Effect of Nitrous Oxide and of Narcotic Premedication on the Alveolar Concentration of Halothane Required for Anesthesia

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Sixty-eight surgical patients were divided into three groups and anesthetized with either halothane and oxygen, halothane-nitrous oxide following narcotic premedication, or halothane-oxygen and 70 per cent nitrous oxide. The minimum alveolar concentration of halothane required to prevent movement in response to surgical incision was 0.74 per cent. Addition of narcotic premedication decreased this value to 0.69 per cent and addition of nitrous oxide (without narcotic premedication) allowed a reduction in the alveolar halothane concentration to 0.29 per cent. Advantages of administering nitrous oxide with halothane are: (1) decreased cost of anesthesia, (2) increased speed of recovery, and (3) possible decreased hepatotoxicity. We believe that these advantages outweigh the disadvantage of decreased percentage of oxygen administered. The narcotic premedication resulted in only a slight decrease in required alveolar halothane concentration. We believe this decrease is insignificant relative to the possible cardiovascular depression that may accompany narcotic premedication.

The objectives of this study were to determine if nitrous oxide or narcotic premedication is effective in reducing the alveolar concentration of halothane required for surgical anesthesia.

Method

Sixty-eight surgical patients age 17 to 78 were divided into three groups (A, B, C). Patients were assigned to each group from a Roman square. All patients were premedicated with 0.4 to 1.2 mg. atropine. In group A anesthesia was induced with halothane and oxygen. Patients in group B were premedicated with 8 to 15 mg. morphine subcutaneously as well as atropine (average of 87 minutes prior to incision). Anesthesia was induced with halothane and oxygen as in group A. Group C patients were induced with N₂O, O₂, and halothane. The inspired N₂O was maintained at 70 to 75 per cent inspired as monitored with a Beckman D Oxygen Analyzer. In all groups, after induction the larynx was sprayed with 1 to 2 ml. of 5 per cent cocaine and the trachea was intubated with auffed endotracheal tube. Nasopharyngeal temperature was recorded in all patients. In several patients, continuous esophageal temperature was recorded and was found to agree with the nasopharyngeal temperatures within 0.2 degrees. End-tidal halothane samples were collected with an Otis-Fenn-Rahn end-tidal sampler, and monitored continuously by means of an ultraviolet halothane analyzer (Analytic Systems Co.). The analyser was calibrated before every case against known concentrations of halothane.¹

We assumed that the alveolar gas was at equilibrium with arterial blood and with brain and that the tension in brain was proportional to anesthetic depth.² Maintaining alveolar concentration (rather than inspired concentration) constant was an indirect way of establishing a steady state in the brain. The end-tidal halothane concentration was controlled by increasing or decreasing the inspired halothane concentration. An end-tidal concentration which appeared to produce a light surgical plane of anesthesia was chosen and held constant for 10 to 15 minutes prior to the surgical incision. The minimum alveolar concentration of halothane necessary to prevent a muscular response to the surgical skin incision was defined as MAC 1. If the patient moved in response to the incision, the concentration was said to be below MAC 1. If he did not move, the concentration was said to be above MAC 1.

A further study was done on four surgical
patient who were premedicated with 0.4 to 1.2 mg atropine, anesthetized with halothane and oxygen, and whose tracheas were intubated as in the previous patients. As before, the end-tidal halothane concentration was stabilized for 15 minutes following which an electrical stimulus of 30 to 45 volts a.c. with a 1.2 milliseconds pulse at 50 cycles per second for a maximum of one minute was applied through two 20-gauge hypodermic needles inserted into the skin of the forearm. The patient was observed for movement. The end-tidal halothane concentration was thereafter adjusted and stabilized at a new level for 15 minutes. The electrical stimulus was reapplied and the patient again observed for movement. This process was continued until that concentration was found which just eliminated movement. Following this, nitrous oxide was added and the response to stimulation at various end-tidal halothane concentrations determined as before. In two of these patients after MAC 1 had been found with nitrous oxide and halothane, the nitrous oxide was discontinued and MAC 1 determined again for halothane and oxygen.

