Effects of Lidocaine on the Anesthetic Requirements for Nitrous Oxide and Halothane

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The effects of various plasma concentrations of lidocaine on nitrous oxide anesthesia in man and halothane requirements in the dog were studied. The response to incision of the skin was observed in 20 patients who were anesthetized with nitrous oxide, 70 per cent inspired, and oxygen, 30 per cent, plus various plasma levels of lidocaine. In addition, changes in the MAC of halothane in dogs were observed at various levels of lidocaine. In both circumstances lidocaine concentrations of 3 to 6 µg/ml decreased anesthetic requirements approximately 10 to 28 per cent. At clinically common concentrations of lidocaine, significant decreases in anesthetic requirements should be anticipated. (Key words: Anesthetics, gases, nitrous oxide; Anesthetics, volatile, halothane; Anesthetics, local, lidocaine; Potency, anesthetic, MAC.)

ALTHOUGH a number of investigators have described the use of lidocaine as part of a general anesthetic combination,[1–4] until recently no quantitative studies have correlated anesthetic effects with plasma lidocaine concentrations. In an earlier report from this laboratory,[5] the MAC of cyclopropane in rats showed a linear decrease with lidocaine concentrations to 1 µg/ml. Above this level, a plateau effect was observed, with a mean decrease of MAC of 42 per cent for lidocaine concentrations of 1.1 to 5.5 µg/ml. As an extension of these data, the following study was undertaken to determine first, the effect of lidocaine on nitrous oxide anesthesia in man; and second, its effects on halothane requirements in the dog.

Methods and Materials

Studies were made on 20 ASA class I and II consenting patients between the ages of 18 and 49 years (mean 29), including three men and 17 women, who were having a variety of surgical procedures involving

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an incision of the skin on the trunk. We excluded any patient taking medication known to influence anesthetic requirements. All were premedicated with morphine, 8 to 12 mg, and atropine, 0.3 to 0.5 mg, intramuscularly approximately an hour before induction of anesthesia. Prior to starting an intravenous infusion of 5 per cent dextrose in lactated Ringer's solution, a venous blood sample was drawn into a heparinized tube. Patients were monitored routinely by ECG, blood pressure by cuff, and pulse rates by palpation. A constant intravenous infusion of lidocaine, 45 to 100 µg/kg/min, was begun with an infusion pump while each patient inhaled oxygen by mask for 4 to 5 minutes. Each patient then breathed nitrous oxide, 90 to 100 per cent, for 60 to 90 seconds to achieve a rapid induction and minimize excitement; thereafter, nitrous oxide, 70 per cent, and oxygen, 30 per cent, were given to maintain anesthesia.

Over the next five minutes, lidocaine, 2 to 2.5 mg/kg, was administered intravenously in divided doses to each patient. Routine surgical preparation of the skin followed, after which the patient's response to incision of the skin was observed. Just prior to the incision, a sample of arterial blood was drawn from a radial artery. Both the arterial and preanesthetic venous blood samples were analyzed by gas chromatography[6] for lidocaine and its first primary metabolite, monoethylglycinexylidide (MEGX).[7] When analysis of the venous control samples revealed any trace contaminating values, these were subsequently subtracted from the results of the arterial blood determinations. Total lidocaine infusion times ranged from 15 to 40 minutes, depending upon the time requirements of the surgical schedule.

In the second part of the study, seven mongrel dogs weighing 14 to 18 kg were anesthetized with halothane and oxygen. The trachea was intubated following administration of succinylcholine, 0.3 to 0.6 mg/kg. An intravenous infusion of dextrose, 5 per cent, in lactated Ringer's solution was started, and a femoral artery was cannulated percutaneously with a 20-gauge plastic catheter. Systemic arterial pressure was monitored with an arterial pressure transducer and was displayed on an oscilloscope. In addition, an 18-gauge plastic catheter was inserted percutaneously into the cisterna magna of each of five dogs for
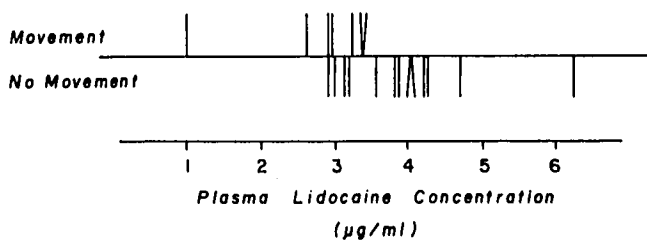
FIG. 1. Individual responses to a skin incision are plotted against plasma lidocaine concentration in the presence of 70 per cent inspired nitrous oxide. Upward deflections indicate movement and downward deflections, no movement. A cross-over zone is evident between 2.9 and 3.5 μg/ml.

sampling of cerebrospinal fluid (CSF). The lungs of each dog were ventilated artificially with a volume-limited, nonrebreathing ventilator to maintain P_{CO_2} between 30 and 35 torr. Body temperature was measured with an electronic rectal temperature probe and was maintained at 37 C with a warming mattress. During the experiment, arterial blood-gas values were determined regularly, and appropriate corrections were made for abnormalities.

