Equipotent Alveolar Concentrations of Methoxyflurane, Halothane, Diethyl Ether, Fluroxene, Cyclopropane, Xenon and Nitrous Oxide in the Dog

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The minimum alveolar concentration of anesthetic (MAC) required to prevent response to a painful stimulus was determined in dogs for 7 agents. These equipotent concentrations (in volumes per cent at sea level) were: methoxyflurane 0.230, halothane 0.87, diethyl ether 3.04, fluroxene 6.0, cyclopropane 17.5, xenon 119, and nitrous oxide 188. MAC thus determined correlated more closely with the oil/gas partition coefficient than any other physical constant.

A PREVIOUS paper evaluated the minimum alveolar concentration of anesthetic (MAC) required in dogs to prevent gross movement in response to a painful stimulus.[1]

It was suggested that because of stability and reproducibility, MAC might serve as a standard of anesthetic potency and a means of comparing different anesthetics. Accordingly, we have determined MAC for 7 anesthetics: methoxyflurane (Penthrane, CH_3-O-CF_2-$CHCl_2$), halothane (Fluothane, CH_3-$CHClBr$), diethyl ether, fluroxene (Fluoromar, CF_3-CH_2-O-$CH{=}CH_2$), cyclopropane, xenon, and nitrous oxide.

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Methods

The techniques for analysis of methoxyflurane, halothane, fluroxene, and cyclopropane have been described.[1] Ether was analyzed in the same manner as halothane, the infrared analyzer being sensitive to both agents.[2] For the initial studies with nitrous oxide, analysis was done with an infrared analyzer sensitive to that agent only. The use of nitrous oxide and of xenon required a pressure chamber to achieve adequate anesthetic partial pressures. The infrared analyzer was outside the pressure chamber, and the pressure within the chamber was used to force end-tidal samples through the sample cell, the outer end of which was exposed to ambient air. A needle valve regulated flow (and pressure) between analyzer and pressure chamber. After 10–15 minutes of nitrous oxide anesthesia, no difference was seen between inspired and end-tidal nitrous oxide concentration. This would be expected from the concentration effect,[3] since the inspired concentrations used usually exceeded 70 per cent. Flow through the analyzer after 15 minutes was reduced to low levels so that the pressure of the gas within the sample cell was that of ambient air. The analyzer was calibrated with known concentrations of nitrous oxide in oxygen. Nitrous oxide concentration within the cylinders thus used in turn was tested indirectly by analysis of the oxygen with a model E Beckman-Pauling meter, accurate to at least 0.1 per cent.

Since there was no difference between inspired and end-tidal nitrous oxide concentration after 15 minutes, a second technique for analysis of nitrous oxide, that of oxygen dif-

ference, was used for the remaining experiments. A model D Beckman-Pauling meter, accurate to ± 1 per cent, was used to measure oxygen from the inspiratory limb of the circle absorption system. The per cent nitrous oxide obtained after correction for water vapor was identical with that determined by infrared analysis. In all cases the actual tension of nitrous oxide was calculated from the concentration and known total pressure in the chamber.

Xenon was also analyzed indirectly by analyzing the residual oxygen content. The xenon used contained 5 per cent krypton; therefore the actual concentration was 95 per cent of the figure obtained by oxygen difference. From the oil/gas partition coefficients of xenon (1.9) and krypton (0.67),[4] we estimate that krypton is 35 per cent as potent an anesthetic as xenon. This is in agreement with the relative narcotic effect stated by Carpenter.[5] Five per cent krypton therefore was taken to represent 1.8 per cent xenon and total xenon concentration calculated accordingly. Determination of xenon and krypton concentration by the oxygen difference technique was checked in two dogs by gas chromatography. The results were essentially the same as those obtained by the difference method.