Results

Figure 1 shows the results of groups A, B, and C. The alveolar concentration at which the surgical incision was made is plotted on the horizontal axis. A positive response is noted by an upward deflection and a negative response by a downward deflection. In group A there were no patients who moved at an alveolar concentration greater than 0.78 and only one who failed to move at a concentration of less than 0.73. In group B there were no patients who moved at an alveolar concentration of greater than 0.71 and none who failed to move at a concentration of less than 0.65. The patients in group A who had alveolar concentrations in the range where the positive and negative responses overlapped were compared with the same group of patients in group B. The mean value of the group B patients was 0.68 as compared with the mean for group A of 0.75. This difference was statistically significant (P less than 0.05). In group C there were no patients moving at an alveolar concentration over 0.33 and there were none who failed to move at a level less than 0.25. The data from each group were then plotted in the following manner. Patients were taken in groups of four starting with the lowest alveolar concentration. The percentage of patients moving within each group was plotted on the vertical axis against the average alveolar concentration of the four which is plotted on the horizontal axis. This is shown in figure 2. The point at which 50 per cent

![Figure 1](https://example.com/figure1.png)

**Fig. 1.** The results of Groups A, B, and C are shown here. The alveolar concentration is plotted along the horizontal axis. If a patient moved with the surgical incision, an upward deflection is recorded at the appropriate alveolar concentration. If he did not move, a downward deflection is recorded.
of the patients moved in group A was 0.74, in group B 0.89, and in group C 0.29. This represents a 7 per cent reduction in alveolar halothane concentration after morphine premedication and a 81 per cent reduction in alveolar halothane concentration when 70 per cent nitrous oxide is used.

Table 1 shows the results of group D. These four patients were found to respond to electrical stimulus when the alveolar halothane concentration was 0.59 and not to respond at 0.76. The addition of 70 to 75 per cent nitrous oxide allowed a reduction of alveolar halothane concentration to 0.08 before a response was elicited. This response was abolished at a concentration of 0.20. In the two patients in whom MAC 1 was redetermined with halothane and oxygen after discontinuing the nitrous oxide, we found that they failed to respond only when the halothane concentration was 0.76 and they responded to the electrical stimulus when the concentration was 0.58. These values were similar to the values obtained for these two patients when MAC 1 was first determined before nitrous oxide was added to the anesthetic.

In all of the groups, there were no differences noted with respect to age (over or under 40), sex, or temperature. (The temperature range was 35.7 to 38.3 with a mean of 36.7 and S.D. of 0.76.)

Discussion

Our results indicate that nitrous oxide is very effective in lowering the alveolar concentration required for anesthesia. The amount of decrease was approximately 60 per cent or an absolute decrease in alveolar halothane concentration of 0.45 per cent. Our findings are in part at variance with previous reports that attempted to quantitate this effect with other anesthetics. Morris reported a series of patients receiving chloroform anesthesia in which N2O was added in some patients and not in others. He concluded that N2O was of little benefit in lowering the amount of chloroform needed. This was based on the fact that the venous blood levels of chloroform were only slightly lower when N2O was used than when it was absent. However, peripheral venous blood is not an indication of the concentration of chloroform in the brain. In addition, his methods of estimation of depth (clinical stages and planes) is, in itself, crude as indicated by the wide range of anesthetic concentrations that can be present at the same depth. There is also no mention made as to whether or not the patients were given...
barbiturates or narcotic and no indication of how long they had been in a stable state.

Fankouer in 1952 determined arterial blood concentration of ether required to obtain comparable EEG levels with and without N₂O. He found that a higher concentration of ether was needed to achieve a given EEG level if N₂O was absent than if it was present in excess of 10 mg per cent in arterial blood. The addition of N₂O resulted in an EEG pattern that was one stage deeper than if nitrous oxide were absent. This represented a decrease in arterial ether concentration of about 15 per cent at EEG level three or four. In our study, the magnitude of change was much greater: the concentration of halothane was decreased by more than 60 per cent.

Potency of an anesthetic may be related to its oil/gas solubility coefficient. The more lipid soluble a given agent, the lower the arterial or alveolar concentration required to produce anesthesia. The alveolar concentration at MAC 1 multiplied by the oil/gas solubility coefficient of a particular anesthetic should then be approximately the same for most anesthetics. Experimentally, the oil/gas solubility coefficient of halothane of 224, times the MAC 1 or 0.73 with halothane-oxygen, equals 164. The oil/gas coefficient of N₂O equals 1.4. An inspired concentration of 70 to 75 per cent would produce an alveolar concentration of nitrous oxide of about 65 per cent. Multiplying this per cent by the oil/gas coefficient gives a figure of 91 which is 55 per cent (91/164) of the figure obtained for halothane. One might expect then a comparable reduction in the required halothane concentration on addition of nitrous oxide, and this agrees with what was found.

