Original Articles

Effect of Nitrous Oxide and Morphine on the Minimum Anesthetic Concentration of Fluroxene

Edwin S. Munson, M.D., Lawrence J. Saidman, M.D., Edmond I. Eger, II, M.D.

Fifty-one surgical patients were studied in three groups: one anesthetized with fluroxene alone, a second with fluroxene preceded by premedication with morphine, and a third with fluroxene and nitrous oxide. The minimum anesthetic concentration of fluroxene required to prevent an overt muscular movement to a surgical incision was 3.4 per cent. The preoperative use of 10–12 mg. morphine reduced the minimum anesthetic concentration of fluroxene to 2.7 per cent (a 20 per cent reduction). Seventy-seven per cent inspired nitrous oxide reduced the minimum anesthetic concentration of fluroxene to 0.8 per cent (a 76 per cent reduction). The contribution of morphine in reducing anesthetic requirement was statistically significant (P < 0.05). The reduction in fluroxene requirement by nitrous oxide to nearly one-fourth the amount when used alone significantly reduced cost and the flammability hazard.

This investigation was undertaken to determine the minimum anesthetic concentration (MAC) of fluroxene in man and to evaluate the impact of morphine premedication and nitrous oxide on this value.

Method

Fifty-one patients were studied in three groups—A, B, and C. In group A, 15 patients were anesthetized with fluroxene-oxygen alone. In group B, 24 patients were similarly anesthetized but received a preoperative injection of morphine. In group C, 12 patients received no narcotic premedication but nitrous oxide was added to the fluroxene-oxygen mixture. All patients received atropine sulfate, 0.4–0.8 mg., 60–120 minutes preoperatively. Morphine dosage in group B ranged from 10–15 mg.;

Accepted for publication October 6, 1964. The authors are in the Department of Anesthesia, University of California Medical Center, San Francisco, California.

on a weight basis a mean of 0.17 ± 0.03 mg./kg. was determined. The narcotic was administered intramuscularly 60 to 140 minutes preoperatively (mean 98 ± 22 minutes).

Anesthesia was induced in all patients via mask with the agents under study. In 6 patients in group A, and in all of the patients in group B, cyclopropane was added to the fluroxene-oxygen mixtures to hasten induction and to avoid the irritating quality of high fluroxene concentrations. As soon as induction was completed, in no case longer than three minutes, cyclopropane was discontinued and the total gas flow to the circle system raised to 4 liters per minute. The interval from onset of anesthesia to the time of surgical incision ranged from 14 to 45 minutes (mean 29 ± 7 minutes). This time was sufficient to allow essentially for complete washout of cyclopropane from the system. Patients in group C underwent induction with fluroxene-oxygen-nitrous oxide mixtures. Gas flows of 10 liters per minute were employed for the first 10 minutes. The inspired nitrous oxide concentration was maintained between 74–80 per cent (mean 77 ± 1.6 per cent) as monitored on a Beckman D oxygen analyzer. The analyzer was calibrated against nitrous oxide and oxygen and appropriate correction was made for the absorption of fluroxene by silica gel drying agent. The inspired nitrous oxide concentration was maintained for 21–49 minutes (mean 31 ± 12 minutes) before the surgical stimulus. Mean alveolar nitrous oxide concentration was approximately 72 per cent, estimated from the dilution of inspired gas by alveolar water vapor (0.77 × 0.94 = 0.72).

Following the induction period patients in all groups received 40 mg. succinylcholine intravenously to facilitate tracheal intubation. Prior to the passage of a cuffed endotracheal
tube the larynx was topically anesthetized with 2 ml. of a 5 per cent cocaine solution.

End-tidal (alveolar) fluoxene concentrations were continuously sampled with an Otis-Fenn-Rahn end-tidal sampler, and monitored on an infrared fluoxene analyzer. In groups A and B the infrared head was filled with 100 per cent carbon dioxide to eliminate the cross-over effects of this gas. Calibration of the analyzer has previously been described. In group C the infrared head was filled with 20 per cent carbon dioxide–80 per cent nitrous oxide to minimize cross-over effects of these gases. Separate calibration curves were made for fluoxene, nitrous oxide, and carbon dioxide so that observed fluoxene readings could be corrected. End-tidal carbon dioxide samples were analyzed with a Severinghaus carbon dioxide electrode.