Anesthesia was induced and maintained with only the agent to be studied in the cases of halothane, fluroxene, and cyclopropane. Induction was achieved with cyclopropane for the study of the remaining gases. With methoxyflurane, ether, and nitrous oxide the cyclopropane was eliminated from the system by inflow rates greater than 4 liters per minute, continued throughout the experiment. The technique with xenon was altered slightly because we had so little of this rare gas. Anesthesia was induced with cyclopropane. After less than 5 minutes, succinylcholine, 10 mg., was administered and the trachea intubated. The endotracheal tube was connected to an anesthetic circle system. Inflow was changed to oxygen at flows greater than 10 liters/minute for a minimum of 20 minutes. Ventilation was controlled during this time. After 20 minutes the inflow was decreased to 0.5–1 liter/minute and the inspired oxygen concentration monitored for 5 minutes. This was always found to be equal to or within 1 per cent of pure oxygen, indicating a virtually complete washout of cyclopropane. Xenon was administered as the animal recovered from the succinylcholine paralysis. The animal and circle system were then placed in the pressure chamber and the experiment begun. Inflow continued throughout the experiment at flows never less than 0.5 liters/minute.

Though the induction technique was not identical for all gases, the result in all cases was an anesthetized dog breathing spontaneously through a cuffed endotracheal tube connected to an anesthetic circle system. All dogs were given deep breaths every 10 to 15 minutes, except the animals receiving nitrous oxide or xenon, these being inaccessible within the pressure chamber. All animals except those in the pressure chamber were given a continuous infusion of 5 per cent dextrose in water. Except for those animals kept at high pressure, an arterial cannula was inserted and arterial blood P_{O_2}, P_{CO_2}, and *p*H determined with appropriate electrodes. Buffer base deficit for all animals, except those receiving ether, rarely exceeded 5 mEq./liter. With ether, deficits of 10 to 15 mEq./liter were common. These were corrected to less than 5 mEq./liter by intravenous injection of sodium bicarbonate. Esophageal temperature was measured in all animals with a Yellow Springs Telethermometer. In one dog receiving nitrous oxide and one receiving xenon, maximum temperatures of 40° C. were recorded. One dog receiving xenon had a minimum temperature of 35° C. With these exceptions, the temperature was held between 36.5 and 38.5° C.

The technique for stimulation has been described.[1] Because they were inaccessible, those animals under nitrous oxide or xenon anesthesia were stimulated by electrical shock of 40 volts. In the remaining animals the tail clamp was used.

We have found an end-tidal to arterial anesthetic partial pressure gradient for nitrous oxide (unpublished data). We believe this gradient is related to the relative size of the inspired to end-tidal pressure gradient. With moderately soluble agents, such as halothane or fluroxene, or poorly soluble agents, such

as cyclopropane, nitrous oxide, or xenon, the inspired to end-tidal and hence end-tidal to arterial pressure gradients are relatively small. In these cases the arterial and brain pressures are accurately reflected in the end-tidal pressures. However, with highly soluble anesthetics such as diethyl ether or methoxyflurane, a large pressure gradient may exist from inspired to end-tidal and hence from end-tidal to arterial samples. This has been demonstrated in man for methoxyflurane by Holaday, Garfield, and Ginsberg.[6] In experiments with diethyl ether and with methoxyflurane these inspired to end-tidal tension gradients were eliminated by prior saturation of the animals with these agents. Since in these experiments essentially no gradient existed from inspired to end-tidal samples, we assume that no gradient existed between end-tidal and arterial samples.

It must be remembered that the concentrations determined in this study apply only at an ambient pressure of one atmosphere, or 760 mm. of mercury. Our basic interest in MAC is not really in alveolar anesthetic concentration, but rather in anesthetic partial pressure. The latter is the real constant for any one gas, while the former varies with ambient pressure. Anesthetic partial pressure as opposed to concentration also has the advantage, at equilibrium, of being equal at all places. At equilibrium then, anesthetic partial pressure in the alveolus is identical to the pressure in brain or any other tissue. On the other hand, at equilibrium, concentration in the alveolus is almost invariably different from brain or other tissue concentrations because of differences in relative solubility.

Results

The results are given in table 1, anesthetics listed in order of decreasing potency.

As in the previous study,[1] MAC did not vary appreciably with duration of anesthesia with any of the agents tested.

TABLE 1

Agent	Number of Dogs Studied	MAC at 760 mm. Hg*
Methoxyflurane	11	0.230± 0.027
Halothane	26	0.87 ± 0.12
Ether	10	3.04 ± 0.53
Fluroxene	6	5.99 ± 1.14
Cyclopropane	12	17.5 ± 3.8
Xenon	5	119 ± 8.3
Nitrous oxide	5	188 ±35

* ± one standard deviation.