After a two-hour equilibration period, the MAC for halothane was determined using a tail-clamp stimulus applied for 45 to 60 seconds[8]; MAC was then redetermined after another 45 minutes. Prior to each stimulus, end-tidal gas samples were drawn into glass syringes through a polyethylene tube that had been inserted beyond the tip of the endotracheal tube. The halothane concentration of this end-tidal gas was assayed by gas chromatography and was compared with known concentrations of halothane that were prepared before each experiment. The differences between the end-tidal halothane concentrations drawn for the two MAC values were small, indicating relatively steady-state conditions. The average of these two MAC values was considered to be the control value.

In each animal a constant lidocaine infusion of 15 to 400 μg/kg/min was then started, followed by a divided-dose, intravenous injection of lidocaine, 1.5 to 2.0 mg/kg. An equilibration period of an hour was allowed, and the MAC for halothane then was redetermined. Arterial blood and CSF were collected and analyzed by gas chromatography for the concentrations of lidocaine and MEGX. Three or four different rates of lidocaine infusion, each greater than the previous rate, and MAC for halothane were determined for each animal.

Results

When individual responses to incision of the skin are plotted against plasma lidocaine concentrations, it is apparent that a cross-over zone exists between

2.9 and 3.5 μg/ml, in which some patients moved and some did not. However, above 3.5 μg/ml none of the patients moved (fig. 1). Therefore, under the conditions of this study, the MAC value may be presumed to be approximately 3.2 μg/ml.

The animal experiments revealed a control MAC of 0.93, which closely approximates previously reported values.[9] The effect of plasma lidocaine upon the MAC for halothane (fig. 2) reveals little or no change at concentrations below 3.0 μg/ml and a rapid decrease of MAC with lidocaine concentrations ranging from 3.0 to 11.6 μg/ml. This is followed by a plateau, above which no further decrease in MAC was observed when higher lidocaine concentrations were administered. From these data, a maximum decrease of MAC of halothane of approximately 45 per cent was observed when lidocaine concentrations were above 11.6 μg/ml. When the CSF lidocaine effect on MAC for halothane is plotted (fig. 3), a rapid decrease in MAC is observed, followed by a peak plateau.

The highest concentrations of MEGX in patients were less than 1 μg/ml. Similarly, the MEGX levels in dogs were small fractions of the lidocaine concentrations (less than 20 per cent). The possible contribution of this metabolite to the total anesthetic effect was thought to be negligible in both instances.

Discussion

Despite the fact that lidocaine has been used to supplement general anesthesia for approximately 25 years, quantitation of its effect is lacking. From studies that show the additivity effectiveness of volatile anesthetics,[10,11] it appears to be possible to determine the independent contributions of the various components of an anesthetic combination. These studies utilize the concept of MAC fractions, and while the combination of a MAC fraction of a fixed drug with a volatile anesthetic has not been established, additivity does appear to be present over a considerable dosage range when morphine and meperidine are used as fixed drugs.[12] If lidocaine behaves in a similar manner, then an estimate of the contribution of lidocaine to the total anesthetic effect can be made.

A 7 to 20 per cent decrease in general anesthetic requirements has been observed after morphine premedication,[13,14] or in terms of anesthetic additivity, 0.07 to 0.20 equivalent MAC fractions. If the MAC for nitrous oxide in man is approximately 100 per cent, as reported,[15] then 70 per cent inspired nitrous oxide (equivalent to 65 per cent alveolar concentration) must be combined with an anesthetic that contributes 35 per cent of the total anesthetic effect necessary to prevent a response to incision of the

skin in 50 per cent of patients. In terms of MAC fractions, if morphine premedication is used and adds 0.07 to 0.20, then we assume that lidocaine must contribute a 0.15 to 0.28 MAC fraction. In the first part of this study, 0.28 MAC was achieved with a blood lidocaine concentration of approximately 3.2 μg/ml.§

The experimental data in the dog demonstrate that halothane requirements are altered by increasing concentrations of plasma or CSF lidocaine. Plasma lidocaine concentrations of 3 to 6 μg/ml produced 10 to 25 per cent decreases in MAC (fig. 2). These concentrations of lidocaine are common in man after regional anesthesia and after its use intravenously for the control of cardiac arrhythmias.[16,17]

The concentration of lidocaine in the cerebrospinal fluid was measured as a first approximation of its concentration in brain tissue. The CSF lidocaine concentration and its effect on MAC for halothane paralleled the plasma lidocaine concentration and its effect on anesthetic requirements. However, in the CSF graph a threshold at which there is no change in MAC at low levels of lidocaine is not observed. This may result from an inability of the methods used to measure the CSF levels of lidocaine produced when the plasma levels are low. In addition, failure to detect lidocaine in the CSF may result from a time lag for equilibration of the drug between plasma and CSF. In fact, no measurable CSF lidocaine was detected at the lowest plasma levels. There is also less scatter of the data points in the graph of the CSF compared with the plasma levels. This may reflect differences in plasma protein binding among the experimental animals, leading to significant differences in measurable amounts of free lidocaine. In contrast, the CSF is relatively protein-free, and concentrations should show less variation.

