Assessment of Recovery from Nitrous Oxide-Oxygen Sedation Using Neuropsychometry

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This study measured changes in adult performance following prolonged exposure (90 minutes) to nitrous oxide at psychosodiative levels. Using a repeated-measures randomized blind design, experimenters exposed 12 subjects to four treatment combinations. These included: room air for 90 minutes (baseline); 100% oxygen for 90 minutes; nitrous oxide-oxygen sedation for 90 minutes followed by 100% oxygen for 2 minutes; and 90 minutes of nitrous oxide-oxygen sedation followed by 10 minutes of 100% oxygen. Following each treatment, participants were asked to perform six standard neuropsychological tests together with a rating scale measurement where subjects self-evaluated their respective levels of alertness. The tests were: digit span; digit symbol; paced auditory serial addition; controlled word association; letter cancellation; and grooved pegboard. Two-way analysis of variance revealed significant differences between mean scores for treatments on only two tests, grooved pegboard (P < 0.05) and controlled word association (P < 0.05). There was also a significant difference in mean scores obtained for the rating scale (P < 0.001). These findings indicate that psychomotor performance and verbal fluency were affected by prolonged exposure to nitrous oxide even after recovery periods. No impairment of vigilance, immediate memory, or mental tracking could be detected as measured by the other tests. Subjective reports by the subjects accurately reflected their underlying impaired status.

Although nitrous oxide-oxygen sedation is widely used in clinical practice,¹ and generally regarded as safe, most of the available data relate to short or interrupted exposures.²³⁴ The relationship between dose level and severity of impairment is well established⁵ and rapid recovery of the patient following sedation cessation is a stated advantage.⁶ Specifically, investigations of shorter periods report complete recovery, whereas studies involving longer sedative periods are more equivocal. The effects of prolonged exposure to this substance are clinically significant: it is not uncommon for patients to be subjected to nitrous oxide-oxygen inhalation for periods of 1 to 2 h.⁷ Therefore, it is of value to assess the extent and duration of any sedative effect, following such prolonged exposure.

Considering the current widespread use of nitrous oxide sedation,⁸ few studies of recovery from this agent have been undertaken. Investigations reporting performance impairment following exposure to nitrous oxide at sedative levels differ widely in study design, concentration used, length of sedation, presence of other pharmacological agents, and types of performance measured.²⁴⁹ Furthermore, no information exists regarding the effects of nitrous oxide-oxygen sedation on subjects who are exposed continuously for periods longer than 45 minutes, although previous investigators have identified the need for such work.⁵⁴⁹¹⁰

The objectives of this study were: (1) to measure recovery of subjects from 90 minutes of nitrous oxide-oxygen sedation followed by 2 minutes of 100% oxygen, using selected neuropsychological tests; (2) to measure recovery of subjects from 90 minutes of nitrous oxide-oxygen sedation, followed by 10 minutes of 100% oxygen, using selected neuropsychological tests; and (3) to investigate the relationship between recovery from nitrous oxide-oxygen sedation and the self-perceived alertness of subjects.

Received April 4, 1988; accepted for publication November 4, 1988.
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ISSN 0003-3006/89/$3.50
METHODS

The subjects were twelve adult dental students, aged 24 to 34 years (x = 27.5). Five of the subjects were male, seven were female. All participants were volunteers informed in accordance with standard practices. The study protocol was approved by the University of Minnesota Committee on the Use of Human Subjects in Research. All subjects completed a medical questionnaire and were healthy at the time of investigation. Subjects were instructed to have a normal night’s sleep prior to the study. They were also instructed to avoid excessive consumption of alcohol or stimulants, such as coffee, and to inform the investigator if they had contracted a respiratory infection.

The experimental procedures were conducted in two adjacent rooms supplied with nitrous oxide and oxygen gases from a central verified supply and delivered nasally via Veriflo NRC-2 Nitrous Oxide/Oxygen Sedation Device (Veriflo Corporation, Richmond, Calif.) according to current guidelines. Each room was maintained with central air conditioning at a constant temperature of 21°C and total room air exchange occurred five times per h.

