design was used to test the effects of two end-tidal concentrations of sevoflurane (0.3% and 0.6%), two end-tidal concentrations of nitrous oxide (15% and 30%) that were equal in minimum alveolar concentration to that of sevoflurane, and placebo (100% oxygen) in 12 healthy volunteers. The volunteers inhaled one of these concentrations of sevoflurane, nitrous oxide, or placebo for 35 min. Dependent measures included subjective, psychomotor, and physiologic effects, and pain ratings measured during a cold-water test.**

Results: **Sevoflurane produced a greater degree of amnesia, psychomotor impairment, and drowsiness than did equal minimum alveolar concentrations of nitrous oxide. Recovery from sevoflurane and nitrous oxide effects was rapid. Nitrous oxide but not sevoflurane had analgesic effects.**

Conclusions: **Sevoflurane and nitrous oxide produced different profiles of subjective, behavioral, and cognitive effects, with sevoflurane, in general, producing an overall greater magnitude of effect. The differences in effects between sevoflurane and nitrous oxide are consistent with the differences in their chemical nature and putative mechanisms of action. (Key words: Anesthetics, inhaled: sevoflurane; nitrous oxide. Recovery: memory; mood; psychomotor; cognitive; subjective. Analgesia: pain.)**

* CA-3 Resident.

† Research Technician.

‡ Assistant Professor.

§ Professor.

Received from the Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois. Submitted for publication March 4, 1997. Accepted for publication June 4, 1997. Supported in part by grant DA08391 from the National Institute on Drug Abuse.

Address reprint requests to Dr. James P. Zacny: Department of Anesthesia and Critical Care, MC4028, University of Chicago, 5841 S. Maryland Avenue, Chicago, Illinois 60637. Address electronic mail to: zacn@midway.uchicago.edu

SEVOFLURANE, recently approved for use in the United States, is a halogenated volatile anesthetic with the novel characteristics of a low blood-gas solubility coefficient, which makes it easy to titrate, and an odor that is less pungent than that of the other volatile anesthetics. Its subjective and other behavioral effects at subanesthetic concentrations have yet to be characterized in humans. Nitrous oxide is a nonvolatile, gaseous, inhaled anesthetic that may have a different subjective and behavioral profile from that of sevoflurane, given the differences in their chemical natures. Indeed, a recent study that characterized the behavioral and subjective effects of equianesthetic concentrations of isoflurane and nitrous oxide detected greater psychomotor impairment and greater sedating effects from isoflurane than from nitrous oxide.[1] In the present study, we examined two subanesthetic concentrations of sevoflurane, in healthy volunteers, and compared them with placebo and equal minimum alveolar concentrations (equi-MAC) of nitrous oxide. Endpoints measured were subjective, cognitive, and psychomotor effects, and analgesic efficacy.

Materials and Methods

Participants

This study was approved by the local institutional review board. Informed written consent was obtained from each participant before we began the study. The participants were told in the consent form that the agents being studied were used commonly in medical settings and may come from one of six classes delivered *via* a gaseous or aerosol form (*i.e.*, sedative/tranquilizer, stimulant, opiate, general anesthetic at subanesthetic dose[s], alcohol, or placebo). Before the first session, the participants attended a screening interview, in which psychiatric and medical assessments were made

to determine if contraindications existed to their participation in the study.[2,3] Seven men and five women completed the study (mean age ± SD, 26.8 ± 3.8 yr). Volunteers were instructed to refrain from using alcohol, illicit drugs, and over-the-counter medications for 24 h before and 12 h after the sessions. Payment for study participation was made during a debriefing session held after the experiment was complete.