Determination of a minimum anesthetic concentration was performed as previously described by Saidman and Eger for halothane. We assume that alveolar gas is in equilibrium with arterial blood and with the brain, and that tension in the brain is proportional to anesthetic depth. By maintaining alveolar concentration constant a steady state in the brain can be established. A period of eight minutes for a constant fluoxene alveolar (arterial) concentration to adequately reflect cerebral tension was calculated from the following equation:

\[ T = \frac{-1}{CBF \cdot \lambda \cdot \log_{e} 20} \]

where:

\[ T = \text{time to 95 per cent brain-blood equilibration in minutes,} \]
\[ \lambda = \text{fluoxene brain-blood partition coefficient (1.43)}, \]
\[ CBF = 54 \text{ ml. blood flow per 100 g. brain per minute.} \]

Alveolar fluoxene concentrations that appeared to produce a light surgical plane of anesthesia were chosen and held constant prior to the surgical incision (table 1). The steady state of alveolar concentrations was always approached from a level of higher concentration. The minimum anesthetic concentration of fluoxene necessary to prevent a gross muscular response is defined as MAC 1.0. This is approximated by noting the alveolar concentration at which 50 per cent of the patients respond to the surgical stimulus. The error introduced by this estimate is small since the range over which patients did and did not move was small. If the patient moved in response to the incision the concentration was said to be below MAC 1.0. All patients were resiping spontaneously prior to the stimulus. Surgical incisions were confined to the abdomen, chest, or neck. End-tidal carbon dioxide tensions in group C patients ranged from 27–32 mm. of mercury. With the usual arterial-alveolar gradient of 4 to 5 mm. of mercury seen under anesthesia these alveolar values probably represent arterial carbon dioxide tensions of 32–37 mm. of mercury. The effect of hyperventilation on cerebral blood flow has been measured in the monkey and in man. A decrease in arterial carbon dioxide tension from 40 to 32 mm. of mercury may reduce cerebral blood flow approximately 20 to 30 per cent. Calculated from the above equation a 30 per cent reduction in cerebral blood flow would increase by an additional three minutes the time required for adequate fluoxene blood-brain equilibration. The duration of constant fluoxene-alveolar concentration in the preincision period in each group extended beyond this interval (table 1).

| TABLE 1. Mean Values for Each Group with One Standard Deviation for Each Parameter Measured |
|---|---|---|---|
| Group | A | B | C |
| Preincision period of constant fluoxene alveolar concentration, minutes | 13±1 | 13±5 | 15±7 |
| Age, years | 44±16 | 45±15 | 43±13 |
| Weight, kg. | 63±12 | 65±10 | 65±11 |
| Temperature, nasopharyngeal, degrees centigrade | 36.4±0.3 | 36.4±0.4 | 36.4±0.5 |
| Hct percent | 43±3 | 41±3 | 40±2 |
The results of groups A, B, and C are shown. The alveolar concentration at which the surgical incision was made is plotted on the horizontal axis. If the patient moved an upward deflection was made. If there was no response a downward deflection was recorded.

Results

Data from all experiments are shown in figure 1. Alveolar fluroxene concentration when the surgical incision was made is plotted on the horizontal axis. A positive movement is noted by an upward deflection and a negative response by a downward deflection. In group A there were no patients who moved above an alveolar concentration of 3.45 and none who failed to move with an alveolar concentration at or below 3.3. This range represents what we call the cross-over area. In group B the range of alveolar concentrations between movement and no movement was much greater. In this group there were no patients who moved above an alveolar concentration of 3.2 and there were no patients who failed to move at an alveolar concentration less than 2.4. In group C there were no patients who moved at an alveolar concentration over 0.82 and none failed to move at a level below 0.72. One patient in this group not shown in figure 1 moved at an estimated mean alveolar concentration of 2.1 per cent. During the preincision period this patient appeared to be very lightly anesthetized at the pre-selected alveolar concentration of 1.4 per cent and moved continuously. The alveolar concentration was raised to 2.2 per cent and six minutes later when the incision was made there was still a positive response. This patient was not included in group C as we could not calculate actual cerebral fluroxene tension.

The value given is only an estimate and is mentioned as an aberrant response. This may indicate greater variability in patient response than shown by this study.

