THE EFFECTS OF NITROUS OXIDE ADMINISTRATION IN THE HEALTHY ELDERLY: N_2O ELIMINATION AND ALVEOLAR CO_2

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SUMMARY

Healthy young and elderly males were administered sedative concentrations of nitrous oxide/oxygen (N_2O/O_2) under a protocol designed to mimic that used in a dental operatory. Samples of end-tidal expired gas were taken at the end of 30-minutes inhalation of, and periodically for 70 minutes after withdrawal from, nitrous oxide/oxygen. Samples were analyzed to monitor the decline of alveolar nitrous oxide levels and any changes in alveolar carbon dioxide levels, to determine if there were any age-related differences. The fall in alveolar N_2O following cessation of administration was rapid, and in a double-exponental manner as was expected. No age-related difference in N_2O decline was observed. Alveolar carbon dioxide (CO_2) levels were lower and more variable in the elderly group. Both groups exhibited elevated CO_2 levels at the end of the N_2O period, and an unexplained rise in CO_2 at approximately 30 min post N_2O.

Both acute and residual psychological and psychomotor effects have been noted with nitrous-oxide analgesia.[1-5] As part of a larger study to examine and compare effects of N_2O on psychomotor and cardiovascular performance of young and elderly subjects, it was deemed necessary to follow the decline in exhaled N_2O levels in both groups following a period of nitrous oxide-oxygen (N_2O-O_2) inhalation designed to mimic that given in a dental operatory. It has been shown that there are both anatomical and functional changes in the respiratory system that can be attributed to aging,[6] as well as age-related differences in response to inhalation anesthetic agents.[7] However, most of the studies involving the effects of N_2O administered in analgesic doses have dealt with young subjects. Therefore, the specific purposes of this study were to (1) determine and compare the levels of N_2O which were required to achieve a simulated dental N_2O-O_2 inhalation sedation in both young and elderly subjects; (2) monitor and compare the decline in alveolar N_2O levels during recovery from N_2O-O_2 inhalation in the two groups; and (3) compare respiratory function in the young and elderly during and after N_2O-O_2 inhalation by measurement of alveolar carbon dioxide (CO_2) levels. The correlation of psychomotor performance and of cardiovascular response with sedative levels of nitrous oxide will be discussed elsewhere.[8,9]

It is important to stress that our study was designed to measure the experimental variables *under a simulated dental setting.* Nitrous oxide was therefore administered at a concentration that was felt to be clinically useful and appropriate for each subject.

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MATERIALS AND METHODS

Gas analysis. The instrumentation (Varian Aerograph Model 90 P3), calibration, and procedures used in this laboratory for analysis of respiratory gases have been discussed in earlier reports.[10,11] As we were primarily interested only in the subjects' N_2O and CO_2 levels, and needed a rapid sample throughput in the gas chromatograph, only a single 8-ft × ⅛-in o.d. column packed with 80/100-mesh Porapak Q was used and attached in the normal manner. An analysis for N_2O and CO_2 in a sample was completed in about 3 min.

Subjects tested. The 20 subjects who took part in this study were all volunteers and participated after giving informed consent. They were divided into two groups: nine healthy elderly males (age 63-69, $\bar{X} = 64.5 \pm 0.7$ yr), and a control group of eleven healthy young adult males (age 22-30, $\bar{X} = 25.4 \pm 0.8$ yr). The elderly belong in the gerontological group commonly called "young-old", that is, all were below age 75. The word "healthy" in regard to this study indicates that subjects had no diagnosed illness, and were not presently taking any medications. The elderly males were selected from a pool of elderly volunteers registered with the University of Kentucky — Sanders-Brown Center on Aging. The control group were primarily drawn from a dental student population.

Administration of gases. Subjects were seated in a dental chair and the following sequence of gases from a standard dental analgesia machine (Quantiflex-M.D.M.) was administered using an ordinary nasal mask: (a) 100% O_2 for 5.0 min. (b) A gradually increasing level of N_2O up to a clinically significant level for each subject; the peak N_2O level, which generally took 3-5 min to attain, was determined by each subject's subjective reporting of clinical symptoms to an attending oral surgeon — the same procedure as is employed in dental practice. (c) The peak N_2O level was maintained for each subject for 30 min; total flow of N_2O and O_2 was kept at about 6 1/min. (d) The N_2O period was followed by 5.0 min on 100% O_2; and finally (e) the subject was allowed to breathe air. On a previous visit, each subject had been introduced to the inhalation procedures and to the sedative and euphoric effects of N_2O. It was emphasized that nasal breathing through the mask was essential, but we did not attempt to control mouth breathing by use of a full face mask.