There are several clinical implications of these data. When a patient has received lidocaine, either as part of a regional anesthetic technique or intravenously for control of arrhythmias, blood levels of lidocaine greater than 3 μg/ml are common. Should a general anesthetic then be administered, an approximate 15 to 28 per cent decrease in anesthetic requirement should be anticipated.

In certain situations, advantage may be taken of this effect as part of a safe, alternative balanced anesthetic technique. In other instances, caution is suggested in the supplementation of an incomplete state of conduc-

§ A schematic equation for the addition of MAC fractions is as follows: $N_2O_{0.65} + M_{0.07-0.20} + Lx = 1.0$, where M and Lx represent the morphine and lidocaine concentrations, respectively. The subscripts refer to the fractional MAC equivalents. Solving for Lx = 0.15 - 0.28.
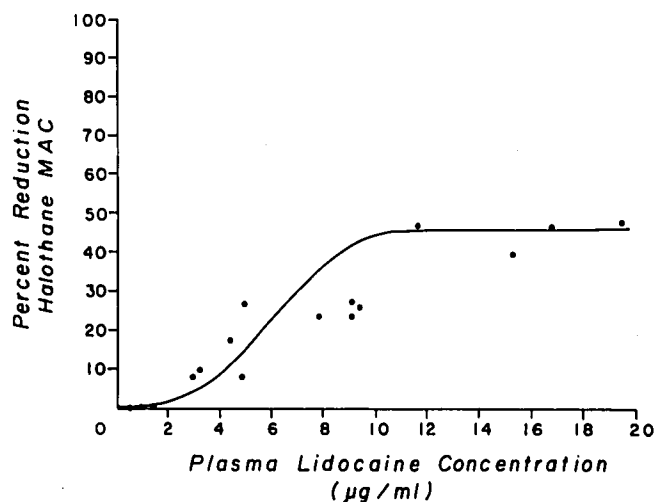

FIG. 2. Graph of the percentage reduction of MAC for halothane in dogs versus plasma lidocaine concentration. The curve is a visual best fit to indicate three parts of the curve: an initial threshold, at which no measurable change in MAC occurs at low levels of lidocaine; an area of rapid reduction in MAC with increasing concentrations of lidocaine; and a plateau at which no further change in MAC is observed. A maximum reduction of MAC of 45 per cent is observed.
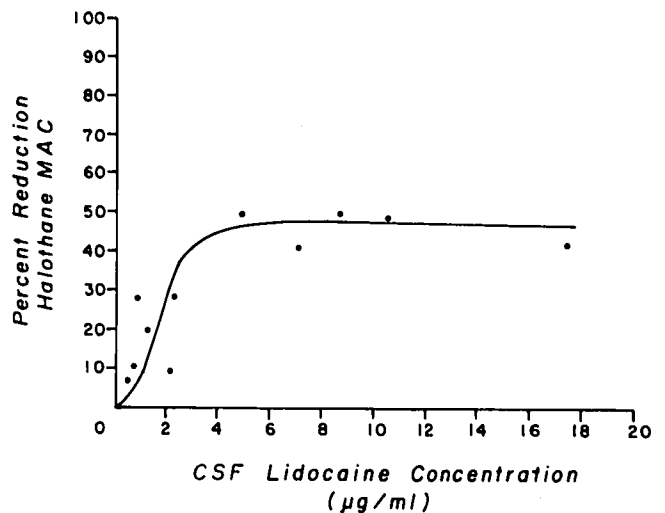

FIG. 3. Graph of percentage change in MAC for halothane in dogs versus CSF lidocaine concentration. Curve is a visual best fit to indicate area of rapid reduction in MAC, followed by a plateau region.

tion anesthesia initiated by lidocaine. In this regard, special caution should apply to the parturient after peridural block anesthesia with lidocaine that is supplemented with 30 to 50 per cent nitrous oxide analgesia. When the plasma lidocaine concentration is high enough to produce a 0.2 MAC fraction and is combined with 0.3 to 0.5 MAC fractions from nitrous oxide, a total of 0.5 to 0.7 MAC results. This subanesthetic range may place the patient in jeopardy of stage II excitement, with the possible

side effects of regurgitation and aspiration. With respect to the use of lidocaine to supplement general anesthesia, particular note should be made of the ceiling effect, suggesting that no further contribution to the desired anesthesia is obtained with higher, possibly toxic, levels of lidocaine.

In this study, a ceiling effect was observed, as increasing concentrations of lidocaine above a given level produced no further decrease in the MAC for halothane. This ceiling may result from a balance of the central sedative and stimulatory actions of lidocaine. It may also be that its sedative contribution depends on the interruption of certain neuronal pathways, and that any dose beyond that necessary to block these pathways produces no further effect. Miller, Way, and Eger[18] have observed a similar phenomenon for depletion of central nervous system catecholamines.

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