

Enflurane Requirement and Ventilatory Response to Carbon Dioxide during Lidocaine Infusion in Dogs

Richard S. Himes, Jr., M.D.,* Edwin S. Munson, M.D.,† William J. Embro, B.S.‡

Arterial plasma lidocaine concentrations of 1 to 3.5 $\mu\text{g/ml}$ produced dose-related decreases in enflurane requirement (MAC) ranging from 15 to 37 per cent in dogs. The ventilatory responses to carbon dioxide at comparable depths of anesthesia with enflurane alone and the enflurane-lidocaine combination were measured in each animal and compared. With both anesthetic regimens there were increases in resting arterial carbon dioxide tension (mean maximal increase = 18 torr) and a 69 per cent decrease in the slope of the ventilatory response as depth of anesthesia increased. The effect of the drug interaction appears to be additive, since the ventilatory depression produced by the enflurane-lidocaine combination was no greater than that produced by enflurane alone at equivalent levels of anesthesia. (Key words: Anesthetics, local: lidocaine. Anesthetics, volatile: enflurane. Potency, anesthetic: MAC. Ventilation: carbon dioxide response.)

LIDOCAINE frequently is administered to surgical patients for the control of cardiac arrhythmias¹ and the blocking of airway reflexes,² and for regional block procedures. Many of these patients subsequently receive general anesthesia. Lidocaine may also be administered as a supplement to inhalational anesthesia.³⁻⁵ Previous studies by Himes *et al.*⁶ have shown that lidocaine decreases minimum alveolar concentrations (MACs) of nitrous oxide and halothane as much as 28 and 45 per cent, respectively. However, there are no data to indicate whether the decrease in anesthetic requirement of the inhalational anesthetic agent is accompanied by a similar decrease in ventilatory depression. Therefore, we first determined the effect of lidocaine on enflurane requirement in dogs. Then we compared ventilatory responses to carbon dioxide administered during three levels of enflurane anesthesia with ventilatory responses at equivalent levels of anesthesia with enflurane and lidocaine.

* Instructor of Anesthesiology.

† Professor of Anesthesiology.

‡ Laboratory Technologist II.

Received from the Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida. Accepted for publication December 27, 1978. Supported by grants from Astra Pharmaceutical Products, Inc., Framingham, Massachusetts; and the Southern Medical Association.

Address reprint requests to Dr. Munson: University of Florida College of Medicine, Department of Anesthesiology, Box J-254, J. Hillis Miller Health Center, Gainesville, Florida 32610.

Methods and Materials

Fifteen experiments were performed on five male mongrel dogs ranging in weight from 13 to 25 kg (mean \pm SD, 19 \pm 5 kg). Each animal was studied on three occasions with an interval of at least one week between experiments. Studies were designed to determine enflurane requirement and evaluate the ventilatory response to carbon dioxide.

Animals were anesthetized with enflurane in oxygen administered by mask, and endotracheal intubation was performed without the use of other drugs. Each dog was allowed to breathe spontaneously from a low-resistance circle-absorber system. Blood pressure was recorded from a cannula placed percutaneously into a femoral artery. The ECG recorded cardiac rate and rhythm, and esophageal temperature was maintained at 37 \pm 0.5 C by means of an external heating lamp. A glucose and balanced salt solution was administered (5 ml/kg/hr) intravenously throughout the period of the experiments. Arterial blood was frequently sampled for measurements of Pa_{O_2} , Pa_{CO_2} , and pH_a and for calculation of base excess.⁷ Sodium bicarbonate was administered as necessary to maintain base excess greater than -4 mEq/l.

Enflurane requirement was determined in each animal using a tail-clamp stimulus.⁸ An equilibration period of at least 15 min was allowed at each level of enflurane anesthesia studied. End-tidal enflurane concentrations were monitored with a Beckman LB-2 halothane analyzer. The instrument, which is also sensitive to enflurane, was calibrated using gas mixtures stored in cylinders. The composition of these mixtures was determined by gas chromatography.⁹ The infrared head was filled with carbon dioxide to eliminate the cross-over effect of this gas.