Experimental Design

An orientation session was held before the first experimental session so that volunteers could practice the psychomotor and cognitive tests. The experiment consisted of five sessions, each separated by at least 2 days. An incomplete Latin square, crossover design was used. The study was double blinded in that the research technician administering tests and the volunteers were unaware of the drug or dose being inhaled. The anesthesiologist administering the drug had minimal verbal contact with the volunteer during the session. The effects of two end-tidal concentrations of sevoflurane (0.3% and 0.6% in oxygen), two end-tidal concentrations of nitrous oxide (15% and 30% in oxygen), and placebo (100% oxygen) were studied. Low and high concentrations of sevoflurane and nitrous oxide were matched to induce equal fractions of a MAC. The MAC of sevoflurane was estimated at 2.05% and the MAC of nitrous oxide was estimated at 105%.[4]

Experimental Sessions

Each session lasted approximately 120 min and took place in the morning or in the afternoon. Participants had been instructed not to eat food for 4 h and not to drink any liquids for 2 h before the sessions. Female volunteers had to have a negative urine pregnancy test before each session could start. Subjects were given a breath alcohol test before beginning each session to ensure that no alcohol was in their systems. Anesthetic agents and oxygen were delivered *via* a semiclosed circuit from an anesthetic machine (Ohmeda Modulus II, Madison, WI), and volunteers inhaled through a clear anesthesia face mask while in a semirecumbent position. Noninvasive measurements of heart rate, peripheral oxygen saturation, and blood pressure were initiated at the beginning of the session and were monitored continuously throughout the session. Inhaled and exhaled levels of oxygen, carbon dioxide, sevoflurane, and nitrous oxide were measured continuously with a gas analyzer (Datex Capnomac, Helsinki, Finland) and recorded at periodic intervals during inhalation.

Each session consisted of three periods: baseline (approximately 5 min), inhalation (35 min), and recovery (60 min). During baseline, participants completed several mood forms and psychomotor tests while inhaling oxygen through the mask. They were told at this time that the air they were breathing (100% oxygen) did not contain any drug. When the baseline testing was complete, the inhalation period began. Volunteers were told that for the following 35 min they would be inhaling air that may or may not contain a drug. The anesthesiologist alerted the technician to begin timing the session and turned on the agent appropriate for the session. The anesthesiologist was allowed to rapidly equilibrate concentrations of sevoflurane and nitrous oxide as monitored with the gas analyzer. Inspired gas concentrations were not to exceed 1.5% sevoflurane or 50% nitrous oxide. Using these maximum concentrations as limits, the anesthesiologist applied over-pressure to equilibrate the exhaled gas concentration with the target concentration as rapidly as possible. Total fresh open flow was held constant at 5 l/min. The anesthesiologist recorded end-tidal concentrations at 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 min. This procedure documented when equilibration to the desired end-tidal concentration had been achieved. In 96% of the active-drug sessions, the desired end-tidal concentration (±15%) was achieved within the first 5 min of the 35-min inhalation period. The anesthesiologist stayed in the immediate vicinity throughout the inhalation. At the end of the 35-min inhalation period, the anesthesiologist removed the mask and the 60-min recovery period began. Participants completed mood forms and psychomotor tests 5 and 15 min after beginning the inhalation and at 5, 30, and 60 min into the recovery period. A 3-min cold water test, in which the participant's nondominant forearm was immersed in 2°C water, was initiated 30 min into the inhalation to determine if nitrous oxide or sevoflurane manifested analgesic effects.[5]

Dependent Measures

Subjective Effects. To assess subjective effects, we used a visual analog scale and a drug effects/liking questionnaire. The visual analog scale consisted of 21 100-mm lines, each labeled with an adjective (*e.g.*, anxious, high, lightheaded, sleepy [tired, drowsy]). Participants were instructed to place a mark on each line indicating how they felt at the moment, ranging from 0 ("not at all") to 100 ("extremely"). The drug effects/liking questionnaire consisted of two items and assessed the extent to which participants 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 the extent to which they liked the drug effect, on a 100-mm line (0 = dislike a lot; 50 = neutral; 100 = like a lot).

Observer Ratings. To assess the volunteers' sedation levels, the blinded technician (D.J.) made a subjective rating based on arousability. The rating was as follows: 1—asleep, not readily arousable; 2—asleep, slowly responds to verbal commands and/or gentle stimulation; 3—drowsy, readily responds to verbal commands and/or gentle stimulation; 4—awake, calm and quiet; and 5—awake and active. Ratings were taken at baseline; at 5, 10, 15, 20, 25, and 30 min during the inhalation period; and at 5, 30, and 60 min into recovery.

