EFFECTS OF TRACE ANAESTHETIC GASES ON BEHAVIOURAL PERFORMANCE OF VOLUNTEERS

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SUMMARY

Nitrous oxide and halothane, in concentrations as low as 50 p.p.m. and 1.0 p.p.m. respectively, caused measurable decrements in performance in psychological tests in healthy male volunteers. Nitrous oxide alone caused similar effects. The functions apparently most sensitive to these low concentrations of anaesthetic agents were visual perception, immediate memory, and a combination of perception, cognition and motor responses required in a task of divided attention to simultaneous visual and auditory stimuli. These effects were absent in subjects exposed to nitrous oxide 25 p.p.m. and halothane 0.5 p.p.m.

Although a causal connection has not been proved in the relationship of organic disease to occupational anaesthetic exposure, a functional impairment has been identified in relation to the inhalation of trace quantities of anaesthetic agents. Performance in psychological tests of perceptual, cognitive and motor skills was decreased in the presence of anaesthetic agents (Bach, Arbit and Bruce, 1974; Bruce, Bach and Arbit, 1974; Bruce and Bach, 1975). In those studies, subjects were exposed to air or air containing anaesthetic agents in concentrations similar to those found in the breathing zone of the working anaesthetist. Following 4 h of such exposure in an ordinary 'oxygen tent' surrounding the subject, he undertook a battery of psychological tests. Significant decrements in performance were shown following exposure to: 500 p.p.m. nitrous oxide in air; 500 p.p.m. nitrous oxide plus 15 p.p.m. halothane in air; and 500 p.p.m. nitrous oxide plus 15 p.p.m. enflurane in air. The tests were performed immediately after the subjects left the exposure tent. Since the anaesthetic agents were exhaled continuously during the tests, the concentrations of agents in the subject's tissues were not those with which he or she had been equilibrated. Concurrent exposure and testing is preferable, in order to assess the dose-response relationship of exposure to performance deficit.

The present studies of halothane and nitrous oxide were undertaken to answer the dose-response question and to establish a lower limit of exposure at which performance decrements were undetectable.

Occupational exposure to halothane is almost always coincident with exposure to nitrous oxide. On the other hand, many techniques of anaesthesia consist of administering nitrous oxide as the only inhalation agent. Accordingly, the present study was designed to detect decrements in performance produced by either a mixture of halothane and nitrous oxide, or nitrous oxide alone. The concentrations selected were those commonly found in the unscavenged operating room. The gas concentrations were then reduced to 10% of the initial values and a second set of studies was made. Finally, a group of subjects was exposed to 5% of the first concentrations, a reduction easily attainable by available methods of scavenging (Bruce, 1973) which can, in fact, lower the concentrations considerably below these nominal figures of halothane 0.5 p.p.m. and nitrous oxide 25 p.p.m.

METHODS

Experimental design

In each of five units of the study 20 subjects were studied twice. Ten were exposed first to air while the other half received the anaesthetic first. There were five such units of exposure:

1. Nitrous oxide 500 p.p.m. + halothane 10 p.p.m.
2. Nitrous oxide 500 p.p.m.
3. Nitrous oxide 50 p.p.m. + halothane 1.0 p.p.m.
4. Nitrous oxide 50 p.p.m.
5. Nitrous oxide 25 p.p.m. + halothane 0.5 p.p.m.

Thus, 100 subjects were exposed to anaesthetic gases and each was tested twice. Each subject was exposed and tested during the same hours of the same day, 1 week separating the two exposures.

Only male subjects were used, since there are data suggesting an increased risk to the pregnant female...
occupationally exposed to anaesthetic gases. The use of females would have necessitated testing each subject for pregnancy before each exposure, greatly complicating the experiment. The subjects chosen were all in the age range 20–30 yr, most of whom were dental, medical or law students at Northwestern University. The others were graduate students or technicians and all were questioned very carefully about exposure to anaesthetic agents. None of the subjects had been exposed as a patient within the previous 3 months or in the course of occupation within the previous 6 weeks. The subjects completed a questionnaire concerning their general health, any recent acute or existing chronic illnesses, and their habits with respect to alcohol and drug use. All the studies began at 9 a.m. The subjects were allowed coffee or tea for breakfast but were told to have the same amount before each test session and they were given no beverages during the time spent in the laboratory.

