

THE ANALGETIC EFFECTS OF LOW CONCENTRATIONS OF NITROUS OXIDE COMPARED IN MAN WITH MORPHINE SULPHATE¹

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In a study of the loss of consciousness under nitrous oxide, Cobb and Beecher (1) found that it was desirable to have information on changes in the pain threshold level during this process. A few measurements were attempted; but it was clearly not practicable to include the necessary tests with the work already in progress, so the observations reported here were made separately.

It can be observed that nitrous oxide, although widely employed, is used in the majority of cases in concentrations nearly great enough, if not great enough, to cause loss of consciousness and even anoxia. It is our belief that this agent also should be much more widely used as an analgetic agent than is now the case. *The purpose of this study is to report, on the basis of quantitative studies, that nitrous oxide in low concentration (consciousness not impaired, beyond a slight euphoria) has power to relieve pain comparable to that of morphine and yet does not have the undesirable side effects which limit the use of morphine.*

Since 1799,² nitrous oxide, in low concentra-

tion, has on many occasions been used effectively for pain relief, without loss of consciousness, but wider usefulness of the agent for this purpose has been limited for several reasons, one of which is the lack of objective data to prove its value in low concentration. Moreover, several statements in the literature on the subject have also tended to discourage the use of really low concentrations. For example, Brown, Lucas, and Henderson (3) state that no analgesia resulted when 85 per cent nitrous oxide with 15 per cent oxygen was used. It seems unlikely that adequate time could have elapsed for even approximate equilibration of their subjects with this gas mixture; at least none of our patients retained consciousness beyond 75 per cent nitrous oxide (with 25 per cent oxygen) and most of them lost consciousness at 60 per cent (with 40 per cent oxygen). Our findings on this score agree with the interesting observations of Seevers, Bennett, Pohle, and Reinardy (4). Not only analgesia but anesthesia is produced by this high concentration of nitrous oxide.

PROCEDURE

The subjects. Fifteen healthy male subjects, varying in age from 18 to 34 years, were used in the heat radiation studies. All of these had been used in the morphine study of Chapman and Jones (5). The same subjects were used here in order to minimize the effects of individual variations, and 10 of these same subjects were used in the muscle ischemia observations. All determinations were made with the subject lying comfortably in the supine position. The nose was closed with a clamp and breathing was carried out through a "basal metabolism" rubber mouth piece. The subject did not know what he was breathing. Seven control tests were run with 100 per cent oxygen, and 3, with air from a tank.

may properly be used with advantage during surgical operations. . . ." It can be recalled only with chagrin that close to a half century went by before Davy's well-informed suggestion was acted on by the medical profession, and even now his great work is often not adequately acknowledged.

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² In Sir Humphry Davy's report of his superb investigation of nitrous oxide (2), made in 1799, at the age of 20, he describes repeatedly the use of nitrous oxide to produce analgesia with little or no disturbance of consciousness. For example, on page 464, ". . . when I had head-ache from indigestion, it was immediately removed by the effects of a large dose of gas. . . ." "The power of the immediate operation of the gas in removing intense physical pain, I had a very good opportunity of ascertaining," for on being disturbed by a painful dental infection, he breathed nitrous oxide and "The pain always diminished after the first four or five inspirations . . . and . . . was . . . swallowed up in pleasure." Later (p. 481), as an experiment he "drank a bottle of wine in large draughts in less than eight minutes." Subsequently he "was awakened by head-ache and painful nausea." On breathing nitrous oxide, he reports that he "was unconscious of head-ache after the third inspiration . . . and continued for some minutes much exhilarated." He concluded (p. 556), "As nitrous oxide in its extensive operations appears capable of destroying physical pain, it

Nitrous oxide was administered (see below) without the subject's knowledge.

At the completion of the experiment, questions were asked to determine the presence of any side reactions not evident to the observer, such as possible nausea. Careful notes were kept of any alterations in behavior.

Pain production and measurement. Two types of pain production have been studied: (a) Pain arising from heat radiation of the skin of the forehead. Our principal conclusions are based upon these observations. (b) Pain arising from muscle ischemia as a result of exercise of the hand under conditions of vascular occlusion by a cuff tourniquet on the arm (5). Here, the observations are highly subjective and have been used only as supplementary support for our conclusions.

