Anesth Prog 37:282–285, 1990

Sensory Experience Induced by Nitrous Oxide Analgesia

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Preliminary findings on a group of 15 dental patients, treated with nitrous oxide indicated frequent occurrence of several, well-defined sensory experiences related to various modalities. A subsequent controlled experiment carried out on 44 volunteers, inhaling a 35% N_2O + 65% O_2 sedative gas-mixture as well as O_2 alone in two different sessions confirmed a large variety of sensations not related to external stimuli. Taste and/or odor and thermal sensations were often reported as well as changes in auditory or visual perception of the environment in addition to reports of general heaviness, relaxation or tingling.

Nitrous oxide (N_2O) was introduced as a clinical analgesic gas by Horace Wells in 1844.[1] Inhalation of this agent under atmospheric pressure causes loss of consciousness, as recognized by Paul Bert in 1879.[2] Bert's pioneering experiments showed that under hyperbaric pressure this agent can provide general anesthesia. Bert also noted that the anesthesia caused by N_2O differed from that induced by other volatile anesthetics by the dream-like state accompanied by fantasies of sexual content and by the absence of the delirium known to be caused by these agents.

One of the first reports on perceptual and sensory changes induced by N_2O is that of Davy (1800) based on his personal experience. He reported a "sensation analogous to gentle pressure on all muscles attended by a highly pleasurable, thrilling in the chest and extremities." Furthermore, he noted a "more acute hearing."[3]

Later it was reported that subanesthetic concentrations of N_2O may cause some peculiar changes in cognitive functions leading to distorted perceptual processes, confusion and the inability to think clearly even a day after being exposed to the inhalation of N_2O.[4]

The electric activity of the brain as reflected in EEG tracings is indicative of fluctuations in wakefulness, drowsy state, sleep as well as for the action of many CNS-depressing or stimulating agents. Encephalographic changes due to the inhalation of N_2O were reported by many researchers as reviewed and summarized by Frost.[4]

Stimulus-dependent, evoked electrical brain-potentials are known to serve as quantitative, objective indicators for the processing of sensory information in the brain. Several studies were carried out to investigate the interaction of N_2O with the processing of pain, visual and auditory information as reviewed and summarized also by Frost.[4]

In searching the relevant literature, only few modern experimental studies could be found aiming the investigation of the effect of N_2O on cognitive, perceptual processes or on performance of motor skills.[5,6,7,8,9,10,11] Our attention was turned to the occurrence of sensations in the perioral area occasionally experienced and reported by dental patients treated under N_2O sedation. We therefore decided to investigate these occasionally mentioned phenomena in a more systematic manner.

The objective of the present study was to assess in a critical experimental design, the frequency of occurrence of the various sensations reported under the influence of nitrous oxide and to evaluate the quality and the distribution of these sensations on different body areas. Prior to this a pilot experiment was conducted whose purpose was to verify that such sensory effect can indeed be found. This report summarizes the findings obtained in both of these investigations.

Received March 1, 1990; accepted for publication July 20, 1990.
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ISSN 0003-3006/90/$3.50

(The 22 items of the questionnaire were as follows)

1) Did you experience oral thermal sensations a) heat? yes __ no__
2) Did you experience oral thermal sensations b) cold? yes __ no__
3) Did you experience shivering? yes __ no__
4) Did you experience tremor in arms and legs? yes __ no__
5) Did you experience tremor in other body areas? yes __ no__
6) Did you experience lip tremors? yes __ no__
7) Did you experience paresthesia or tingling in the palms of your hands or fingers? yes __ no__
8) Did you experience paresthesia or tingling of the tongue or lips? yes __ no__
9) Did you experience tinitus (a ringing sensation in the ears)? yes __ no__
10) Did you experience diminished sound intensity of voices or ambient noises? yes __ no__
11) Did you experience accentuated acuity in hearing? yes __ no__
12) Did you experience blurred vision? yes __ no__
13) Did you experience changes in color perception? yes __ no__
14) Was any taste sensation perceived? yes __ no__
15) If yes, specify sweet__salty__sour__bitter__
16) If yes, did the experienced taste resemble any particular food? yes __ no__
17) If yes,please name the food item: _____
18) Did you experience any odor? yes __ no__
19) If yes, the perceived odor resembled.(name or label material) _____
20) Did you experience a heaviness of the extremities? yes __ no__
21) Did you experience marked relaxation? yes __ no__
22) Comments _____

Figure 1. English translation of questionnaire.

SUBJECTS, MATERIALS AND METHODS

In the pilot study, 15 patients (10 females, 5 males) were included from the patient pool, receiving regular dental treatment at the Dental Anxiety and Sedation clinic at the Hospital Oral Medicine Service at the Hebrew University Hadassah School of Dental Medicine. Their median age was 26 years (ranging 16–50). These patients were requested to indicate on a questionnaire (Figure 1) any special body-sensations which occurred during the inhalation of the N_2O + O_2 anesthetic mixture. From the results it became evident that many patients experienced various sensations including taste, smell and thermal feelings.