The data from each group were re-plotted as shown in figure 2. Starting with the lowest alveolar concentrations, patients were grouped into fours and the percentage of patients moving was plotted on the vertical axis. The average alveolar concentration of the corresponding four patients is plotted on the horizontal axis. The patients at the lowest three concentrations in group A were omitted to permit convenient grouping of responses and to produce a 50 per cent cross-over area. These three patients were studied only to be certain that negative responses could be elicited at these lower concentrations. The concentration at which 50 per cent of the patients moved in group A was 3.4, in group B, 2.7, and group C, 0.8 per cent. This represents a 20 per cent reduction in minimum fluroxene alveolar concentration when morphine was given preoperatively and a 76 per cent reduction in MAC when the alveolar nitrous oxide concentration was 72 per cent. The fluroxene alveolar concentrations in group A patients were the same for those who did and did not receive cyclopropane inductions. The mean concentrations obtained in the cross-over areas

![Graph](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931629/)

**Fig. 2.** Patients were taken in groups of four from figure 1, starting from the lowest alveolar concentration. The patients at the lowest three concentrations in group A were omitted to permit convenient grouping of responses. The percentage of patients moving is plotted on the vertical axis against the average alveolar concentration of the four which is plotted on the horizontal axis.
for each group fell within the standard deviation from the mean of the group as a whole.

Alveolar fluoxetine concentrations were compared for the cross-over areas in groups A and B. Difference from the means of each were statistically significant ($P < 0.05$).

Figure 3 shows fluoxetine equivalents for morphine and nitrous oxide. Morphine reduced the fluoxetine MAC by 20 per cent and therefore is equivalent to an alveolar fluoxetine concentration of 0.7 per cent. Seventy-seven per cent inspired nitrous oxide reduced the fluoxetine MAC by 76 per cent and is therefore equivalent to an alveolar fluoxetine concentration of 2.6 per cent.

There appeared to be no correlation of the results with age, weight, nasopharyngeal temperature, or sex. Mean values for each group are shown in table 1. However, 82 per cent of the patients were females. This was an unintentional selection but resulted from our selection of healthy middle-aged patients who were primarily from the gynecological and general surgical services.

**Discussion**

Potency of an anesthetic agent may be related to its oil/gas solubility coefficient.$^3,^10$ The greater the lipid solubility, the lower the alveolar (arterial) concentration required to produce anesthesia. The minimum anesthetic concentration multiplied by the oil/gas partition coefficient should thus be the same for each agent.$^{11}$

We had previously determined the blood and tissue partition coefficients for fluoxetine.$^1$ Based on an oil/gas partition coefficient of 47.7, we predicted a fluoxetine MAC of 3.5. This value was substantiated by the determination of a MAC value of 3.4 per cent in our group A patients. Expressed in terms of minimum anesthetic tension (MAT), 3.4 per cent would equal an alveolar fluoxetine tension of 25 mm. of mercury.

The addition of 10–15 mg. morphine preoperatively reduced the fluoxetine MAC by 20 per cent. In the previously mentioned halothane study$^2$ morphine was shown to reduce the MAC by only 9 per cent. However, in that study the narcotic dosage was not uniform and smaller doses of both morphine and meperidine were used. The difference in dosages may account for the variability in morphine response. However, time and site of injection, as well as dosage, may influence the uptake and distribution of parenterally administered drugs.

Several reports in the older literature make reference to the reduction in anesthetic concentration after morphine premedication. Seevers et al.$^{12}$ and Waters and Schmidt$^{13}$ commented that in both dogs and man there appeared to be a reduction in cyclopropane dosage in the presence of morphine. Robbins et al.$^{14}$ showed a 27 to 48 per cent reduction in arterial blood cyclopropane concentration in dogs medicated with 2 mg./kg. morphine during surgical levels of anesthesia. Taylor et al.$^{15}$ using a dosage of 10 mg. morphine in 7 patients, showed a 15 per cent reduction in arterial ether levels required to produce the same electroencephalographically determined levels as in patients with narcotics.

There are several factors which might influence our estimate of alveolar nitrous oxide concentration. Removal of nitrous oxide from
alveolar gas by uptake would tend to reduce alveolar concentration. For example, removal of 20 per cent of the nitrous oxide by uptake from an 80 per cent nitrous oxide–20 per cent oxygen mixture would result in a reduction of nitrous oxide concentration to 75 per cent \[(80-20)/(80-20) + 20 = 75\]. However, Severinghaus \(^{18}\) has shown that nitrous oxide uptake after 30 minutes of inhalation of such a mixture is minimal (200 ml. per minute). With an alveolar ventilation of 5 liters per minute of 80 per cent nitrous oxide, uptake of 200 ml. per minute would represent only 5 per cent removal as opposed to the value of 20 per cent in the above example. The tendency of nitrous oxide uptake to reduce alveolar concentration is further minimized by the concentration effect \(^{17}\) which says that differences between alveolar and inspired concentrations are reduced at high concentrations.