Anaesthetic administration
Compressed air, passed through a filter, was delivered at a flow rate of 8 litre/min into a standard anaesthetic circle system, composed of a soda-lime canister for absorbing carbon dioxide, a reservoir bag, the mask worn by the subject, lightweight plastic breathing tubes that delivered and removed gas from the mask and a "pop-off" valve to vent overflow gases from the circle. The mask was fashioned from an inhalation therapy mask. No subject complained of discomfort in wearing the mask and those who needed to wear spectacles could do so. Low gas flows from one or both of two cylinders containing respectively 10% nitrous oxide in air and 1% halothane in nitrogen were introduced into the main, carrier flow of air. The subject was never able to tell when the anaesthetic was being administered, either by looking at the apparatus or by smell.

During the first 2 h of every exposure, 10 ml of gas was sampled from the inspiratory limb of the breathing circle into a gas-tight glass syringe, which was then capped. If the subject was breathing air only, the sample was later discarded, but at the outset the samples were analysed to check that there was no residual anaesthetic agent in the circuit to contaminate subsequent air exposures. This was never the case but, as a safeguard, the air flow was always left on overnight. For the analysis of nitrous oxide and halothane, the samples were injected into a gas chromatograph. In the first phase of the study, in which nitrous oxide 500 p.p.m. and halothane 10 p.p.m. were studied, we used an F and M (Model 500) chromatograph. This was replaced later by a Packard Becker (Model 419) gas chromatograph equipped with $^{63}$Ni and $^3$H electron capture detectors, which was much more sensitive: its lower limits of detection are 5 p.p.m. nitrous oxide and 0.001 p.p.m. halothane. At about 1 h and 45 min from beginning the exposure, samples of the subject's end-expired air were also taken for analysis. The subject removed the mask, exhaled to the end-tidal position, then forcefully exhaled as much as possible, the gas being sampled from the pharynx into a gas-tight glass syringe. This sampling was performed for every exposure, even in the air condition. Ratios for inspired and end-expired contents of the anaesthetics were calculated. After the subject had begun breathing the appropriate gas mixture, he was cautioned not to sleep and was allowed to read if he wished. Two hours later, testing began.

Psychological tests
These tests (fig. 1) were chosen to assess anaesthetic effect on several indices of performance.

<table>
<thead>
<tr>
<th>Hours of Exposure</th>
<th>Test</th>
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<tr>
<td>1</td>
<td>Tachistoscope</td>
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<td>Raven matrices</td>
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<td></td>
<td>O'Connor dexterity</td>
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<tr>
<td>3</td>
<td>3-min audiovisual</td>
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<tr>
<td>4</td>
<td>60-min vigilance</td>
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<td>7-min audiovisual</td>
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<td>Digit span</td>
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Fig. 1. Sequence of exposure and testing.
Tachistoscope. This is a test of visual acuity. For 50 ms, the subject saw a nine-square grid containing four, five or six filled black circles. After each presentation, he entered the position of the circles on a blank grid. He viewed each of 10 grids twice, for a maximum correct response of 20. Each subject viewed two practice patterns on the tachistoscope before his first exposure in the study.

Raven Matrices. This tests ability to recognize a pattern of changes in a sequence and to decide logically which pattern would be expected to appear next. Twenty patterns were selected from the Raven Progressive Matrices Test, 10 for each of the two sessions. Each pattern of one set was matched with one in the second set for which the scores accompanying the set indicated a pattern of equal difficulty. Even though care was taken to match the two tests for difficulty, our subjects found the second form to be the more difficult. This was corrected in all phases of study after the first phase (halothane 10 p.p.m.; nitrous oxide 500 p.p.m.): half of the subjects received one form first and the other half received the remaining form first. The subjects were given printed instructions containing two examples of practice patterns which were not used in subsequent testing.

O'Connor Dexterity test. In this test, the subject places three pegs in each of 100 holes as rapidly as possible using only his preferred hand. As a large learning effect usually occurs in a motor task, each subject filled the entire board in the practice session. His time was recorded at this session, but these data were not used in the analyses. The task during the testing session consisted of 3 min in which to fill as many holes as possible with three pegs each. The number of holes filled correctly during this time period was recorded and the data analysis assumed that the better the eye-hand co-ordination of a subject, the more holes he would fill.