Discussion

The MAC values obtained agree with the work of others. The few discrepancies may be owing to the differences in the sample source. For example, if inspired ether or methoxyflurane concentrations are compared with alveolar concentrations, appreciable, even five-fold differences may be found even after a "steady state" appears to be present.[6, 7] This is due to the continuing high and relatively constant uptake of these very soluble agents. Similar, though smaller, differences occur with halothane[8] and fluroxene.[9] On the other hand, little difference should be found for the relatively insoluble agents cyclopropane, xenon, and nitrous oxide.[10]

Making allowance for such differences in sampling, the MAC values we have obtained are close to the concentrations which others have found necessary for light anesthesia.* For example, methoxyflurane MAC of 0.230 per cent found by us approximates the 0.28 per cent which abolished response to manipulation of an endotracheal tube in dogs.[12] It is considerably less than the 0.45 per cent which gave surgical anesthesia in dogs,[13] but is similar to the 0.28 per cent concentration required to abolish response to electrical stimulation in goldfish.[14] The latter figure, of course, is not an alveolar concentration, but is the equivalent obtained by calculation from partial pressures extrapolated to 2.1 mm. Hg at 37° C.

Published reports give halothane percentages of 1.1,[13] 1.0–1.2,[15] or 0.6 [16] as the alveolar concentration necessary for surgical anes-

* The succeeding values from others' work are often not available as alveolar concentrations. They are often given as tension measurements which may be converted to volume per cent by multiplying by 100/760. Arterial blood concentrations may be changed to alveolar concentrations through the use of known blood/gas partition coefficients.[11]

TABLE 2

Agent	Oil/Gas *	MAC × Oil/Gas	VP†	VP/MAC
Methoxyflurane	825	190	56	243
Halothane	224	195	480	552
Ether	65	198	820	270
Fluroxene	47.7	286	600	100
Cyclopropane	11.8	207	7,450	426
Xenon	1.90	227	60,800‡	511
Nitrous Oxide	1.40	263	59,300	315

* Oil/gas refers to the partition coefficient at 37° C.

† VP is saturated vapor pressure in millimeters of mercury at 37° C.

‡ Extrapolated valve.

thesia in the dog. These values are close to the 0.87 per cent we obtained. Similar figures are obtained for a wide variety of creatures: man 0.74 per cent,[17] mice 0.86[15] to 1.7[18] per cent inspired, monkeys 1.0–1.2 per cent inspired,[15] and goldfish 1.8 per cent.[14]

There are few values published for the alveolar fluroxene concentrations required for anesthesia in the absence of supplementary agents. In man a concentration of 3.4 per cent is sufficient to eliminate movement in response to surgical incision.[19] This is somewhat less than the 6.0 per cent figure given by our study. However, 3.4 per cent is consistent with the less severe stimulus used in man.

The ether MAC of 3.04 per cent we obtained is close to that obtained by others when compared to arterial or alveolar values. For example, concentrations of 2.2 per cent,[13] 3.2–3.5 per cent,[20] 2.9 per cent,[21] and 3.1–3.7 per cent[22] are reported to give light surgical anesthesia in dogs. Other values are: mice 3.4 per cent (inspired),[23] goldfish 3.8 per cent.[14]

There is close agreement between our MAC of 17.5 per cent for cyclopropane and the published figures. Others find that light anesthesia in dogs is produced by 18 to 23.4 per cent.[21, 24]

Few figures are available with which to compare the xenon MAC of 119 per cent in dogs, actually 1.19 atmospheres of xenon. The most comparable study is that of Domino *et al.*[25] in which 1.84 atmospheres of xenon were required for light anesthesia. The reason for this difference is not apparent. Domino *et al.* were seeking to determine the effects of xenon on the electroencephalograph and perhaps were more concerned with this aspect. They did find that the xenon concentration required for anesthesia during recovery (about 1.6 atmospheres) was less than during induction, possible indicating incomplete equilibration early in the experiment. One other possible explanation exists for the discrepancy between our data and that obtained by Domino *et al.* We have used a 95-5 per cent xenon-krypton mixture, whereas Domino used pure xenon. We have assumed that the krypton anesthetic effect was simply added to that of xenon. If, however, the krypton acts synergestically, this might explain our lower MAC values.