Reduction of alveolar halothane concentration may be important if halothane is metabolized by the body. The possibility that halothane is metabolized is suggested by the work of Van Dyke who showed that chloroform is metabolized in vivo, and by the work of Heppel and Porterfield who demonstrated the in vitro metabolism of other halogenated compounds. If a toxic degradation product is formed and is found to be toxic to man, then by the law of mass action, decreasing the concentration of halothane administered should decrease the rate of production of this product.

### Table 1. Response to Electrical Stimulation

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<thead>
<tr>
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<th>Positive</th>
<th>Negative</th>
</tr>
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<tbody>
<tr>
<td>Halothane/oxygen</td>
<td>0.59±0.05</td>
<td>0.76±0.08</td>
</tr>
<tr>
<td>Halothane/nitrous oxygen/oxygen</td>
<td>0.08±0.03</td>
<td>0.20±0.15</td>
</tr>
<tr>
<td>Halothane/oxygen (two patients) after elimination of nitrous oxide</td>
<td>0.58</td>
<td>0.78</td>
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The results of Group D are shown here. These patients were given halothane and oxygen, stimulated electrically, and the alveolar concentration at which they moved and failed to move were determined. Then nitrous oxide was added and the process repeated. Following this, in two patients the nitrous oxide was eliminated and the patients stimulated again under halothane and oxygen.

Further advantages of the addition of nitrous oxide to halothane are: (1) The increased rapidity with which recovery takes place. Because of the lower blood/gas and tissue/blood partition coefficients, the alveolar tension of nitrous oxide falls faster than for halothane and recovery occurs at a more rapid rate. (2) The decreased cost of anesthesia that results from the decreased amount of halothane required. We believe the advantages that are offered by the addition of nitrous oxide to halothane outweigh the disadvantage of the decreased oxygen tension presented to the patient.

The finding that narcotic premedication lowers the MAC for halothane agrees with other reports. Taylor and co-workers gave 10 mg. morphine sulfate intravenously ten minutes prior to anesthesia with ether and found a 15 per cent decrease in the arterial ether concentration required to produce EEG level four. The difference between 15 per cent and the 9 per cent reduction that we found could be explained by the fact that morphine given intravenously ten minutes prior to anesthesia would certainly be expected to produce greater change in anesthetic requirements than the same dose given intramuscularly an hour and a half before the surgical incision because of the higher peak found with intravenous administration.

Seegers et al. found that premedication with morphine-scopolamine in dogs reduced the concentration of C₂H₆ needed for a given
plane of anesthesia. The reduction that he found was greater than that which we found. Their guide to depth of anesthesia was based on Guedel’s signs and they freely admit that these signs are not applicable to the dog with this agent. Also, the amount of morphine used, the time of injection before surgery, and route of administration are not mentioned.

The impression that patients receiving narcotics for premedication need much less anesthetic to achieve and maintain a given plane of anesthesia might be explained in the following manner. Narcotics will cause a decrease in cardiac output with inhalation anesthetic. Since uptake of anesthetic is directly related to cardiac output, the patient receiving a narcotic takes up less anesthetic at a given alveolar concentration than a similar patient who has not received the narcotic. The alveolar concentration, the index used in our study, would be the same for both patients. Although opiate premedication may be economical in terms of the amount of anesthetic used, it may result in a large physiological cost to the patient. The vital tissues of such a patient are exposed to much the same tension of anesthetic but with decreased tissue perfusion.

Summary

Surgical patients were given halothane with and without nitrous oxide and with and without morphine premedication. We found a 61 per cent decrease in the alveolar concentration of halothane needed to obtain an overt muscular response (movement) to the surgical incision when N₂O was used. The advantages of administering nitrous oxide with halothane are increased speed of recovery, possible decreased amount of hepatotoxicity, and decreased cost. Morphine given as premedication did decrease the required alveolar halothane concentration 9 per cent. It is thought that narcotic premedication causes a decrease in cardiac output without a great decrease in alveolar concentration of anesthetic requirements.

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References