Audiovisual task. This has been described previously (Bach, Arbit and Bruce, 1974; Bruce, Bach and Arbit, 1974; Bruce and Bach, 1975), but was modified slightly during these studies by decreasing the difference in beat frequency of the sound stimulus and by putting the visual pattern on one beam of the oscilloscope, rather than two. A 4-channel FM instrumentation tape recorder (Hewlett-Packard, Model 3960) played a pre-recorded test pattern to the earphones and oscilloscope. The subject responded by pushing one of four buttons on a battery-powered response box. These were recorded on an empty channel of the tape as 0.5 or 1 V, positive or negative square waves. The auditory signal was the clicking of a metronome either at 100 or 160 beat/min. The visual signal was a flat line or a pattern of ventricular fibrillation recorded from an electrocardiographic simulator. Thus there was a 2 x 2 design: visual flat line, auditory slow; visual flat line, auditory fast; visual spikes, auditory slow; visual spikes, auditory fast. In the 3-min task, there were 10 changes to each of the four conditions, making a total of 40 changes. The task later lasted 7 min and required the detection and appropriate response to 100 changes, 25 to each of the four conditions. The subject responded as quickly as possible to each change by depressing a button corresponding to the condition to which the change had been made. A set of instructions for this task was dictated on the sound channel of the tape before the test was begun. The subject practiced for 15 min before the test began, a time previously shown to allow the asymptote of performance to be achieved and retained for 1 week. The test was given in two segments,—3 min at this point in the test sequence and then 7 min after the vigilance task. After the subject's departure, the tape was replayed through a Grass polygraph, giving a printout of both the test and the subject's performance. Scoring was manual and the mean reaction time was computed and used as the measure of performance. There were 97% or more correct responses. The rare error was not scored. With manual scoring, it was possible to see where the subject made an incorrect response, recognized this, and immediately pushed the correct button. Automatic scoring would have counted this as an error, whereas in the present studies it was counted as correct and the time to the correct response was measured. The lag time for the response from the subject to be encoded on the tape was estimated by the following procedure: a response pulse was generated and sent either directly to the input of the polygraph or through the tape recorder to the polygraph. The difference in arrival time, representing the lag time in the recorder, was constant at 0.3 s and this was subtracted from all data to derive real reaction time. The accuracy of scoring itself was estimated to be ± 0.02 s.

Vigilance test. For 60 min the subject watched a continuous display of a normal e.c.g., recorded previously from an e.c.g. simulator, on an oscilloscope. Twelve times during this hour, at intervals from 3 to 8 min, a brief (1-2 s) change to a pattern of atrial fibrillation was interposed among the otherwise normal complexes. Recorded instructions were heard by the subject while he practiced this task for 3 min (during the practice session changes occurred more
often than during testing). His response was simply to depress a button when he saw the change occur. The mean reaction time was used as the dependent measure for this test since it was soon evident that the subjects were able to detect every change.

Digit span. This test was used to assess immediate memory. Since the subject had to speak to the experimenter, it was performed last and the subject was allowed to remove the mask. He was given a standard series of numbers, from the Wechsler Adult Intelligence Scale, which had to be repeated correctly to the experimenter. The series increased in length (maximum: 9 digits forward, 8 digits backward). The subject had to recall them both in the order given and in the opposite order. The mean number of digits recalled correctly was scored for each test session.

Statistical treatment of these data was by analysis of variance whereby the relative significance of anaesthetic effect and practice effect and their interaction could each be evaluated (Winer, 1962). The null hypothesis was that neither anaesthetic nor practice (order of exposure) would cause changes greater than that expected by chance alone. An additional analysis was made of the correlation between correctly guessing which condition they were in, and audiovisual test performance, in the subjects exposed to nitrous oxide 500 p.p.m. and halothane 10 p.p.m. (Underwood, Duncan and Taylor, 1954).

RESULTS AND DISCUSSION

The gas analyses (table I) showed considerable variation in the anaesthetic concentrations of end-expired air samples. This was particularly true of the first group of subjects, exposed to nitrous oxide 500 p.p.m. plus halothane 10 p.p.m., and may explain why their test scores were actually better than those exposed to 500 p.p.m. nitrous oxide only in a subsequent set. At first, the tightness of mask fit was not checked closely, and a few subjects had very low end-expired nitrous oxide concentrations. It would appear from these data that the measured expired nitrous oxide concentrations correlate closely with decrements in test scores.

The test data (table II) indicate that measurable and statistically significant decrements in performance may result from exposure to anaesthetic agents in concentrations as small as 50 p.p.m. nitrous oxide, a figure well below those measured in studies of anaesthetic content of operating room air. The tests were not equally sensitive to the effects of the anaesthetic gases, varying from the extreme sensitivity of the audiovisual task to no change in the O'Connor Dexterity test.

Visual perception was impaired by anaesthetic agents, as shown by the effects on both the tachistoscopic and audiovisual tasks. This was not confirmed by the vigilance task, however, which was primarily a test of visual perception. Perhaps the infrequent changes in that task, compared with the rapid
reactions required in the tachistoscopic and audiovisual tasks, allowed the subject to focus his attention more effectively on the changes requiring a response. The improvement in vigilance response in the group exposed to nitrous oxide 50 p.p.m. and halothane 1 p.p.m. cannot be explained.