Our nitrous oxide MAC value of 188 per cent agrees with a 1.7–2.0 atmosphere value given by Domino *et al.* for one dog.[25] In rabbits gross muscular response to painful electrical stimulation is not abolished in the absence of hypoxia by 1.7 atmospheres of nitrous oxide.[26] In mice the righting reflex is lost at 1.5 atmospheres.[18]

Several authors have shown that a close correlation exists between the solubility of an anesthetic in oil, expressed as the oil/gas partition coefficient, and anesthetic potency.[5, 23, 27, 28] Multiplying the oil/gas partition coefficient by the equipotent tensions of several anesthetics gives a number which usually varies over a four- to five-fold range.[5, 23, 27, 28] This is a small variation compared to the thousand-fold difference in anesthetic tension from which it is derived. In table 2 we have made a similar manipulation of oil/gas and MAC figures from our data. The correlation here is far better than previously reported, the extremes of the oil/gas times MAC figures being 190 (methoxyflurane) and 286 (fluroxene). The latter is only half again as great as the former. As in other studies, this occurs over a nearly eight hundred-fold range of anesthetic tensions (table 1). This remarkably close correlation is illustrated in figure 1.

There are a number of other physical properties such as Van der Waals forces,[29] molecu-

lar weight[30] or volume,[31] the dissociation pressure of hydrate crystals,[32, 33] or vapor pressure[34, 35] that may be related with potency. However, no other correlation known to us approaches the consistency with which the oil/gas coefficient is related to potency. The next closest is that of vapor pressure. With increasing pressure there is a decrease in potency, expressed as an increase in MAC. Therefore, vapor pressure/MAC is roughly a constant. Table 2 provides this relationship for the 7 gases studied. Vapor pressure/MAC has a low of 100 for fluroxene and a high of 552 for halothane—a 5½ fold difference. The correlation is illustrated in figure 2.

Similarly, a correlation exists between the anesthetic partial pressure and hydrate dissociation pressure at 0° C. such that the ratio of the two pressures is constant. Miller[33] calculated these ratios for 25 gases or vapors and found approximately a 150-fold variation for an 1,100-fold range in anesthetic partial pressures. Even if the more aberrant gases such as carbon dioxide and sulfur hexafluoride are excluded, there remains a large (10-fold) variation in ratios. For example, among the gases we considered, nitrous oxide gives a ratio of 0.09, while xenon gives a ratio of 0.7—roughly an 8-fold variation.

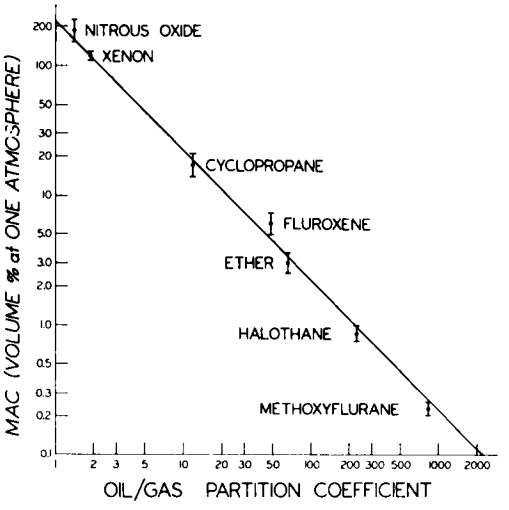

FIG. 1. Relation between MAC and the oil/gas partition coefficient. The bars through the points indicate the limits of one standard deviation from MAC. The line drawn through the points is given by the equation: MAC times oil/gas partition coefficient equals 223.7, 223.7 being the average figure given by all such multiplications of MAC and oil/gas partition coefficient from the experimental data (see table 2).