Psychomotor Performance. To assess cognitive and psychomotor functioning, we used the Digit Symbol Substitution Test (DSST), a computer-based auditory reaction time test, and a time estimation test. The DSST is a paper-and-pencil test in which participants must replace digits with corresponding symbols for 60 s.[6] The score is the correct number of symbols that the participant draws. Different forms of the test (*i.e.*, different symbol-number codes) were used each time the test was presented to the volunteer in a particular session. For the auditory reaction time test, the volunteers were instructed to depress a computer space bar as soon as they heard a tone from the computer.[7] Ten tones were presented over 60 s at random intervals. The volunteer's average time to respond to the ten tones was calculated. For the 20-s time estimation test, the volunteer was told to estimate 20 s and to indicate once they thought that the 20 s had passed.[8] The technician started a stop watch and stopped it once the volunteer had indicated that 20 s had passed.

Memory. Fifteen minutes into the inhalation period, participants were shown 15 words on a computer screen. Each word was presented for 2 s with an interword interval of 1 s. To assess immediate recall, participants were instructed to record as many words as they could remember from the list, in any order, for 2 min after the last word was presented. To assess delayed recall, 60 min after the inhalation period had ended, they were instructed to record as many words as they could remember from the original list. The words were selected from norms[9,10] and had ratings of imagery and concreteness greater than 4, ratings of meaningfulness greater than 5, and frequency of usage greater than 20 per million.

Pain Assessments. Participants were instructed to verbally rate the pain and the degree to which the pain bothered them on a scale of 0–10 during the immersion of the arm in the ice-cold water (0 = not painful/bothersome at all and 10 = extremely painful/bothersome). The questions, "How painful is it?" and "How much does it bother you?" were asked 30, 70, 110, and 170 s into the immersion.

Physiologic Measures. Pulse, systolic and diastolic blood pressure, and hemoglobin oxygen saturation were measured noninvasively (Hewlett Packard model 54; Waltham, MA). These measures were monitored continuously throughout the session and were recorded at baseline; 5 and 15 min after initiation of inhalation; and 5, 30, and 60 min after inhalation had ceased. Clinically significant changes (20% deviation from baseline values) were not noted in any of the physiologic variables, so there will be no further mention of these data.

Data Analysis. Repeated measures of analyses of variance were done with drug condition (five levels) and (with the exception of the memory test) time (four to ten levels) as the factors. F values were considered significant for $P \leq 0.05$, with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of sphericity. Tukey *post-hoc* comparison tests were used when significant condition or condition X time effects were obtained.

Results

Subjective Effects

In general, subjective effects were concentration related with both anesthetics. Both anesthetics at one or both concentrations significantly increased ratings of coasting (spaced out), difficulty concentrating, drunk, high, floating, lightheaded, sedated, and tingling. Differences in subjective effects between the two drugs were as follows: sevoflurane but not nitrous oxide increased ratings of sleepiness, and nitrous oxide but not sevoflurane increased ratings of being confused, feeling good, and having pleasant bodily sensations. Figure 1 shows that self-reported strength of drug effect was concentration dependent for both agents and that the agents had fairly similar time courses and magnitudes of effects. Drug-liking ratings were neither significantly increased nor decreased by sevoflurane or nitrous oxide, although inspection of the individual participant data revealed substantial intersubject variability with this measure across the active-drug conditions.