After the determinations of MAC, each animal received a constant intravenous infusion of lidocaine at rates of 50, 100, and 200 $\mu\text{g/kg/min}$ by means of a constant-volume infusion pump. This sequence of infusions was always the same. At the onset of each infusion rate, an additional 1.5 mg/kg bolus of lidocaine was given intravenously over a five-minute period. We had previously determined that in five animals this dosage schedule produced steady-state plasma lidocaine concentrations (with a variation of 7.1 \pm 2.1 per cent of the final value) for periods as

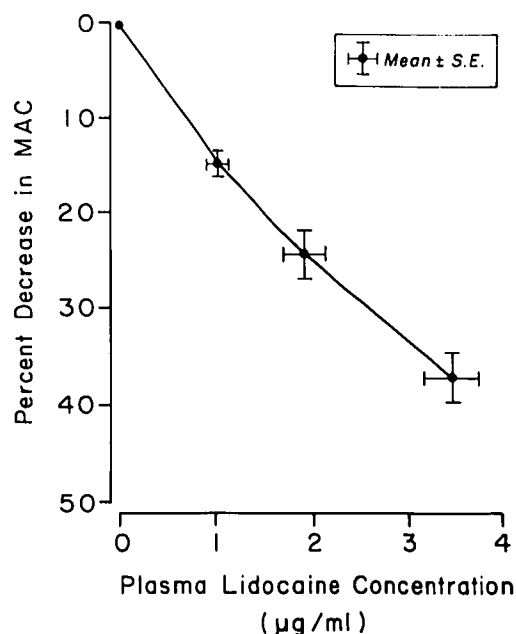


FIG. 1. Graph of the percentage decrease in MAC of enflurane in dogs versus plasma lidocaine concentration. For the concentration range studied, approximately 1.5 to 3.5 $\mu\text{g/ml}$, the mean values showed a 15 to 37 per cent linear decrease in enflurane MAC.

long as 60 min. After a period of at least 15 min for each administration of lidocaine, MAC of enflurane was redetermined. Heparinized samples of arterial blood were drawn for subsequent gas chromatographic analysis of plasma lidocaine concentration at each determination of MAC.¹⁰

After establishment of equivalent levels of anesthesia in each dog with enflurane alone and with the enflurane-lidocaine combination, the ventilatory response to carbon dioxide was measured in the same five animals at 1.1, 1.3 and 1.5 MAC enflurane, and on a separate occasion at equivalent levels of anesthesia with the enflurane-lidocaine combination. The sequences of enflurane and enflurane-lidocaine experiments were reversed in alternate animals. In addition to the analysis of plasma concentrations of lidocaine in animals tested with the enflurane-lidocaine combination, we also analyzed plasma for the presence of lidocaine metabolites at the termination of each experiment.

The animals were prepared and monitored in the same fashion as described for the experiments on anesthetic requirement. A recording ventimeter¹¹ was added to the anesthetic system in place of the reservoir bag to record minute ventilation. Measurements of ventilation were made at the resting level of carbon dioxide and then after stepwise increases of Pa_{CO_2} as carbon dioxide was added to the inspired gases. End-tidal concentrations (F_{ETCO_2}) were kept constant by continuous monitoring with a Godard capnograph. After a six-minute period at a constant F_{ETCO_2} , an arterial blood sample was obtained for determination

of Pa_{CO_2} . In addition, minute ventilation, respiratory rate, heart rate, and arterial blood pressure were measured over a two-minute period. Ventilation was measured at a minimum of four levels of increased Pa_{CO_2} over a range of at least 10 torr more than the resting level. Data were analyzed using a two-way analysis of variance and Tukey's multiple-comparison procedure.¹²

Results

The mean (\pm SEM) MAC for enflurane was 2.19 \pm .07 per cent. The administration of lidocaine resulted in dose-related decreases in the MAC of enflurane that ranged from 15 to 37 per cent (individual values ranged from 9 to 44 per cent). These decreases in enflurane MAC bore a linear relationship to arterial plasma lidocaine concentrations (fig. 1). The animals that had the greatest decreases in MAC of enflurane at the lowest plasma lidocaine concentrations also had the greatest decreases at the highest concentrations of lidocaine.