The ability to reason logically was relatively resistant to the effect of anaesthetic gases, as judged by the Raven Matrices test. This function may be ingrained so deeply that it is relatively insensitive to stressors. Alternatively, there might exist a different test which would have been sensitive. The results are nevertheless consistent with the clinical impression that an anaesthetist who is not at his best, either from fatigue or other causes, knows what to do but may be slow in appreciating the situation in which he should do it.

The negative results from the O'Connor Dexterity tests suggest that manual dexterity is resistant to those concentrations of anaesthetic agents. Of real concern, however, is the high sensitivity of immediate memory as shown in the Digit Span test. This is a very important function of the anaesthetist, who is usually the only person in the surgical team who is required to observe the patient's general condition on a minute-by-minute basis. Of all the tests, the one most closely allied to the anaesthetist's work was the audiovisual task, where two modes of perception were challenged continuously and rapidly, requiring recognition of changes, decisions about their nature and appropriate responses. This test was the most sensitive of all to the anaesthetic effect.

The job performance of an anaesthetist cannot presently be measured objectively. The 100 subjects in the present study were not anaesthetists, 87% of them being postgraduate students in medicine, dentistry, law or biomedical sciences. They were highly motivated "achievers" who were accustomed to performing at a high level of excellence and who, accordingly, gave remarkably uniform scores on the tests. The error values in the statistical analyses were very small, allowing significance to be assigned to differences as small as 5% in mean scores. Clearly, the choice of subjects is important, and would be "tolerance" to the effects of chronic exposure to traces of anaesthetic agents. The present study does not show that the performance of an anaesthetist is affected adversely by occupational exposure to anaesthetic agents. It only suggests strongly that this could be the case.

ACKNOWLEDGEMENT

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REFERENCES


EFFETS DES TRACES D'ANESTHESIANTS SUR LE COMPORTEMENT DE VOLONTAIRES

RESUME
Le protoxyde d'azote et l'halothane en concentrations de seulement 50 p.p.m. et 1 p.p.m. respectivement, ont provoqué des baisses mesurables de performances au cours des tests psychologiques effectués sur des volontaires mâles en bonne santé. Le protoxyde d'azote seul a provoqué des effets similaires. Les fonctions qui ont apparemment été les plus sensibles à ces faibles concentrations d'agents anesthésiants ont été la perception visuelle, la mémoire immédiate et une combinaison de perception, de connaissance et de réactions motrices requises pour une tâche exigeant une attention divisée à des stimulants visuels et auditifs simultanés. Ces effets n'ont pas été constatés sur les sujets soumis à des doses de 25 p.p.m. de protoxyde d'azote et de 0,5 p.p.m. d'halothane.

AUSWIRKUNGEN VON NARKOSEMITTEL-SPUREN AUF DIE VERHALTENSWEISE VON FREIWILLIGEN
ZUSAMMENFASSUNG
Stickstoffoxyd und Halothan in so niedrigen Konzentrationen wie 50 p.p.m., bzw. 1,0 p.p.m. verursachten messbare Leistungsverringerungen bei psychologischen Tests mit gesunden, männlichen Freiwilligen. Stickstoffoxyd allein verursachte ähnliche Effekte. Offenbar am empfindlichsten auf diese niedrigen Konzentrationen von Narkosemitteln waren visuelle Aufnahmefähigkeit, unmittelbares Gedächtnis sowie eine Kombination von Aufnahmefähigkeit, Erkenntnis und motorischen Reaktionen, wie sie bei einem Test mit geteilter Aufmerksamkeit auf gleichzeitige visuelle und auditiv stimulieren erforderlich waren. Diese Wirkungen zeigten sich nicht bei Versuchspersonen, denen 25 p.p.m. Stickstoffoxyd und 0,5 p.p.m. Halothan verabreicht worden war.

LOS EFECTOS DE ANESTESICOS INDICIARIOS SOBRE EL COMPORTAMIENTO DE SUJETOS VOLUNTARIOS
SUMARIO
El óxido nitroso y el halotano, en concentraciones tan bajas como 50 p.p.m. y 1,0 p.p.m., respectivamente, produjo deterioros mensurables en la ejecución de pruebas psicológicas en voluntarios varones sanos. El óxido nitroso, por sí solo, produjo efectos parecidos. Las funciones más sensibles aparentemente a estas bajas concentraciones de agentes anestésicos fueron la percepción visual, memoria inmediata, y una combinación de percepción, razonamiento cognitivo y respuestas motoras requeridas en una tarea de atención dividida ante estímulos simultáneos visuales y auditivos. Tales efectos no ocurrieron en los sujetos expuestos a óxido nitroso 25 p.p.m. y halotano 0,5 p.p.m.