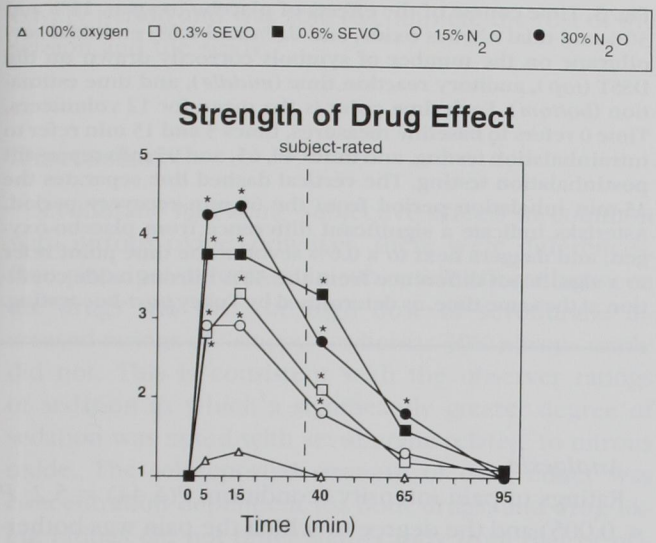

Fig. 1. Time course of the effects of placebo-oxygen, 15% and 30% end-tidal nitrous oxide, and 0.3% and 0.6% end-tidal sevoflurane on drug-effect strength ratings. Each time point is the mean for 12 volunteers. The scale ranged from 1 (no drug effect) to 5 (strong drug effect). Time 0 refers to baseline measures, times 5 and 15 min refer to intrainhalation testing, and times 40, 65, and 95 min represent postinhalation testing. The vertical dashed line separates the 35-min inhalation period from the recovery period. Asterisks indicate a significant difference from placebo-oxygen.

Observer Ratings

There was a significant effect on observer ratings of subject sedation during the inhalation of both concentrations of sevoflurane and 30% nitrous oxide (condition X time: $F(36,396) = 5.2$; $P < 0.001$; figure 2). There was a time course difference in that the observer noted sedation during the 0.6% sevoflurane inhalation at an earlier time than during the 30% nitrous oxide inhalation. In addition, Tukey *post-hoc* testing revealed that at two inhalation times, observer sedation ratings were significantly more extreme with 0.6% sevoflurane than with 30% nitrous oxide.

Psychomotor Performance

Significant decreases in DSST scores were obtained with 0.3% and 0.6% sevoflurane and 30% nitrous oxide compared with placebo at both 5 and 15 min during the inhalation period (condition X time: $F(20,220) = 33.4$; $P < 0.001$; figure 3, top). Tukey *post-hoc* testing further revealed that there was a significantly greater decrease in DSST performance at 5 and 15 min during inhalation with 0.6% sevoflurane compared with 30% nitrous oxide. In general, there was a rapid return to baseline in DSST performance during the recovery period, except with the 0.6% sevoflurane concentration, which was decreased at the 5-min but not at the 30-min recovery time interval. Auditory reaction time was significantly increased during the inhalation of 0.6% sevoflurane (condition X time: $F(20,220) = 8.8$; $P < 0.001$; figure 3, middle). Return to baseline functioning occurred by the 5-min recovery time interval for this psychomotor endpoint.

Performance on the 20-s time estimation task was affected when participants were breathing end-tidal concentrations of 0.6% sevoflurane (condition X time: $F(20,220) = 6.3$; $P < 0.01$; figure 3, bottom). In the high sevoflurane group, participants overestimated the passage of time (*i.e.*, on average, 20 s was perceived as approximately 35 s).

Memory

Memory was significantly affected by the drug manipulation (condition X time: $F(4,44) = 5.9$; $P < 0.001$). Tukey *post-hoc* testing revealed a significant decline

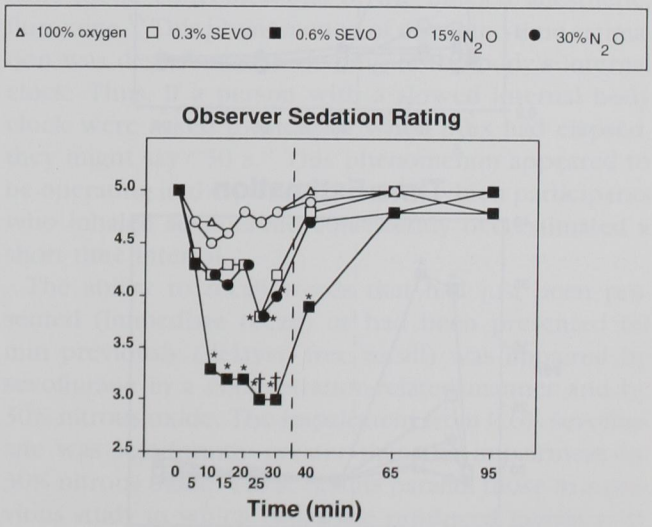

Fig. 2. Time course of the effects of placebo-oxygen, 15% and 30% end-tidal nitrous oxide, and 0.3% and 0.6% end-tidal sevoflurane on observer sedation ratings. Each time is the mean across 12 volunteers. The observer scale ranged from 1 (asleep, not readily arousable) to 5 (awake and active). Time 0 refers to baseline measures, times 5–30 refer to intrainhalation testing, and times 40, 65, and 95 min represent postinhalation testing. The vertical dashed line separates the 35-min inhalation period from the 60-min recovery period. Asterisks indicate a significant difference from placebo-oxygen, and daggers next to a 0.6% sevoflurane time point refer to a significant difference from the 30% nitrous oxide condition at the same time, as determined by Tukey *post-hoc* testing.