During anesthesia with enflurane and the enflurane-lidocaine combination, Pa_{CO_2} values increased as depth of anesthesia increased (table 1). With the exception of the 1.5 MAC levels, Pa_{CO_2} values at comparable levels of anesthesia were similar. However, because the plasma lidocaine concentration at the 200 mg/kg/min infusion rate was lower than anticipated, only 1.4 MAC was achieved. Extrapolation of the Pa_{CO_2} to a level of 1.5 MAC ($\Delta\text{Pa}_{\text{CO}_2}/\Delta\text{MAC} = 39.7$) yields a calculated Pa_{CO_2} of 58.2 torr, which is close to the 61.5 torr measured at 1.5 MAC enflurane.

The slope of the ventilatory response to carbon dioxide decreased as anesthesia depth increased in both anesthetic groups (table 1; fig. 2). Intragroup comparisons showed no significant difference between the enflurane and enflurane-lidocaine values at equivalent depths of anesthesia. No significant difference between heart or respiratory rates, values for minute ventilation, or arterial blood pressures was observed in the two anesthetic groups. No motor seizure activity was observed in any animal during the study. Lidocaine metabolites were detected in only two of five dogs. In these animals, monoethylglycinexylide concentrations were 0.37 and 0.55 $\mu\text{g/ml}$.

Discussion

Until more effective, short-acting, antiarrhythmic drugs or local anesthetics become available, lidocaine will continue to be used widely in the operating room. In this setting many patients will receive it in addition to other drugs. We have examined two aspects of the lidocaine-enflurane interaction, namely the impact on anesthetic requirement and the effect on ventilation. Our findings show that plasma lidocaine concentrations of 1 to 4 $\mu\text{g/ml}$ decreased enflurane MAC 15-37 per cent. This lidocaine-

induced decrease in enflurane requirement is consistent with results of similar studies with nitrous oxide in man⁶ and cyclopropane in rats,¹³ but differs quantitatively from observations with halothane. Himes, DiFazio and Burney⁶ reported that 3–6 $\mu\text{g/ml}$ of lidocaine were necessary to produce 10–25 per cent decreases in halothane MAC in dogs. We have no explanation for this discrepancy in lidocaine potency. However, when the present study was completed, we studied three additional dogs to quantify the effects of lidocaine on the MACs of halothane and isoflurane. With both anesthetics, we found decreases in MAC of 16–36 per cent for the same range of plasma lidocaine concentrations as used in our enflurane studies (1–4 $\mu\text{g/ml}$). For the range of lidocaine concentrations used in the present study, increasing levels of lidocaine in plasma made greater contributions to the total anesthetic effect and reached a maximum effect at 37 per cent. The magnitude of this change in anesthetic requirement is similar to those reported for diazepam,¹⁴ narcotics,¹⁵ and drugs that deplete central nervous system catecholamines.¹⁶

In both human beings and dogs during basal anesthesia with barbiturate,¹⁷ diethyl ether¹⁸ or halothane with and without partial neuromuscular blockade,¹⁹ gross evidence of ventilatory depression has been observed after intravenous or intra-arterial injection of large doses (3 to 10 mg/kg) of lidocaine. The relevance of these observations to clinical practice is difficult to assess, since doses of lidocaine of this magnitude are rarely given and since lidocaine levels achieved with this technique have not been measured.

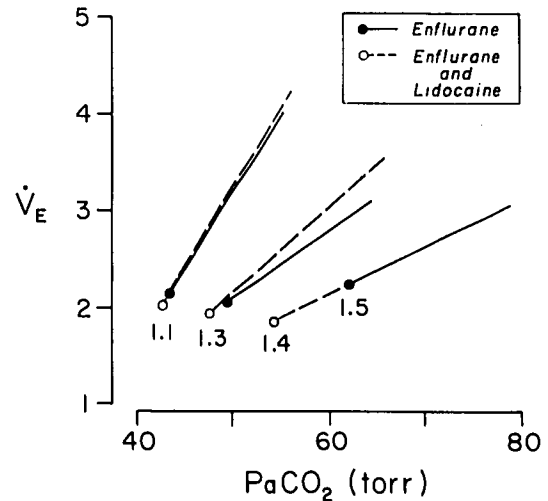


FIG. 2. Schematic illustration of the ventilatory responses to carbon dioxide in dogs anesthetized with enflurane alone or with various combinations of enflurane and lidocaine. Numbers refer to the MAC values at which individual ventilatory responses were measured. Notice the similarity of the increase in resting PaCO_2 and the decrease in slope as MAC increased in dogs anesthetized with enflurane alone (closed circles) and in those anesthetized with similar MAC levels of enflurane plus lidocaine (open circles).