Two components of the pain experience were measured, the threshold of pain perception, and as far as was possible, the pain reaction.³ The observations under nitrous oxide were compared in the same subjects with effects previously produced by morphine sulphate (gr. $\frac{1}{4}$, 15 mgm., administered subcutaneously), Chapman and Jones (5).

(a) Cutaneous pain. The technic employed here utilizes the Hardy, Wolff, and Goodell apparatus (6) and follows their procedure with a minor exception, in that we have used a somewhat stronger and, as a result, more definite end-point, as described (5). Briefly, the method consists in focusing the heat from a 1000 watt Mazda lamp on the midline of the forehead, already blackened with India ink. The exposure was kept constant for 3 seconds and then interrupted by a shutter operated by a telechron motor. The heat intensity was varied with a wire rheostat. The quantity of heat needed to produce the sharp piercing end-point of pain was measured directly by a radiometer and potentiometer. The quantity of heat was expressed in absolute end-point values of gram calories per second per square centimeter of skin surface.

The usual procedure was to establish first the base-line of the normal pain perception threshold and the threshold of pain reaction while the subject breathed room air but with the respiratory apparatus in place. (This plan was varied often enough so that the subject did not know what he was breathing.) After establishment of the normal pain threshold, nitrous oxide was administered (see below). Six minutes later, pain threshold determinations were made and repeated at 2-minute intervals, until a plateau effect of the analgetic action had been established for the given concentration of nitrous oxide. Changes in threshold level were finally expressed in percentages of the initial base-line level. On the average, 10 minutes were required, following the beginning of administration, to obtain the maximum analgetic effect of the nitrous oxide. This was the same in a given individual for

all concentrations used, with constant respiratory minute volume and the cardiac output constant (assumed).⁴

After the position of the plateau was clearly established, the administration of the nitrous oxide was stopped (without the subject being aware of this) and the pain threshold followed until the base-line level had been reached. Further controls were occasionally run with air or oxygen, the subject believing that the gas administered was nitrous oxide.

(b) Muscle ischemia pain. In order to study a sustained type of aching pain, muscle ischemia was produced by having the subject clench his fist at 1-second intervals with the circulation as completely occluded as possible just above the elbow by a blood pressure cuff, inflated and maintained at a pressure of 200 mm. Hg (5). The vascular occlusion was maintained for 600 seconds. As soon as the blood pressure cuff was inflated to 200 mm. Hg, the subject began clenching his fist and continued until his grip showed the first signs of weakening. At 200 seconds, this was repeated and again at 450 seconds. The cuff was released at 600 seconds. The time of these 3 different periods of contraction was recorded by a stopwatch. As it was assumed that the amount of pain produced was directly related to the amount of work done by the contractions, it was necessary that the degree of each contraction be kept uniform. This factor was controlled by having the subject squeeze the 2 extended fingers of an assistant, making sure that before each contraction the subject's fingers were fully extended and that each grip exerted a uniform pressure. The same number of contractions was repeated for each period of exercise during the gas inhalation. Since each subject showed a tendency to have a more forceful grip during the breathing of nitrous oxide, as a result of diminished pain, any error was on the side of more exercise when the nitrous oxide was used than otherwise. The effect of the nitrous oxide was evaluated by asking the subject the following questions at the completion of the tests: 1. During which test (nothing or nitrous oxide) was the pain more severe? If, on either of the tests, the pain was less severe, estimate how much less intense it was than in the other case. 2. How did each test compare in the time it took to complete it?

As already pointed out, the evaluation of the effect of the nitrous oxide was so much less accurate here than in the heat stimulation of the skin, much less importance is attached to these observations than to the foregoing ones. It was reassuring, however, to observe the obvious diminution in pain, as indicated by the strong grip and greater work performance under the low concentrations of nitrous oxide than without it.

Nitrous oxide administration. This agent was administered with oxygen by means of a Foregger gas apparatus through a hydraulic flowmeter that had been calibrated

³ Judged by wincing, and shown by the first muscular contraction of the outer canthus of the eye. In the cases where no wincing occurred, it finally became necessary to interrupt the test to avoid burning the patient.