Other tests performed. No dental procedures were performed on the subjects during the course of these experiments. However, the subjects were connected to physiological testing equipment to measure heart rate, digit blood-flow, respiratory rate, skin temperature, and blood pressure before and during inhalation of N_2O.[9] Subjects also underwent psychomotor-skills and short-term-memory testing during the protocol.[8]

Sampling of end-tidal expired gases. Two samples of end-tidal gas were taken within one to two minutes of the end of the 30-min N_2O period using a technique described previously;[10] these reflected the level of alveolar N_2O attained in the subjects. After N_2O was withdrawn and the subjects were breathing 100% O_2, usually 6 gas samples were taken fairly rapidly: at approximately 0.5, 1, 3, 4, 9, and 10 min after the end of the N_2O period. After that, duplicate samples were generally taken about 0.5 min apart at 10-min intervals, from 20 min through 70 min after the end of the N_2O period. Exact sampling times were recorded for each subject. Generally, therefore, 20 gas samples were taken per subject — two just prior to the end of the N_2O period, and 18 during the N_2O-elimination period.

Statistical analysis techniques. To compare the alveolar CO_2 levels in the two groups as a function of time, a two-way analysis of variance (ANOVA) with repeated measures on the time factor was performed using the SAS General Linear Models (GLM) Procedure.[12] The GLM was used rather than the simple ANOVA procedure due to unequal cell frequencies. Least squares lines were fit to the % N_2O exhaled vs. time plots (double-exponential decay) in the conventional manner to obtain, from the slopes of the lines, the half-lives ($t_{1/2}$'s) as well as their associated uncertainties (standard deviations).

RESULTS

After 30 min on a sedative concentration of N_2O, the alveolar N_2O levels of both the elderly and the young subjects decreased in a conventional, double-exponential manner.[13] Figure 1 illustrates a typical decline in the level of alveolar N_2O as a function of time. There was an initial very rapid drop in the expired N_2O level such that after 5 min on 100% O_2 and 5 min on room air, the N_2O level had usually decreased to below 1% by volume. A slower process then became dominant, such that the expired N_2O levels were reduced to about 0.1% after 70 min. Careful analysis of the data indicated there was a very sharp step decrease in alveolar N_2O in the first 30 sec after changing to 100% O_2 in both groups. This was then followed by what appeared to be a conventional double-exponential decay.[13] The early washout phenomenon can be seen in Fig. 1 in that the sum of the intercepts at time zero (withdrawal of N_2O) is less than the measured N_2O level. The initial very rapid drop results from ventilatory washout.[14]

Averages for the half lives for N_2O elimination for the elderly and the control (young) group are shown in Table 1. The average half lives for the elderly and the young are comparable within statistical limits. There were no significant differences in the variances by the F-test ($P >> 0.05$). Given the equality of variances, there are no significant differences in $t_{1/2,1}$ and $t_{1/2,2}$ by the t-test ($P > 0.2$ and $P > 0.7$, respectively). The standard deviations in the average values for $t_{1/2,1}$ and $t_{1/2,2}$ for both groups are significantly larger than the pooled standard deviations for all the measurements within a set; by the F-test, generally $P < 0.01$. This indicates there is a significant person-to-person variation in the $t_{1/2}$'s over and above the measurement error and the uncertainty resulting from the linear least-squares fitting of the data.