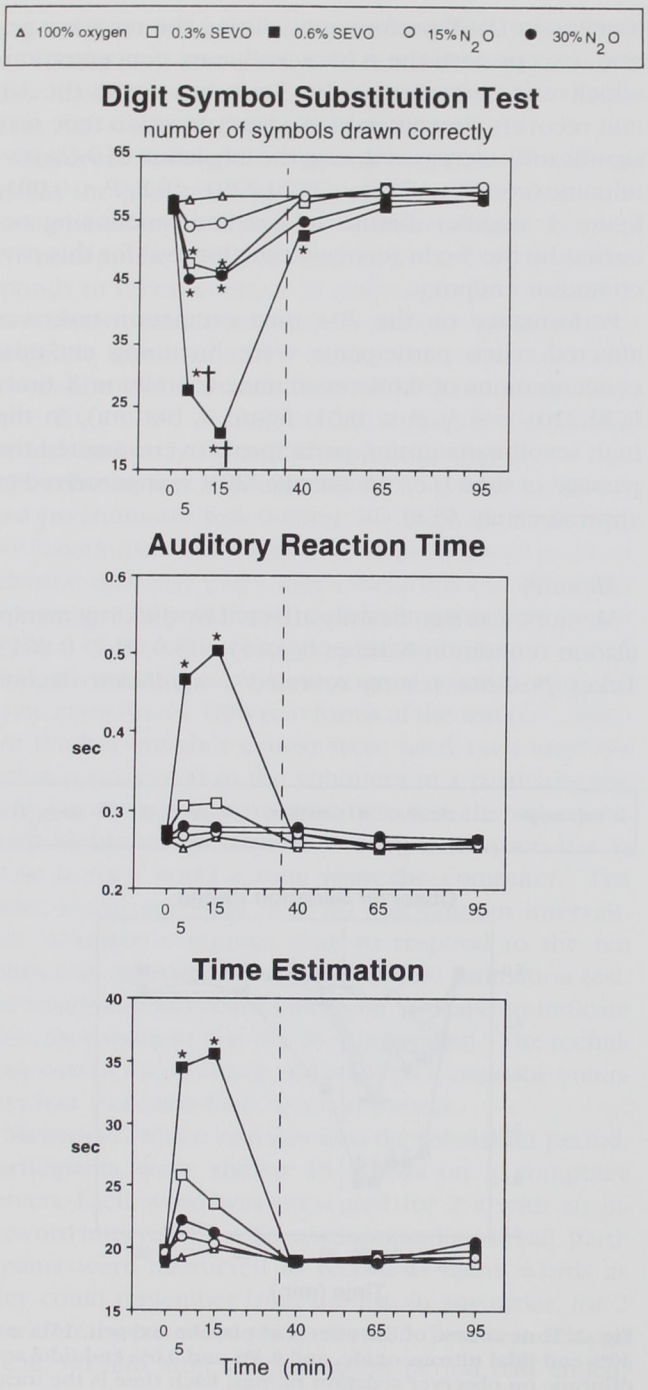

Fig. 3. Time course of the effects of placebo-oxygen, 15% and 30% end-tidal nitrous oxide, and 0.3% and 0.6% end-tidal sevoflurane on the number of symbols correctly drawn on the DSST (*top*), auditory reaction time (*middle*), and time estimation (*bottom*). Each time point is the mean for 12 volunteers. Time 0 refers to baseline measures, times 5 and 15 min refer to intrainhalation testing, and times 40, 65, and 95 min represent postinhalation testing. The vertical dashed line separates the 35-min inhalation period from the 60-min recovery period. Asterisks indicate a significant difference from placebo-oxygen, and daggers next to a 0.6% sevoflurane time point refer to a significant difference from the 30% nitrous oxide condition at the same time, as determined by Tukey *post-hoc* testing.

in both immediate and delayed free recall with both concentrations of sevoflurane and 30% nitrous oxide. Tukey *post-hoc* testing further revealed a significantly greater decline with 0.6% sevoflurane compared with 30% nitrous oxide (figure 4, left and right).