⁴ Because of the low solubility coefficient of nitrous oxide in the blood, considerable variation of cardiac output could occur without appreciably affecting the assumption.

against a spirometer flow. At temperatures of 70 and 75° F., the errors are less than 3 per cent. The gases flowed continuously into and out of a 3 liter breathing bag at the rate of 4 liters per minute. As already mentioned, special care was taken to keep the subject in ignorance of what he was breathing whether air, oxygen, or nitrous oxide-oxygen mixture. Attention was directed chiefly to the effects of 10, 20, or 30 per cent nitrous oxide in oxygen mixture, where the subject's cooperation is well within normal limits. Occasionally, the effects of 40 per cent, 50 per cent, and even higher concentrations were observed; but the analgetic results are of little interest at the high concentrations, for the subjects' cooperation at these concentrations was too poor to give reliable results.

RESULTS AND DISCUSSION

In this study, we have demonstrated that 20 per cent nitrous oxide in oxygen is comparable in analgetic power to that of a rather large dose of morphine. Moreover, once equilibrium is established, the effect produced by a given concentration of nitrous oxide in a closed system is sustained at a maximum, without further addition of nitrous oxide, as long as the system remains closed (except for the addition of oxygen as it is used up and the removal of carbon dioxide as it is formed), for nitrous oxide is essentially not excreted when the respiratory system is closed and, so far as is known, is not metabolized. The situation is different with morphine; in this case, the effect passes through a maximum about 90 minutes after administration and then declines and disappears.

In presenting data of this type, based upon 15 subjects, it has seemed to us that the best one can do is to establish an order of magnitude with the typical range of variation encountered in such a series. This can be done most concisely by a presentation of means with their standard errors, rather than by the tabulation of the individual results. Our concern has been to demonstrate that the analgetic power of 20 per cent nitrous oxide is of the same order as the maximum obtained from subcutaneous administration of morphine gr. $\frac{1}{4}$ (15 mgm.), and this we have done.

There are many occasions in the clinic where the use of morphine is undesirable, either because repeated pain relief may be necessary and habituation is feared or because the nauseating or other undesirable effects of the agent make its use unwise. On the other hand, nitrous oxide is without such effects and since it is a powerful analgetic

agent it should help to fill a clinical need. Aside from its desirable central nervous system effects, nitrous oxide is lacking in important metabolic effects. When adequate oxygen is administered with it, no toxic effects are known at the partial pressures used here. This suggests that it should be possible to employ low concentrations (low partial pressures) for many hours without danger. This we plan to do, keeping a careful watch for any unexpected toxic effects.

SeEVERS, BENNETT, POHLE, and REINARDY (4) describe 20 per cent nitrous oxide as producing "ineffectual analgesia," according to their standards, although they have found, as we have also, that this produces a real elevation in the pain threshold. Their comparisons were between nitrous oxide, ethylene, and cyclopropane, and their estimations were made upon the basis of a modification of the von Frey technic. Our comparison, on the other hand, is between nitrous oxide and morphine,⁵ rather than with another anesthetic agent. In our hands, the von Frey technic is less satisfactory for quantitating the analgetic effect of a drug than is the more recently developed technic of HARDY, WOLFF, and GOODELL (6).

Cutaneous pain. The mean results are compared in Figure 1, and numerically are as follows: Morphine, in gr. $\frac{1}{4}$ (15 mgm.) dose, produced a 21.0 ± 3.0 per cent elevation of the pain perception threshold and 10, 20, and 30 per cent nitrous oxide produced respectively 6.0 ± 2.2 , 17.0 ± 4.1 , and 22.0 ± 4.8 per cent elevation of the pain threshold (means with standard errors). The 20 per cent nitrous oxide and the morphine data are based upon 15 subjects; the same individuals were used in each case. The 30 per cent nitrous oxide data were obtained from 7 subjects and the 10 per cent nitrous oxide, from 11 subjects.

Our conclusions are based chiefly upon comparison of the 20 per cent nitrous oxide and the morphine data. The number of subjects in these 2 groups is the same, 15, and the variability of the analgetic effects of the 2 agents are fairly comparable, as indicated by the standard errors.