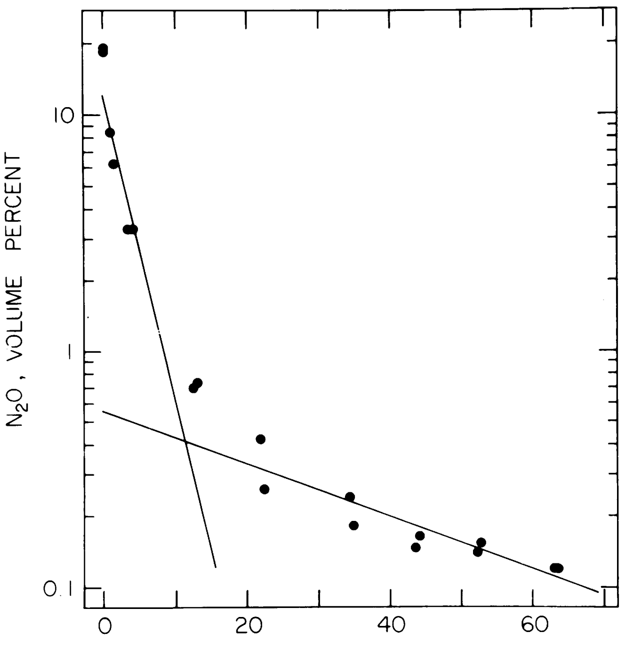

Fig. 1 — A typical N_2O-elimination curve. Time O is the point at which the subject (elderly, in this case) was switched over from breathing (40%) N_2O to 100% O_2. The two lines are (logarithmic) linear least squares lines fit to the data.

Carbon Dioxide Levels. The data in Table 1 indicate that there is a significant breath-to-breath variation in the CO_2 levels over and above the normal measurement error for both groups during the recovery period. The pooled standard deviation for the CO_2 measurements (the "within individual" variation) is about ±9% relative for the elderly and about ±7% relative in the control group. From analysis of a number of other experiments, the normal chromatographic *measurement* error to be expected in this case is about 4% relative. Therefore, there is a significant breath-to-breath variation in the CO_2 level within an individual, which may be due to sampling error.

In contrast to the similarity of results for the rates of elimination of N_2O, the elderly group exhibited a significantly higher variance in the average of their expired CO_2 levels than did the control group; by the F-test, $P < 0.01$. This indicates that the average CO_2 output of the elderly group during the recovery period varied substantially more than that of the control group. In addition, the pooled standard deviation (s_p) for all the measurements within the elderly group is also significantly higher than for the control group ($P < 0.05$), indicating a greater breath-to-breath variation for the individuals within the elderly group. By the F-test, there was no significant difference in the control group in the standard deviation between individuals vs. the s_p for all measurements within that group ($P >> 0.05$); whereas there is a significant difference for the elderly ($P < 0.05$) — the variation between individuals being larger.

Figure 2 illustrates the average CO_2 levels for the elderly and for the young as a function of time during the recovery period. The standard deviations for the data points are fairly large, ranging from ±0.24 to ±0.51% CO_2 for the young, and ±0.46 to ±0.80% CO_2 for the elderly. The data in Figure 2 suggest that, on average, the elderly exhale a lower level of CO_2, and that there were certain times during the protocol when the CO_2 levels expired were different from other times. A two-way ANOVA performed on the data confirmed that the elderly do have a lower average CO_2 output, and that there was a significant ($P < 0.001$) time effect. Duncan's Multiple Range test indicated that the CO_2 levels at $t = 0$ min, i.e., at the end of the N_2O period, and $t = 30$ min, were significantly higher than those at all the other times (and all these were statistically the same). Because all the CO_2 levels within the control group were statistically equal, the high CO_2 levels at $t = O$ and $t = 30$ min for the total 20 subjects were due primarily to the elderly.

The ANOVA also indicated there was no significant ($P > 0.3$) group (elderly vs young)-time interaction. That is, whatever the dependence of CO_2 level on time may be, it is the same for the elderly and for the young.

Levels of N_2O Inhaled and Expired. In general, there were no significant differences ($P > 0.05$) in the average levels of N_2O at which the two groups, elderly and control, were maintained for the 30-min period. Nor was there any significant difference in the percent N_2O (by volume) exhaled by the two groups at the very end of the N_2O period. The standard deviation in the respective values for elderly and control groups are comparable by F-tests ($P > 0.05$). Along with these results, Table 2 displays the fraction of N_2O the subjects were exhaling relative to the "expected" exhaled level. The average values for the elderly and control groups were not significantly different ($P > 0.1$).