The participants were placed in the same position and same room for each treatment. In accordance with the technique described by Langa, a flow of oxygen was started at 8 L per minute followed by increments of nitrous oxide while communication with the subject was maintained. Oxygen flow was simultaneously reduced to maintain the total flow of gases of 8 L per minute. Participants were then asked, using the same words on each occasion, to report the onset of any of the following symptoms: a warm feeling, a comfortable glow throughout the body, pleasant sensations, tingling of the fingers, toes, or lips, floating sensations, buzzing, or heaviness of the limbs. When one or more of the symptoms were present, the subjects were asked if they were comfortable. The gas volumes were then recorded and maintained at that level, and sedation was deemed to be present. Induction was accomplished within 4 minutes of initiation. Subjects were not allowed to sleep and were questioned at 10-minute intervals about their comfort and the continued presence of sedation symptoms. Respiration, eye movements, skin color, and body movements were closely observed. Subjects did not have a means of telling time nor was reference made to it by the investigator.

Each subject attended four sessions within a 6-day period. Experimental sessions for each subject were conducted at approximately the same time of day, with an interval of at least 24 h between sessions.

The experimental procedure had two major components: sedation treatments and neuropsychological tests. One of four treatments, denoted by the letters A, B, C, and D, was administered at each experimental session. Treatment A (baseline) involved the subject reclining in a dental chair breathing room air for 90 minutes. For Treatment B, the subject was exposed to 90 minutes of 100% oxygen at a flow rate of 8 L per minute. Treatment C consisted of a 90-minute exposure to nitrous oxide-oxygen at the individually designated sedative level. Sedation was followed by 2 minutes of 100% oxygen. Treatment D also involved a 90-minute exposure of the subject to nitrous oxide-oxygen at the sedative level. Following sedation the subject was given 100% oxygen for 10 minutes. The actual percentages of nitrous oxide used during Treatment C and Treatment D are shown in Figure 1. Treatments B, C, and D were administered blindly.

A within-subject design was used with each subject, bringing the same personality, sex, age, and strategy for doing the tests to each experimental session. Treatment A was administered first to all subjects to overcome the steepest part of the learning curve and served as a control. Treatments B, C, and D were administered in a counterbalanced manner following Treatment A. This was to ensure that any residual practice effect was distributed equally among treatments. Mean values obtained following baseline Treatment A were subtracted from those obtained for Treatments B, C, and D. Two-way analysis of variance was performed on those adjusted values to test for significant differences.

Six neuropsychological tests were used to evaluate recovery following sedation. A Paced Auditory Serial Addition Test was used to measure vigilance, the ability to sustain attention. Subjects were required to add 60 pairs of randomized digits, presented verbally, so that each was added to the digit immediately preceding it. There was a 1.6-second lapse between each digit presen-

Figure 1. Percent nitrous oxide used during sedation treatment C and sedation treatment D for each subject. Mean percentage differences between treatments were not significant (t = 0.49, P > 0.05).
tail. Scores were derived by recording errors of omission and commission. A Controlled Word Association Test measured verbal fluency. This is known to be a sensitive indicator of brain dysfunction.15,17,18 Subjects were asked to give as many words as they could think of beginning with the letters F, A, and S. The Digit Span Test was used to measure immediate memory,15 a function sensitive to drug effects.19 Digit Symbol Tests and Grooved Pegboard Tests evaluated psychomotor performance and a Letter Cancellation Test measured vigilance.20 After completion of testing, subjects were asked, using a uniform presentation, to subjectively report their respective levels of wakefulness. "Drowsy" was placed at the lower end of a 1-to-10 rating scale, while "alert" corresponded to the upper end.

RESULTS

Study results are summarized in Table 1. Paced Auditory Serial Addition Test scores after baseline Treatment A were much poorer than scores after later treatments. Mean scores for Treatment B, C, and D were uniform, showing no significant differences. For the Controlled Word Association Test, a significant difference (P < 0.05) was seen between Treatment B and both nitrous oxide treatments (C and D), indicating decreased performance in subjects after nitrous oxide sedation, regardless of recovery time. The subjects showed no significant differences between treatments B, C, and D on either Digit Forward or Digit Backward. Analysis of data obtained from the Digit Symbol Test showed no significant difference between treatments, although control treatment scores were somewhat lower. "Speed" and "error" elements of the Letter Cancellation Test were considered separately. Subjects showed a difference between treatments on the time component of the test, which approached significance (P < 0.06). Examination of the "error" component of the Letter Cancellation Test showed that the mean scores closely reflected those of the "speed" component and differences between treatment groups were not significant (P < 0.08).