The reduction in nitrous oxide concentration is also counterbalanced by fluoroxyne uptake and a respiratory quotient of less than 1.

When nitrous oxide was added to fluoroxyne-oxygen mixtures, the fluoroxyne MAC was reduced by 76 per cent. In the similar study with halothane \(^2\) nitrous oxide reduced the MAC by 60 per cent. The alveolar nitrous oxide concentration used with fluoroxyne was slightly greater than that used with halothane (72 versus 65 per cent). The contribution of nitrous oxide in reducing the MAC in these two studies is much greater than previously reported.

This greater effect of nitrous oxide in reducing anesthetic requirement may be the result of measurements made at truly light anesthetic levels. Heretofore, studies with nitrous oxide have been made using less well-defined endpoints such as electroencephalography and anesthetic blood levels as guides to anesthetic depth. Often determinations were made on venous blood or before complete equilibrium with inspired concentrations had occurred.

Our results with nitrous oxide confirm the observations of several other investigations. Sadove et al. \(^{18}\) reported alveolar fluoroxyne concentrations as low as 3.2 per cent in anesthetized patients who had also received barbiturates, narcotics, and/or nitrous oxide. They commented that the amount of fluoroxyne required to achieve surgical anesthesia was diminished with the use of nitrous oxide. Dundee and his associates \(^{19}\) also reported arterial fluoroxyne concentrations during anesthesia with nitrous oxide. Alveolar concentrations calculated from their data are as low as 1.2 per cent during light levels of surgical anesthesia.

The data in figure 3 suggest that the combination of morphine and nitrous oxide would require very little, if any, fluoroxyne for a minimum anesthetic effect, since the equivalent fluoroxyne concentration of the two in combination would equal \(2.6 + 0.7 = 3.3\) per cent. Studies to investigate this facet have already been initiated.

Nitrous oxide potency can be predicted from our data. The oil/gas partition coefficient of fluoroxyne is 47.7. \(^{1}\) Multiplying by MAC 1 (3.4), 162 is obtained. An inspired nitrous oxide concentration of 77 per cent would be about 72 per cent alveolar. Multiplying by the oil/gas partition coefficient of nitrous oxide (1.4), \(^{11}\) a value of 100 is obtained. The figure is 62 per cent (100/162) of that found for fluoroxyne. This suggests that the addition of nitrous oxide to fluoroxyne would result in a comparable decrease in the required fluoroxyne alveolar concentration, just what was found. Also suggested is that 115 per cent nitrous oxide (162/1.4) or a tension of about 860 mm. of mercury would provide a MAC 1 for nitrous oxide.

Fluoroxyne is reported to be flammable in concentrations above 4.5 per cent. \(^{20}\) Clinically, if fluoroxyne anesthesia is combined with nitrous oxide, narcotics, and muscle relaxants, inspired concentrations during maintenance need not exceed 4.5 per cent. However, concentrations of 7–14 per cent may be required during the first few minutes for a rapid induction of anesthesia. \(^{21}\)

**Summary**

Surgical patients were anesthetized with fluoroxyne-oxygen with and without morphine premedication, and with fluoroxyne with and without nitrous oxide. A minimum anesthetic concentration (MAC) of 3.4 per cent for fluoroxyne was required to abolish patient movement in response to surgical incision. A 20 per cent decrease in this value (2.7 per cent fluoroxyne) was found when morphine was given preoperatively. A 76 per cent decrease
in required fluroxene (0.8 per cent) was found when an alveolar concentration of 72 per cent nitrous oxide was added to the fluroxene anesthetic. With the use of nitrous oxide non-flammable inspired and alveolar fluroxene concentrations may be maintained at light levels of anesthesia.

Supported in part by United States Public Health Service grants USPHS 5T1-GM-63-06, USPHS 5-K3-GM-17, 685-03, and USPHS HE 07946-02.

Fluroxene (Fluromar) for this study was supplied by the Ohio Chemical and Surgical Equipment Company, Madison, Wisconsin.

References


7. Reivich, M.: Arterial PCO2 and cerebral hemo-