It should be noted that the subjects were not fully saturated with N_2O by the end of the 30-min inha-

TABLE 1

HALF-LIVES FOR THE ELIMINATION OF N_2O AND AVERAGE CO_2 LEVELS IN END-TIDAL EXPIRED GAS

		Half-Life		
Group	Measurement	$t_{1/2,1}$, min	$t_{1/2,2}$, min	% CO_2
Elderly	Avg. Value, $\bar{X}$	1.853	20.08	4.300
(n=9)	Std. dev., s	±0.369	±3.01	±0.639
	Range, R	1.34-2.35	17.0-26.7	3.64-5.30
	Pooled std. dev. of all measurements, s_p	±0.198	±1.78	±0.405
	ν for s_p*	61	94	169
Control	Avg. value, $\bar{X}$	1.684	19.58	4.815
(n=11)	Std. dev., s	±0.260	±3.98	±0.283
	Range, R	1.13-2.09	14.1-27.3	4.40-5.31
	Pooled std. dev. of all measurements, s_p	±0.184	±1.60	±0.344
	υ for s_p	61	107	182

*υ = degrees of freedom

lation period. The half-life for the slower elimination process illustrated in Figure 1 is about 20 min (Table 1). Assuming the buildup of N_2O in various body compartments mirrors the elimination process, the fraction of the "expected" level of N_2O the subjects should actually be expiring at the end of 30 min inhalation ought to therefore be a bit lower than expected for a subject at steady state.

On inspection of the individual values for the fraction exhaled, two subpopulations of subjects, each of which contain both elderly and young, were identified: one subpopulation (Group B) was exhaling about 30-50% of that expected, the other (Group A) was exhaling about 70-85% of the expected level. This is more clearly illustrated in Figure 3 in which the % N_2O exhaled by each subject is plotted as a function of the % N_2O being inhaled. There are two classes of data points in this plot, an upper set (A) of 12 points (4 elderly and 8 control subjects) that appear to be fairly linearly distributed, and a lower set (5 elderly and 3 controls) that are less linearly distributed. The two straight lines on the plot are linear-least-squares lines fit to the two sets of data points. Both lines go through zero, within experimental error; correlation coefficients are quite good — $r = 0.95$ for the upper line and 0.78 for the lower. Linear-least-squares fits to the 9 points for the elderly alone, to the 11 points for the control alone, or to the combined 20 points indicate very poor correlation ($r = 0.4 - 0.5$). Moreover, these latter forced linear fits have a large positive intercept for % N_2O exhaled, which is not logical. To a first approxima-

TABLE 2

AVERAGE N_2O LEVELS INHALED AND IN END-TIDAL EXPIRED GAS AFTER 30-MINUTES INHALATION OF N_2O/O_2

Group	Measurement	% N_2O Inhaled †	% N_2O Exhaled‡	Fraction of "expected" level of N_2O exhaled§
Elderly	Average Value, $\bar{X}$	39.2	19.6	0.54
(n = 9)	Std. deviation, s	±9.6	±6.8	±0.17
	Range, R	24.5-49.2	7.9-30.8	0.31-0.74
Control	Average Value, $\bar{X}$	33.3	20.4	0.66
(n = 11)	Std. deviation, s	±5.9	±4.6	±0.13
	Range, R	25.6-45.2	13.4-26.3	0.45-0.83

† The level of (dry) N_2O in O_2 actually inhaled by each subject was measured by the same procedures used to determine the % N_2O exhaled because of the notorious inaccuracy of the dial readings on dental analgesia machines. For each subject, the level inhaled was the average of 3-4 measurements.

‡ For each subject, this was generally the average of two separate measurements on samples taken near the end of the N_2O period.

§ The level of N_2O expected to be exhaled by each subject was calculated by assuming N_2O was an inert gas, and simply correcting the (dry) level of N_2O inhaled for the dilution effect of water vapor on the level of N_2O in exhaled gas. This was then divided into the % N_2O actually exhaled near the end of the N_2O period to get the fraction of the level expected.