<table>
<thead>
<tr>
<th>Table 1. Test Scores for Each Treatment and Their Significance</th>
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<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Test</td>
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<tr>
<td>Paced Auditory†</td>
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<tr>
<td>Controlled Word** Association</td>
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<td>Digit Span** Forward</td>
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<td>Digit** Symbol Test</td>
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<td>Letter Cancellation† Test (Time)</td>
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<td>Grooved Pegboard (Left)</td>
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<tr>
<td>Grooved Pegboard (Right)</td>
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<td>Alertness Rating** Scale</td>
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Data are mean ± SEM.
* Baseline, room air for 90 min.
† Oxygen (100%) for 90 min.
‡ Nitrous oxide-oxygen for 90 min followed by 100% Oxygen for 2 min.
§ Nitrous oxide-oxygen for 90 min followed by 100% Oxygen for 10 min.
‖ Lower scores represent improved performance.
** Higher scores represent improved performance.
** Significance level refers to treatments B, C, and D only. Analysis was performed on differences between baseline treatment A and the other treatments.
obtained from the Grooved Pegboard Test for the right hand show significant differences (P < 0.01) between Treatments B, C, and D. Best scores were obtained following exposure to oxygen only. Scores diminished after nitrous oxide sedation (Treatment C). This decline was still evident 10 minutes after termination of sedation (Treatment D). Although the difference was less significant (P < 0.06), a similar effect could be seen for the left hand.

DISCUSSION

This was a single blind study. Subjects were not aware of the nature of agent being used during treatments B, C, and D. The nitrous oxide delivery system was out of view of subjects. Changes in nitrous oxide levels (after correct sedative levels had been established), termination of nitrous oxide, or initiation of post-sedation oxygenation were all accomplished without reference to subjects. At no time was direct information given to subjects as to the agent being used. Blinding was compromised to the extent that there was a specific procedural requirement associated with the nitrous oxide treatments that may have distinguished them from the oxygen-only treatment. Specifically to help establish the correct sedative level, subjects were questioned about the symptoms they experienced. This questioning was not done during the oxygen-only treatment, as it would have been deliberately misleading to subjects. In all other respects, treatments B, C, and D were delivered in an identical manner.

Important strengths of this study are its within subjects design and its baseline testing strategy. Since individual factors such as sex, age, personality, and intellectual ability were constant across each trial for each subject, important confounding variables were eliminated. A modified crossover design protected against unwanted learning effects. Treatment A was administered first to all subjects, and, as anticipated, a learning effect did occur on most of the tests. Because treatments B, C, and D were counterbalanced, any residual learning/practice effect was distributed equally among treatments. This counterbalanced design also controlled for unwanted effects due to asymmetric transfer, i.e., the order of treatment.

Each subject underwent testing at the same time each day, having been instructed to maintain normal sleeping habits. This would seem to be important given Folkard’s observation that performance can vary throughout the day. Time-lapse between treatments also warranted consideration. Separating each treatment by at least 24 hours was thought necessary to prevent carryover of treatment effects.

Mean scores for subjects on the Paced Auditory Serial Addition Test were remarkably uniform following the three test treatments B, C, and D. These scores contrast with the much poorer performance by subjects at baseline and is suggestive of a learning effect.

The Controlled Word Association Test showed differences among treatment B, 100% oxygen, and both nitrous oxide treatments. This indicates decreased performance of subjects regardless of recovery time and suggests a disturbance of verbal function, which was still evident 10 minutes after termination of nitrous oxide.

The Digit Span Test is composed of two subtests, Digit Forward and Digit Backward. Because each focuses on slightly different learning/memory functions, they were treated separately, and the scores obtained on each were not combined. In addition to passive span of attention, Digits Backward calls more upon mental manipulation and working memory. Performance on Digit Span is also related to mental tracking ability, the ability to handle several pieces of information simultaneously. Bender has suggested that this process is related to the brain’s normal function and is sensitive to adverse influence. Our failure to demonstrate significant treatment effects using this test are consistent with those of Norton et al., who used a similar subject group and similar levels of nitrous oxide.

For most adults, Digit Symbol is a highly speeded test of psychomotor performance that is relatively unaffected by level of education, memory, or learning and as such was particularly suited to this subject group. It is sensitive to the pharmacologic effects of anesthetic agents. The test was administered for 60 seconds following a practice trial on the first 10 squares. No psychomotor impairment was measured using this test.