Analgesia

Ratings of pain intensity (condition: $F(4,44) = 5.2$; $P < 0.005$) and the degree to which the pain was bothersome (condition: $F(4,44) = 6.0$; $P < 0.001$) were significantly decreased by 30% nitrous oxide. The mean ratings (±SD) of pain intensity in the placebo and 30% nitrous oxide conditions were 7 ± 1.8 and 5.3 ± 2, respectively. The mean ratings (±SD) of the degree to which the pain was bothersome in the placebo and 30% nitrous oxide conditions were 6.8 ± 2.1 and 5 ± 2.1, respectively. No hypo- or hyperalgesic effect was noted with either concentration of sevoflurane.

Adverse Events

Two participants vomited during the session in which they received 0.6% sevoflurane. One of them dropped out of the study (his data were not included in the analysis). The other participant vomited during the re-

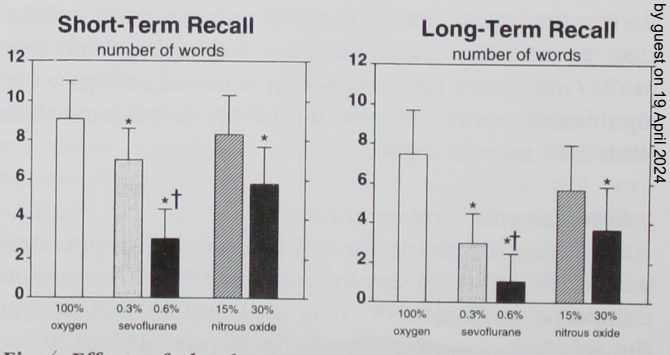

Fig. 4. Effects of placebo-oxygen, 0.3% and 0.6% end-tidal sevoflurane, and 15% and 30% end-tidal nitrous oxide on immediate free recall (*left*) and delayed free recall (*right*). Each bar is the mean for 12 volunteers. Brackets indicate SD. Asterisks indicate a significant difference from placebo-oxygen, and daggers refer to a significant difference from the 30% nitrous oxide condition, as determined by Tukey *post-hoc* testing.

covery period and was able to complete the rest of the session and the study.

Discussion

Sevoflurane had some subjective effects in common with nitrous oxide; however, there were differences. One principal difference in subjective effects between the drugs was that the high dose of sevoflurane increased ratings of "sleepy," whereas 30% nitrous oxide did not. This is consistent with the observer ratings of sedation in which a significantly greater degree of sedation was noted with sevoflurane relative to nitrous oxide. The self-reported strength of drug effect was concentration dependent for both drugs, and drug liking ratings did not differ significantly from that of placebo.

Although the subjective effects data were for the most part orderly (*e.g.*, concentration related), it should be noted that participants often had to be awakened during 0.6% sevoflurane inhalation. The extreme degree of sedation from 0.6% sevoflurane may have negatively influenced the degree to which participants were able to accurately describe the qualitative and quantitative aspects of this sevoflurane concentration. For example, the ratings of "sleepy" were not elevated a great deal during 0.6% sevoflurane inhalation: the mean (±SD) "sleepy" rating on a scale of 0–100 for 0.6% sevoflurane at 15 min during inhalation was 33 ± 36.5. This somewhat low rating was surprising given the marked drowsiness that participants exhibited both before and during completion of the visual analog scale. Further research should determine whether accuracy of self-reporting is affected at higher subanesthetic concentrations of sevoflurane by examining several concentrations between 0.1% and 0.6% end-tidal sevoflurane (perhaps at 0.1% increments) and determining 1) whether a clear dose-response relation exists on such measures as "sleepy," "high," and "feel drug effect," and 2) if observer ratings correlate with subject ratings.