The main study was initiated by recruiting 44 volunteer students (range 22–33 years). These subjects were not under dental treatment but volunteered for the sensory-experience study and received inhalation of 35% N_2O + 65% O_2 at one session and inhalation of only O_2 at another session. The two different sessions occurred 2–8 days apart. All sessions were scheduled during the morning-hours. Subjects were requested to refrain from eating about 5 hours prior to the experiment. Subjects were informed that they would inhale either an N_2O + O_2 mixture or O_2 only, respectively, given in a randomized alternating order and were requested to report their sensory experiences during the inhalation using the same questionnaire as did the patients in our pilot study. Following the instructions and explanations on potential risks and complications, they were asked to sign a consent-form. The sessions were held in a quiet dental clinic room. The anesthetic apparatus was not visible from the chair in which the subjects sat. The subjects remained blind to the order of the gaseous mixture administered. The questionnaire used in both phases of the study is presented in its English translation in Figure 1.

Means of subjective estimates and of the frequencies of sensations were calculated from the individual data reported by examinees. The differences between means were compared and tested for significance using McNemar's Z-test.[12]

RESULTS

Body sensations related to the oral and other areas were reported under the influence of N_2O by a large number of subjects. Under the influence of O_2 however, the reported sensations were rare and restricted to 4 out of the 17 possible items in the questionnaire. The comparison of frequencies of the reported sensations for subjects under N_2O and O_2 during the pilot and main studies is presented in Table 1.

The percentage of occurrence of the various sensations

Figure 2. Frequency of various sensory experiences induced by N_2O-O_2 in both of the tested groups.

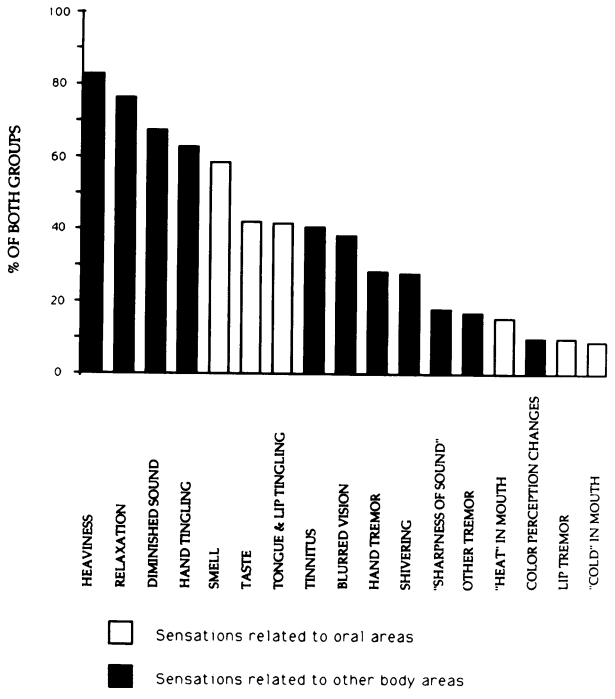

Table 1. Sensory Experience by N_2O or O_2 in the Tested Groups

Sensation	*Pilot Study n = 15* %	*Main Study n = 44* Induced by N_2O	%	Induced by O_2*	*P*
Heat in mouth	20	5	11.4	—	0.031
Cold in mouth	6	5	11.4	1	n.s.
Lip or tongue tingling	33	22	50	—	<0.0001
Smell sensation	66	22	50	—	<0.0001
Taste sensation	40	19	43.2	—	<0.0001
Tinnitus	26	24	54.6	—	<0.0001
Diminished sound	73	27	61.4	1	<0.0001
Sharpened hearing	13	10	22.7	—	<0.0001
Tingling in hands	66	26	59.1	—	<0.0001
Heaviness	86	35	79.5	1	<0.0001
Relaxation	86	29	65.9	3	<0.05
Blurred vision	40	16	36.4	—	<0.0001
Change in color perception	13	3	6.8	1	n.s.
Hand tremor	40	7	15.9	1	<0.0001
Lip tremor	6	6	13.6	—	n.s.
Other tremor	13	9	20.5	1	<0.0001
Shivering	26	13	29.6	—	<0.0001

p = significance comparing N_2O versus O_2 induced sensations
* = The incidence of O_2-induced sensations is not expressed in % due to low values.

reported by both of the groups was combined since inhalation of the anesthetic gas mixture was a common feature to both. The values were arranged in descending order producing the bar graph presented in Figure 2.