TABLE 3

AVERAGE N_2O LEVELS INHALED AND IN END-TIDAL EXPIRED GAS AFTER 30-MINUTES INHALATION OF N_2O/O_2

Group	Measurement	% N_2O Inhaled	% N_2O Exhaled	Fraction of "expected" level of N_2O exhaled
A	Average Value, $\bar{X}$	33.4	22.6	0.72
(n = 12: 4 elderly,	Std. deviation, s	±6.4	±4.7	±0.05
8 young)	Range, R	24.5-44.5	15.9-30.8	0.67-0.83
B	Average Value, $\bar{X}$	39.7	16.2	0.43
(n = 8: 5 elderly,	Std. deviation, s	±9.3	±4.7	±0.08
3 young)	Range, R	24.5-49.2	7.9-22.3	0.31-0.50

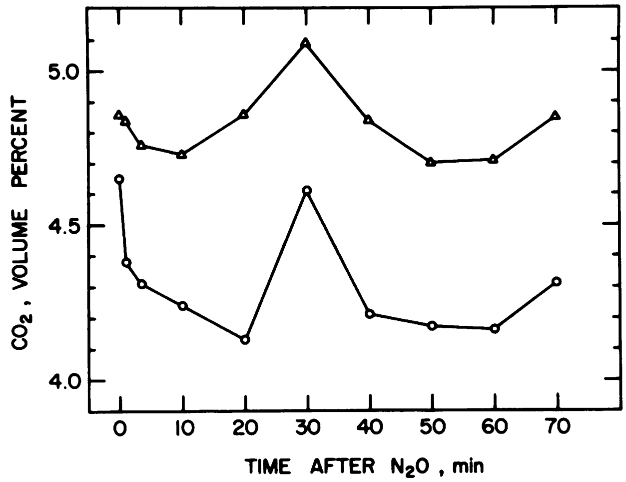

Fig. 2 — Variation in average CO_2 levels in end-tidal respired gas as a function of time after breathing a clinically significant level of N_2O for 30 min. Circles: Averages for a group of 9 elderly subjects. Triangles: Averages for a group of 11 young subjects (only 8 and 7 values for times 20 and 30 min, respectively). The typical standard deviation of the mean for any one point in time is ± 0.21 for the elderly and ± 0.12 for the young.

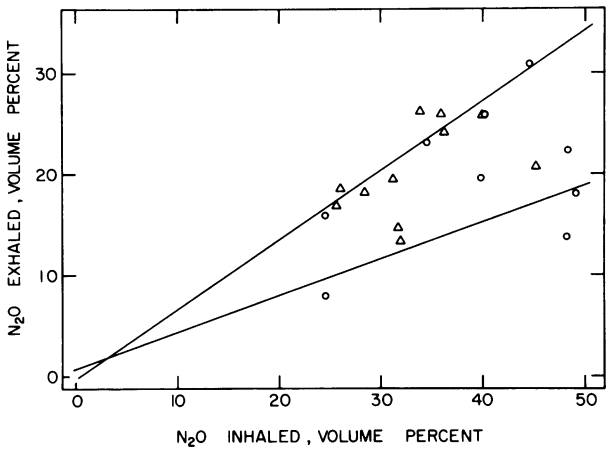

Fig. 3 — Percent nitrous oxide (by volume) in end-tidal gas as a function of the percent nitrous oxide inhaled for a 30-min period, sampled immediately at the end of that period. Circles: 9 elderly subjects; Triangles: 11 young subjects. The straight lines are linear-least-squares fits to the two sets of data points. For the upper line, the correlation coefficient, r = 0.95; for the lower line, r = 0.78.

tion, if all subjects breathed N_2O for the same period of time, the level exhaled would be expected to be some constant fraction of that inhaled — that is, a straight line with zero intercept for a plot such as that in Fig. 3.

Table 3 summarizes the results for these two subpopulations. On average, the young and elderly subjects making up Group A were inhaling about 33% N_2O, those in Group B about 40% N_2O; the latter value is higher, but not significantly so ($P = 0.09$). On the other hand, at the end of the N_2O period the subjects in Group A were exhaling a significantly ($P < 0.01$) higher level of N_2O — about 23% vs. about 16%.