Sevoflurane demonstrated marked psychomotor impairment on both the DSST and the auditory reaction time test. The only previous study that tested psychomotor performance of subanesthetic concentrations of sevoflurane (0.2 MAC) showed an elevation of auditory reaction time similar to that obtained with nitrous oxide.[11] Our results differed in that we found a pronounced increase in reaction time with the high dose (0.3 MAC) of sevoflurane and no significant effect with equi-MAC nitrous oxide. The difference in findings between studies may be accounted for by the higher concentrations of agents that we tested. In addition, we found 0.3 MAC sevoflurane to impair DSST performance to a greater degree than equi-MAC concentrations of nitrous oxide. The psychomotor performance differences between sevoflurane and nitrous oxide are consistent with results obtained in a study examining the relative psychomotor-impairing effects of isoflurane and nitrous oxide.[1] In that study, isoflurane but not nitrous oxide increased auditory reaction time and impaired eye-hand coordination, and a greater degree of DSST impairment was noted with isoflurane than with nitrous oxide. However, recovery from sevoflurane- and isoflurane-induced psychomotor impairment was as rapid as that noted with nitrous oxide-induced impairment.

The phenomenon of altered time perception was reported previously when other volatile anesthetics have been administered at subanesthetic concentrations. With subanesthetic isoflurane, 70% of patients were found to underestimate the duration of their operative procedure.[12] Similar results were observed with subanesthetic concentrations of the inhaled anesthetic, fluroxene.[13] This phenomenon of disrupted time estimation was described as a slowing of the body's internal clock. Thus, if a person with a slowed internal body clock were asked to indicate when 30 s had elapsed, they might say "50 s." This phenomenon appeared to be operating in the present study, in which participants who inhaled sevoflurane consistently overestimated a short time interval.

The ability to recall words that had just been presented (immediate recall) or had been presented 60 min previously (delayed free recall) was impaired by sevoflurane in a concentration-related manner and by 30% nitrous oxide. The impairment from 0.6% sevoflurane was significantly greater than the impairment by 30% nitrous oxide. These results parallel those in a previous study in which isoflurane produced significantly greater memory decrements than did nitrous oxide.[14] Our results also call into question the notion that the interaction between nitrous oxide and volatile anesthetics on suppression of learning is additive. An additive interaction implies that all anesthetics act in the same way at the molecular level on a given endpoint. Although some studies have shown evidence indicative of additivity,[1,15] others have not.[14,16–18] The difference in degree of memory impairment between a gaseous and volatile anesthetic in the present study suggests

different neural mechanisms of action that mediate nitrous oxide-induced and volatile general anesthetic-induced suppression of learning.

Nitrous oxide has a well-established analgesic effect in both animals and humans in subanesthetic concentrations.[19–22] In the present study, nitrous oxide, but not sevoflurane, manifested analgesic effects. The lack of analgesia by sevoflurane is consistent with results from a recent study that examined the effects on pain thresholds of sevoflurane and nitrous oxide in doses equivalent to 0.2 MAC.[11]

In conclusion, when tested at equi-MAC concentrations, sevoflurane had a greater magnitude of effect than did nitrous oxide. Sevoflurane produced a significantly greater degree of amnesia, drowsiness, and psychomotor impairment. These results are consistent with a previous study that documented differences in degree of effect between nitrous oxide and another volatile anesthetic, isoflurane.[1] The differences in subjective, behavioral, and cognitive effects between nitrous oxide and the volatile general anesthetic[5] are consistent with the differences in their chemical nature and putative mechanisms of action.[23–25]

References

1. Zacny JP, Sparacino G, Hoffmann PM, Martin R, Lichtor JL: The subjective, behavioral and cognitive effects of subanesthetic concentrations of isoflurane and nitrous oxide in healthy volunteers. Psychopharmacology 1994; 114:409–16

2. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric rating scale-preliminary report. Psychopharmacol Bull 1973; 9:13–7

3. American Psychiatric Association: Diagnostic and statistical manual of mental disorders. Washington, DC, American Psychiatric Association, 1987

4. Koblin DD: Mechanisms of action, Anesthesia, 4th ed. Edited by Miller RD. New York, Churchill Livingstone, 1994, pp 67–99