The Letter Cancellation Test is a measure of vigilance. This is an essential feature of “street fitness.” Low scores on the Letter Cancellation Test can reflect a general response slowing and inattentiveness. The test itself requires visual selectivity at high speed. Examination of the mean Letter Cancellation Test times for Treatments B, C, and D indicated, however, that this difference was attributable to performance improvement on Treatment D. This unexpected reduction in mean time for the group is not readily explainable. The subjects performed better following nitrous oxide sedation than they did after exposure to oxygen only. Performance improvement may have been associated with 10 minutes of post sedation oxygenation. At least one other study has reported performance enhancement following nitrous oxide sedation. McKercher et al. noted improved reflex reaction times in a group of subjects 15 minutes after sedation had ended.

The Grooved Pegboard Test has been used previously to measure psychomotor performance after exposure to nitrous oxide. Psychomotor performance was signif-
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Significantly impaired following both nitrous oxide treatments, as measured by this test. These findings confirm an earlier report by Korttila et al,9 who, using a finger-tapping test to measure psychomotor performance, reported distinct impairment in hand-eye coordination 12 minutes after cessation of a 45-minute administration of 30% nitrous oxide. They suggested that even in healthy young subjects, total recovery following its inhalation was not instantaneous and concluded that outpatients needed supervision for at least 20 to 30 minutes following nitrous oxide administration. Ayer et al6 used the pegboard test to measure recovery from 35% nitrous oxide sedation in conjunction with dental treatment and could find no impairment immediately post treatment. Their exposure time was, however, only 25 minutes. In a study of the psychomotor effects of nitrous oxide-oxygen sedation on children, Machen et al10 also used the Grooved Pegboard Test. Exposure time was between 25 and 40 minutes, depending on treatment needs. They found no impairment of psychomotor function 3 minutes after termination of the agent. Information available from these earlier studies, together with the present findings, further suggests that recovery of psychomotor function, particularly fine manipulative dexterity, is related to the length of exposure. In our study, the 90-minute sedation period was significantly longer than that used in earlier investigations.2-4,7,9

Subjective methods of assessing sedation status are used extensively. Clinicians typically decide when to dismiss patients on the basis of self-reported “street fitness.” In this study, a rating scale was developed allowing subjects to report their respective levels of “wakefulness.” Examination of the data obtained from this scale revealed that subjects reported themselves to be drowsier following both nitrous oxide treatments than after an exposure to oxygen only. These differences were statistically significant (P < 0.001). The subjective reports following Treatments C and D require further explanation. Subjective evaluation was always done at the end of a testing session. Therefore, following Treatment C, subjective evaluation would have occurred approximately 22 minutes after termination of sedation. Subjective assessment at the end of Treatment D would have been done 30 minutes after ending of nitrous oxide. These findings suggest that subjects may be aware of the nitrous oxide influence for a considerable period after it had ended. It is even more significant when one notes that this influence could not be detected using many of the other cognitive tests.

The tests used were selected to maximize sensitivity to toxic conditions by testing a range of higher cortical functions. They are not independent, as several measure the same components of performance. Examination of the data also shows that for each test there was a similar trend in performance of subjects across all treatments. For these reasons, and because multiple testing was done on subjects, the levels of significance noted should be interpreted with caution.

We conclude that nitrous oxide-oxygen sedation is free from major postrecovery side effects, even after extended exposure. A 90-minute sedation with nitrous oxide-oxygen did, however, cause measurable change in psychomotor function by compromising fine manual dexterity. This impairment was detectable 10 minutes after termination of treatment and may have continued for a longer period. Nitrous oxide-oxygen sedation for 90 minutes caused impairment of verbal fluency, an indication of brain dysfunction. Impaired verbal fluency was detectable 10 minutes after termination of treatment. Subjective reports from the study group reflected their underlying impaired status. Using the tests described, experimenters detected no impairment of vigilance, immediate memory, or mental tracking ability in the group, following prolonged nitrous oxide-oxygen sedation.

While individually the changes measured are not clinically significant, definite negative effects on cortical functions were demonstrated in a highly functioning homogeneous group. A more behaviorally diverse population might be expected to show greater impairment.

ACKNOWLEDGMENT

We thank Dr. JoAnn Boraas for her valuable comments during preparation of the manuscript.

REFERENCES

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