DISCUSSION

Carbon Dioxide Levels. On average, the elderly have a lower CO_2 output than the control group during the recovery period after N_2O/O_2 inhalation (Fig. 2). Relative to their average CO_2 output, the elderly have an elevated CO_2 level immediately at the end of the 30-min N_2O inhalation period. Others have attributed the general increase in alveolar CO_2 level during N_2O inhalation to a second gas effect[15] or to an increase in physiologic dead space.[16] However, the exact mechanism remains controversial. There does not seem to be, however, any clear explanation for the surprising increase in CO_2 levels at 30 min after the end of the N_2O period. At this point, the subjects are typically exhaling only about 0.2% N_2O. After 5 min of breathing 100% O_2 and 5 min of breathing air, subjects are generally exhaling less than about 1% N_2O. Therefore, it is questionable to ascribe any significant changes in CO_2 output after 10 min to the effect of the remaining low level of N_2O. The general trend of the data for the control group does seem to follow that of the elderly — an initial decrease in CO_2 level followed by a (broader) maximum at about 30 min; but none of the differences for the control group is significant.

Although we did not monitor other respiratory parameters that would allow a thorough analysis of respiratory control, our findings suggest that there may be some disturbance in the control of alveolar CO_2 level following N_2O inhalation. We are unable to explain the increase seen 30 min into the recovery period. The increased CO_2 variability and high CO_2 levels at 0 and 30 min in the elderly may indicate some loss of stability in respiratory control with age.

We had earlier reported[11] that CO_2 levels for a group of young subjects did not change significantly (over an air-breathing control period) on inhaling 100% O_2 and during the first 10 min of breathing 40% N_2O. This study extends those findings for a longer N_2O-inhalation period, and into the recovery period.

Expired N_2O Levels. There was no difference in the decline in N_2O levels between the young and the elderly groups following the 30-minute N_2O inhalation. The initial (30-sec) rapid decline has been attributed to ventilatory washout, the second phase to removal of N_2O from highly vascular tissue, and the third phase to removal from relatively avascular sites.[14]

Because the subjects were breathing the N_2O/O_2 mixture for 30 min and the two compartments of the elimination curve for N_2O have half-lives of about 2 and 20 min (see Fig. 1 and Table 1), it would be expected that the subjects ought to be exhaling something close to the expected level. Clearly, this is not the case: The subjects were exhaling only about 30 to 80% of the N_2O expected. There are at least two possible explanations for this finding. One is that there was a greater saturation of the fatty tissues (with N_2O) in Group B (Fig. 3) than in Group A, such that Group B would be exhaling a lower fraction of the gas inhaled. However, Eger[17] has calculated that saturation of the fatty tissues with an alveolar concentration of N_2O would require inhalation of the gas for 2 to 2½ hours. Therefore, with the 30 min inhalation for all subjects in this study we are safe in assuming that in neither Group A nor Group B was there equilibrium of N_2O with the fatty tissues. A far simpler explanation for the observations plotted in Fig. 3 is that Group B was characterized by mouth breathers, whereas the subjects in Group A, following the instructions they were given, breathed through the nasal mask. This could account for the closer match of exhaled to inhaled levels of N_2O in Group A. It would appear to be of clinical interest that our subjects, both young and old, fell into these two groups. The implications for the administration of N_2O-O_2 by nasal mask in the dental office are that any given patient may be receiving far less N_2O than the dentist realizes.

CONCLUSIONS

Within experimental error, both young and elderly healthy male subjects, on the average, report clinically significant symptoms at the same level of administered N_2O; and after 30 minutes inhalation of N_2O, both groups were exhaling equivalent levels of N_2O. Both groups eliminated N_2O from their systems at similar rates. There was a significant person-to-person variation in these rates over and above the experimental measurement error. The elderly exhibited a greater breath-to-breath variation in the CO_2 levels in end-tidal gas during the recovery period from N_2O inhalation, as well as a significantly greater variance in their average CO_2 output. The elderly group also exhibited a significantly higher CO_2 level at the end of the 30-min N_2O period and at 30 min after withdrawal from N_2O than at other times. Although the changes in CO_2 levels of the young group seemed to mirror those in the older group during the recovery period, none of the differences was statistically significant in the young group.

These findings suggest that healthy young and healthy elderly patients should recover from N_2O sedation at similar rates. Our findings also corroborate those of others, who have suggested that dental analgesia machine readings are a poor indication of alveolar levels of N_2O, possibly because of the tendency of many subjects to mouth-breathe despite instructions.

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