However, our findings suggest that relatively low concentrations of lidocaine in plasma in the presence of enflurane significantly depress ventilation.

Although the administration of lidocaine during constant-depth enflurane anesthesia produces a dose-dependent depression of ventilation, this depression is proportional to the total anesthetic requirement. Therefore, the interaction of enflurane and lidocaine appears to be additive, since ventilatory depression

TABLE 1. Ventilatory Response Data (Means \pm SE) during Enflurane and Enflurane-Lidocaine Anesthesia in Five Dogs

	Enflurane			Enflurane-Lidocaine		
	End-tidal enflurane (per cent)	2.39 ± 1.08	2.82 $\pm .09$	3.27 $\pm .09$	2.09 $\pm .08$	2.42 $\pm .08$
Enflurane MAC	1.1 $< \pm .01$	1.3 $< \pm .01$	1.5 $< \pm .01$.95 $\pm .02$	1.1 $\pm .04$	1.1 $\pm .04$
Plasma lidocaine concentration ($\mu\text{g/ml}$)	—	—	—	1.2 $\pm .2$	1.4 $\pm .1$	2.5 $\pm .3$
Combined MAC	—	—	—	1.1 $\pm .01$	1.3 $\pm .04$	1.4 $\pm .04$
Frequency (breaths/min)	8 ± 1	7 ± 1	5 ± 1	9 ± 1	7 ± 1	6 ± 1
Minute ventilation (l/min)	2.2 $\pm .2$	2 $\pm .3$	1.6 $\pm .4$	2.1 $\pm .3$	1.9 $\pm .4$	1.7 $\pm .2$
PaCO_2 (torr)	43 ± 2	49 ± 1	62† ± 6	42 ± 3	47 ± 4	54 ± 3
Slope (ml/min/torr)	154 ± 15	72 ± 28	53 ± 21	155 ± 47	99 ± 36	47 ± 12
Fraction of control 1.1 MAC enflurane slope	1	.46† $\pm .18$.34† $\pm .13$	1 $\pm .31$.64 $\pm .23$.31† $\pm .08$

† Significantly different from control 1.1 MAC enflurane values, $P < 0.05$.

was no greater than that observed with enflurane alone at equivalent levels of anesthesia. Since both charged and uncharged forms of local anesthetics have been shown to be active,²⁰ we do not believe that increased blood pH during CO₂ inhalation depressed the level of anesthesia as calculated from measurements of total plasma lidocaine concentration.

It is well known that most inhalational anesthetics depress the ventilatory response to carbon dioxide. Similar effects are observed with barbiturates and narcotics, but usually after loss of consciousness.^{21,22} This indicates that drug-induced or natural loss of consciousness as a stimulus to breathing potentiates the depressant effects of these drugs. Therefore, the effect of lidocaine in anesthetized subjects may be quite different from that in awake patients. There is information to support this. The use of lidocaine in coronary care units usually is not associated with respiratory depression. Also, Jorfeldt *et al.*²³ observed neither a decrease in minute ventilation nor an increase in PaCO₂ values at mean plasma lidocaine concentrations of less than 5 mg/kg in awake man. Furthermore, results of unpublished studies by T. C. Smith (personal communication) in awake, human volunteers suggest that neither the apneic threshold nor the slope of the ventilatory response curve is changed by the intravenous administration of a total cumulative dose of lidocaine of 0.5 mg/kg.

The design of this experiment necessitated as much as four hours of enflurane anesthesia. It is possible that, during this period of exposure to enflurane, the ventilatory responses in our animals changed. Change in resting ventilation has been reported to occur in man after five hours of enflurane anesthesia,²⁴ although we are unaware of any report of this phenomenon in animals. However, if an adaptation to ventilation had occurred during the exposure to enflurane, we would have underestimated the ventilatory depression, and the respiratory depressant effects of lidocaine would have been more profound than those observed.

The authors are grateful to Dr. Benjamin G. Covino, Ph.D., M.D., Astra Pharmaceutical Products, Framingham, Massachusetts, for the analysis of lidocaine concentrations, and to Dr. Cosmo A. DiFazio, M.D., Ph.D., University of Virginia, Charlottesville, Virginia, for the analysis of monoethylglycinexylidide concentrations and for his helpful assistance and review of the manuscript.