As can be seen from both Table 1 and Figure 2, general heaviness and the feeling of body relaxation were indeed the most frequently reported experiences, both in patients and subjects. Almost all these reports were directly related to the inhalation of N_2O-containing mixture while under the inhalation of O_2, only one subject experienced heaviness and 3 reported relaxation. Tingling in various body regions was experienced due to the inhalation of the N_2O-containing mixture. Here no "false positive" reports were noted. As to the other sensory experiences reported, changes in auditory and visual acuity occurred frequently. Among the 44 subjects only 1 mentioned such changes under control conditions.

The questionnaire presented 6 possibilities (out of the 17) to relate the sensations experienced to the oral area. The frequency of these reports can also be seen in both Table 1 and in Figure 1. It should be noted that only one subject reported an orally-related sensation (cold) under O_2 inhalation; all other reports on such experience were due to the inhalation of N_2O.

Taste and smell sensations were experienced by a rather high percentage of the subjects. Taste was reported by 40% to 43% while smell-sensations were aroused in 50–66% of subjects in the two studies. Inhalation of O_2 alone in all of the 44 subjects was not found to induce either of these sensations. The distribution of the reported sensations, according to taste qualities, is summarized in Table 2. From this table it can be seen that "sweet" was perceived in the majority of cases, "sour" and "salty" were also frequent, while "bitter" was rarely reported. The most frequently used describers of olfactory sensations were associated with food and beverage items. A large variety of such labels were used, but no uniformity was observed. Therefore a systematic classification of the reported sensations was not possible.

As to the other sensations reported by the testees, feelings associated with tremor, occurring in different body-regions, was also a frequent phenomenon (59% in the pilot study, 49% in the main study, see Table 1). Thermal sensations were also predominantly reported in connection with the inhalation of the anesthetic gas-mixture (23.6% of the sample) and only in one isolated case related to O_2 inhalation. Statistical evaluation verified that all sensations were significantly specific ($p < 0.05$) to the inhalation of the anesthetic mixture, except for "cold in the mouth," for "tremor in lips" and for changes in color-perception.

Table 2. The Distribution of the Reported Taste Sensations

Taste	*Pilot Study*	*Main Study*	%
Sweet	2	11	58
Salty	—	2	10
Sour	1	4	21
Bitter	2	1	5
Other	1	1	5

DISCUSSION

Under the present experimental procedure, the occurrence of sensations, not generated by external stimuli, was significantly higher when the anesthetic gas-mixture was inhaled than under control conditions (inhalation of O_2 alone). Furthermore, it is clear from the results that the inhalation of the N_2O-containing mixture produced specific and well defined sensations or certain changes in sensations, which could be reported by the subjects by means of the questionnaire. It seems of specific interest that a marked percentage of both the pilot and experimental groups mentioned clearly definable taste or smell experiences. A systematic search in the relevant literature did not yield any comparable reports. Therefore it seems that the present findings are the first ones to bring evidence as to the induction of the illusion of gustatory and olfactory experiences causally related to the inhalation of N_2O and to classify the taste experience.

The results also suggested changes in vision and auditory perception. These findings seem to be in disagreement with those of Houston et al.[13] who reported subjective pure tone thresholds not to be affected by N_2O in different concentrations. It should be stressed that in our design no comparable psychophysical testing was performed. Subjects were requested only to relate to general changes in the perception of loudness of the ambient noises. The alternating randomized order of the exposure of the subjects to N_2O and O_2 inhalations should have minimal patient expectation.

The pharmacological mechanism of action of N_2O is not yet sufficiently clarified in spite of the long history of the use of this agent. Bert in 1879[14] mentioned that this agent does not induce the "initial delirial state" so characteristic of induction with other volatile anesthetics. Still the occurrence of distorted sensations, illusions or even hallucinary phenomena caused by this agent have been reported and documented.[15] Our results point mainly to the frequent occurrence of well defined, different sensations not related to external stimuli. The study was not designed to assess any delirial states, confusion, and incoherent speech in any of our patients or subjects.

The gas by itself is odorless and tasteless but it often is mentioned as having a sweetish flavor. Therefore, the frequent taste and odor experience repeatedly reported by our subjects indicates a particular, not sufficiently investigated type of illusion due to the inhalation of this agent. Since there is no evidence of any metabolic products originating from N_2O which could be considered as a blood born stimulus for taste and smell, one can speculate that the illusionary or even hallucinatory odor and taste experiences might be attributed to a stimulation of brain-substances related to pleasure or sensations.[16,17] Further systematic studies involving large samples of different age groups, of different ethnic and cultural backgrounds, will be necessary to elucidate further on the phenomena reported here. We would also suggest investigating the N_2O-induced changes in general oral and taste sensation by the application of local anesthetics to the dorsal surface of the tongue and to the oral mecosa. By such procedure, the actual peripheral adequate sensory stimulation can be eliminated. Such a combination would lead to further clarification of the mechanism of oral sensations aroused by N_2O inhalation.

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