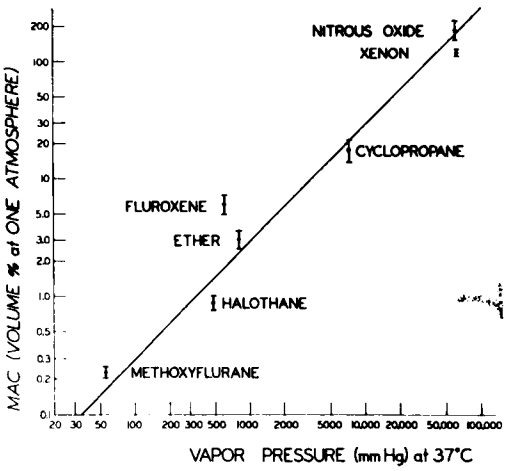

FIG. 2. Relation between MAC and the vapor pressures (VP) in millimeters of mercury of the anesthetics at 37° C. (extrapolated in the case of xenon). The bars through the points indicate the range of 1 standard deviation from MAC. The line drawn through the points is given by the equation: VP/MAC equals 345.3, where 345.3 is the average figure given by all such VP/MAC ratios obtained experimentally (see table 2).

The far closer correlation of oil solubility with anesthetic potency suggests the importance of lipid solubility in the mechanisms by which anesthetics act. As others have pointed out, this is not a theory of anesthesia. But any theory must either explain the coincidental nature of this correlation or suggest a direct relationship between the presence of anesthetic in a lipid phase and anesthetic action. The lipid phase may be the phospholipid portion of lipoprotein forming various cell membranes. However, the correlation of potency and olive oil solubility may not be directly transferable to solubility in phospholipids or lipoproteins. No data exist yet by which this may be tested.

MAC is of more than theoretical interest. If used as a common measure of anesthetic potency it will allow a comparison of data among laboratories. A comparison of cardiovascular, respiratory, or other effects of two or more anesthetics may be made if the alveolar (or arterial) tension is known along with

the change in the parameter studied. A proportionate change of MAC may be used to define a similarity or dissimilarity between depths of anesthesia. Thus, in dogs 0.230 per cent methoxyflurane represents a depth equal to that achieved by 17.5 per cent cyclopropane. Similarly, 35 per cent cyclopropane (two times MAC) is equivalent to 0.46 per cent methoxyflurane, but both represent a far greater depth than 6.0 per cent fluroxene.

Summary

The minimum alveolar anesthetic concentration (MAC) required (at sea level) to prevent movement in response to a painful stimulus was determined in dogs for 7 anesthetics. These were: (in volumes per cent) methoxyflurane 0.230, halothane 0.87, diethyl ether 3.04, fluroxene 6.0, cyclopropane 17.5, xenon 119, and nitrous oxide 188. These values provide a useful reference standard for the definition and comparison of anesthetic depths.

These MAC values correlate closely with lipid solubility. Correlation with other parameters such as vapor pressure or the dissociation pressure of hydrate crystals is considerably less exact.

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AWAKE INTUBATION To achieve limited spread of local anesthetic agent, translaryngeal, transtracheal, or superior laryngeal nerve block should not be performed. Instead, a direct transoral spray should be employed so as to anesthetize only the base of the tongue, vallecula, and epiglottis, thus making laryngoscopy painless. The patient is instructed to take a deep inspiration, and a well-lubricated tube is inserted between the abducted cords. The cuff is immediately inflated and general anesthesia induced. Limited topical anesthesia has been used several hundred times without a single case of aspiration; in particular the technique has allowed the safe management of intestinal obstruction and upper gastrointestinal hemorrhage. (*Walts, L. F.: Anesthesia of the Larynx in the Patient With a Full Stomach, J.A.M.A. 192: 705 (May 24) 1965.*)

HEPATIC TOXICITY Prolonged ether-oxygen anesthesia has a toxic effect on the liver as indicated by the fall of serum albumin and the rise of alpha globulin demonstrable on the fifth postoperative day. Nitrous oxide has not such hepatotoxic effect but is also not perfectly safe as it alters the distribution of protein between the blood and the tissues (total serum protein rises). The toxic effect of anesthesia is further increased by combining ether with nitrous oxide. (*Toritsyn, V. A.: Effect of Anesthesia and Operation on Liver Function as Shown by Studies of Serum Protein Fractions (Russian), Eksper. Khir. 5: 71 (1964.)*