Enflurane (Éthrane) and isoflurane (Forane) for these studies were supplied courtesy of Ohio Medical Products, Division of Aircor, Inc., Madison, Wisconsin. Halothane (Fluothane) was provided by Ayerst Laboratories, Inc., New York, New York.

References

- Harrison DC, Sprouse JH, Morrow AG: The antiarrhythmic properties of lidocaine and procaine amide. *Circulation* 28:486-491, 1963
- Denlinger JK, Ellison N, Ominsky AJ: Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. *ANESTHESIOLOGY* 41:409-412, 1974
- Phillips OC, Lyons WB, Harris LC, et al: Intravenous lidocaine as an adjunct to general anesthesia: A clinical evaluation. *Anesth Analg (Cleve)* 39:317-322, 1960
- Steinhaus JE, Howland DE: Intravenously administered lidocaine as a supplement to nitrous oxide-thiobarbiturate anesthesia. *Anesth Analg (Cleve)* 37:40-46, 1958
- de Clive-Lowe SG, Gray PWS, North J: Succinylcholine and lignocaine by continuous intravenous drip. Report of 1000 administrations. *Anaesthesia* 9:96-104, 1954
- Himes RS, DiFazio CA, Burney RG: Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. *ANESTHESIOLOGY* 47:437-440, 1977
- Ruiz BC, Tucker WK, Kirby RR: A program for calculation of intrapulmonary shunts, blood-gas and acid-base values with a programmable calculator. *ANESTHESIOLOGY* 42:88-95, 1975
- Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. *ANESTHESIOLOGY* 26:756-763, 1965
- Tham MK, Hardy CA, Shah DO: Gas-chromatographic method using surfactants for analysis of volatile anesthetics in blood. *ANESTHESIOLOGY* 37:647-649, 1972
- Keenaghan JB: The determination of lidocaine and prilocaine in whole blood by gas chromatography. *ANESTHESIOLOGY* 29:110-112, 1968
- Severinghaus JW: Continuously recording ventimeter. *ANESTHESIOLOGY* 23:582-583, 1962
- Mendenhall W: Introduction to Linear Models and the Design and Analysis of Experiments. Belmont, California, Wadsworth Publishing, 1968, pp 204-205
- DiFazio CA, Niederlehner JR, Burney RG: The anesthetic potency of lidocaine in the rat. *Anesth Analg (Cleve)* 55:818-821, 1976
- Perisho JA, Buechel DR, Miller RD: The effect of diazepam (Valium) on minimum alveolar anaesthetic requirement in man. *Can Anaesth Soc J* 18:536-540, 1971
- Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. *ANESTHESIOLOGY* 25:302-306, 1964
- Miller RD, Way WL, Eger EI II: The effects of alpha-methyl-dopa, reserpine, guanethidine, and iproniazid on minimum alveolar anesthetic requirement (MAC). *ANESTHESIOLOGY* 29:1153-1158, 1968
- DeKornfeld TJ, Steinhaus JE: The effect of intravenously administered lidocaine and succinylcholine on the respiratory activity of dogs. *Anesth Analg (Cleve)* 38:173-177, 1959
- Siebecker KL, Kimmey JR, Bamforth BJ, et al: Effect of lidocaine administered intravenously during ether anesthesia. *Acta Anaesthesiol Scand* 4:97-103, 1960
- Telivuo L, Katz RL: The effects of modern intravenous local analgesics on respiration during partial neuromuscular block in man. *Anaesthesia* 25:30-35, 1970
- Ritchie JM, Greengard P: On the active structure of local anesthetics. *J Pharmacol Exp Ther* 133:241-245, 1961
- Eckenhoff JE, Helrich M: The effect of narcotics, thiopental and nitrous oxide upon respiration and respiratory response to hypercapnia. *ANESTHESIOLOGY* 19:240-253, 1958
- Smith TC: Pharmacology of respiratory depression. *Int Anesthesiol Clin* 9(3):125-143, 1971
- Jorfeldt L, Lofstrom B, Pernow B, et al: The effect of local anaesthetics on the central circulation and respiration in man and dog. *Acta Anaesthesiol Scand* 12:153-169, 1968
- Calverley RK, Smith NT, Jones CW, et al: Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. *Anesth Analg (Cleve)* 57:610-618, 1978