5. Chen ACN, Dworkin SF, Haug J: Human pain responsivity in a tonic pain model: physiological determinants. Pain 1989; 37:143–60

6. Wechsler D: The measurement and appraisal of adult intelligence. Baltimore, Williams and Wilkins, 1958

7. Nuotto EJ, Kortilla K: Evaluation of a new computerized psychomotor test battery: effects of alcohol. Pharmacol Toxicol 1991; 68:360–5

8. Thorndike EL, Lorge L: The teacher's word book of 30,000 words. New York, Columbia University Press, 1944

9. Adam N, Rosner BS, Hosick EC, Clark DL: Effect of anesthetic drugs on time production and alpha rhythm. Perception Psychophysics 1971; 10:133–6

10. Paivio A, Yuille JC, Madigan SA: Concreteness, imagery, and meaningfulness values for 925 nouns. J Exp Psychol 1968; 76:1–25

11. Tomi K, Mashimo T, Tashiro C, Yagi M, Pak M, Nishimura S, Nishimura M, Yoshiya I: Alterations in pain threshold and psychomotor response associated with subanesthetic concentrations of inhalation anaesthetics in humans. Br J Anaesth 1993; 70:684–6

12. Parbrook GD, James J, Braid DP: Inhalational sedation with isoflurane: an alternative to nitrous oxide sedation in dentistry. Br Dent J 1987; 163:88–92

13. Adam N, Castro AD, Clark DL: Production, estimation, and reproduction of time intervals during inhalation of a general anesthetic in man. J Exp Psychol 1974; 102:609–14

14. Dwyer R, Bennett HL, Eger EI, Heilbron D: Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. ANESTHESIOLOGY 1992; 77:888–98

15. El-Zahaby HM, Ghoneim MM, Block RI: The interaction between nitrous oxide and isoflurane on suppression of learning: a study using classical conditioning in rabbits. Acta Anaesthiol Scand 1996; 40:798–803

16. Yli-Hankala A, Lindgren L, Porkkala T, Jantti V: Nitrous oxide mediated activation of the EEG during isoflurane anaesthesia in patients. Br J Anaesth 1993; 70:54–7

17. Chortkoff BS, Bennett HL, Eger EI: Does nitrous oxide antagonize isoflurane-induced suppression of learning? ANESTHESIOLOGY 1993; 79:724–32

18. Zacny JP, Yajnik S, Lichtor JL, Klafta JM, Young CJ, Thapar P, Rupani G, Coalson DW, Apfelbaum JL: The acute and residual effects of subanesthetic concentrations of isoflurane/nitrous oxide combinations on cognitive and psychomotor performance in healthy volunteers. Anesth Analg 1996; 82:153–7

19. Pirec V, Patterson T, Thapar P, Apfelbaum JL, Zacny JP: Effects of subanesthetic concentrations of nitrous oxide on cold pressor pain in humans. Pharmacol Biochem Behav 1995; 51:323–9

20. Chapman WP, Arrowood JG, Beecher HK: The analgesic effect of low concentrations of nitrous oxide compared in man with morphine sulfate. J Clin Invest 1943; 22:871–5

21. Berkowitz BA, Finch AD, Ngai SH: Nitrous oxide analgesia: reversal by naloxone and development of tolerance. J Pharmacol Exp Ther 1997; 203:539–47

22. Quock RM, Curtis BA, Reynolds BJ, Mueller JL: Dose-dependent antagonism and potentiation of nitrous oxide antinociception by naloxone in mice. J Pharmacol Exp Ther 1993; 267:117–22

23. Rampil I, Buck L, Bickler P: Differential effects of nitrous oxide or halothane on turtle cortical pyramidal neurons. ANESTHESIOLOGY 1996; 85:A688

24. Moody E, Bambha K, Skolnick P: Nitrous oxide does not modulate $GABA_A$ receptors in mouse cortical tissue. ANESTHESIOLOGY 1996; 85:A707

25. Ropcke H, Schwilden H: Interaction of isoflurane and nitrous oxide combinations similar for median electroencephalographic frequency and clinical anesthesia. ANESTHESIOLOGY 1996; 84:782–8