⁵ If one compares the data of SeEVERS and his group on 20 per cent nitrous oxide (4) with their morphine (10 mg.) data published elsewhere (7), it is evident that they found about the same analgetic effect produced by the two agents, the nitrous oxide being somewhat more effective than the dose of morphine used.

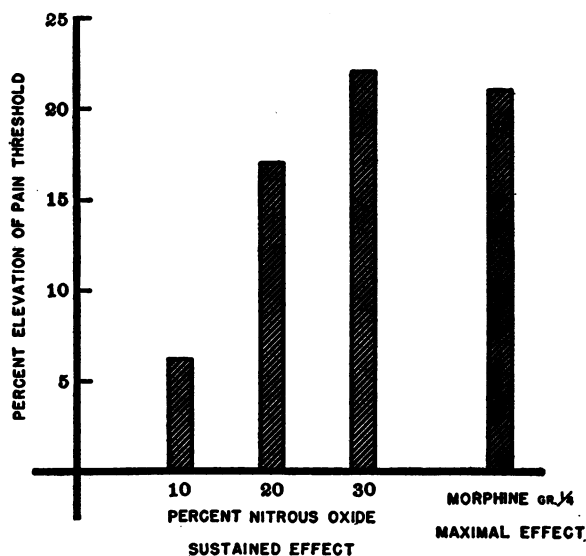


FIG. 1. COMPARISON OF ANALGETIC EFFECTS

It was impracticable to observe the reaction to pain at 2-minute intervals as we had done in the case of the pain perception threshold level. It was, however, possible to determine this, once the plateau effect of the nitrous oxide had been established, provided the altered pain perception value was not so high that any increased stimulus would have blistered the subject's skin. In 10 instances where it was feasible to determine the pain reaction (wincing) level, all these subjects showed the same spread between pain perception and pain reaction as found for their base-line values. The control tests with 100 per cent oxygen and air were without effect on the pain perception threshold.

Muscle ischemia pain. Seven of the 10 subjects were enthusiastic in their statements that 20 per cent nitrous oxide (in 80 per cent oxygen) greatly reduced the muscle ischemia pain; one said the effect was about the same as without the agent. Two subjects who did not agree with the majority qualified their remarks in a curious way: one said the pain was greater under nitrous oxide than without it, but it "took longer to hurt"; one said the "Pain was as bad with the nitrous oxide, but did not bother so much." It was apparent that on the average the nitrous oxide strikingly diminished this type of pain. This painful test was described as of much shorter duration under nitrous oxide than without it. Also, with this test, the

100 per cent oxygen and air inhalation did not alter the pain levels.

Loss of consciousness. Seven men, studied at another time, received nitrous oxide to the point of unconsciousness. Starting with about 25 per cent nitrous oxide in 75 per cent oxygen, the anesthetic agent was increased 10 to 15 per cent at a time, with a pause of about 15 minutes in each concentration. In the 7 subjects, the percentage concentrations (in oxygen) which produced unconsciousness were as follows: 60, 60, 65, 75, 50, 66, 50; on the average, 61 per cent nitrous oxide produced unconsciousness in robust young men.

Side effects. While 14 of the 15 subjects were nauseated and vomited under morphine, *no nausea or vomiting was present under nitrous oxide.*

In the 15 subjects under the several concentrations of nitrous oxide used, 11 laughed spontaneously without apparent cause. Eight out of 11 subjects questioned were somewhat euphoric. One was distinctly irritable. In 13 patients questioned, there was no subjective feeling of depression. Six out of 8 questioned had some sensation of lightheadedness. No disorientation could be discovered on concentrations of 40 per cent nitrous oxide or less.

CONCLUSIONS

Nitrous oxide in 20 per cent concentration in oxygen is as effective an analgetic agent as morphine in gr. $\frac{1}{4}$, or 15 mgm., dose, judged from the 2 types of pain considered here. Nitrous oxide at this concentration does not impair consciousness and is effective as long as it is not allowed to escape from the "closed" respiratory system, whereas the morphine effect passes through a maximum and, since it is metabolized, the effect disappears. Unlike morphine, nitrous oxide in this concentration is not usually associated with undesirable side effects.

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