The Potency of Anesthetics in Frog Gastric Secretion in Cl^- Solutions (34366)

GLENN K. BLACKBURN, WILLIAM CRENSHAW, THOMAS N. MACKRELL, AND MANUEL SCHWARTZ
(Introduced by G. Carrasquer)
Departments of Anesthesiology and Engineering Physics, University of Louisville, Louisville, Kentucky 40202

Bubbling methoxyflurane (Penthrane), chloroform, and halothane into the chloride solutions bathing the secretory and nutrient surfaces of the frog gastric mucosa decreased the H^+ secretory rate and increased the transmembrane resistance (1). It was established that both the H^+ and Cl^- mechanisms (2) in frog gastric mucosa were inhibited. Further, in the case of methoxyflurane, it was found that the decrease in the H^+ secretory rate was dose related.

A question which arose in this work was whether the MAC (3) (the minimum anesthetic concentration in man necessary to prevent a gross muscular response to a surgical incision) was in any way related to the anesthetic potency in frog gastric secretion. It is the purpose of this paper to show that such a relation exists.

Methods. The experiments were performed on gastric mucosae of *Rana pipiens* with an *in vitro* method described elsewhere (2). Two pairs of electrodes were used, one for sending current across the mucosa and the other for measuring the PD. The resistance was determined as the change in PD per unit of applied current. The H^+ secretory rate was measured by the pH stat method of Durbin and Heinz (4). The pH of the solution on the secretory side was maintained at 4.90. The nutrient bathing solution contained (m*M*): Na^+, 101; K^+, 4; Ca^{2+}, 1; Mg^{2+}, 0.8; Cl^-, 81; HCO_3, 25; phosphate, 1.0; and glucose 10; and the secretory solution: Na^+, 102; K^+, 4; Cl^-, 106. During the control part of the experiment, both sides were gassed with 95% O_2 and 5% CO_2 whereas, after the application of a fixed percentage of anesthetic, the oxygen content was correspondingly reduced and the CO_2 content was maintained essentially at 5%. Since the temperature in the vaporizer and the curve relating vapor pressure and temperature were both known, the percentage of anesthetic could be maintained at a constant level. A peristaltic pump bubbled the gas mixture through the chambers, thereby reducing the effects due to back pressure upon the anesthetic vaporizer.

Results. Figure 1 depicts the effects of chloroform on the H^+ secretory rate and the related parameters of resistance and PD. At the time indicated by the first arrow, both sides of the gastric mucosa were gassed with fresh solutions, preequilibrated with 2% chloroform, and then were continuously gassed with 2% chloroform bubbling through the Cl^- solutions. As indicated in Fig. 1, the resistance rose about 50% above the control level and the H^+ rate fell about the same amount below the control level. In this experiment, the percentage of anesthetic was altered when the resistance attained essentially a constant value. Increasing the gas bubbling to the chambers to 3% chloroform produced a greater increase in resistance and a fall of the H^+ secretory rate to zero. In general 3% chloroform produced a 94% decrease in H^+ rate, as shown in Table I. A decrease of the anesthetic to 2, to 1, and finally to 0% produced successive decreases in resistance, but no return of the H^+ secre-

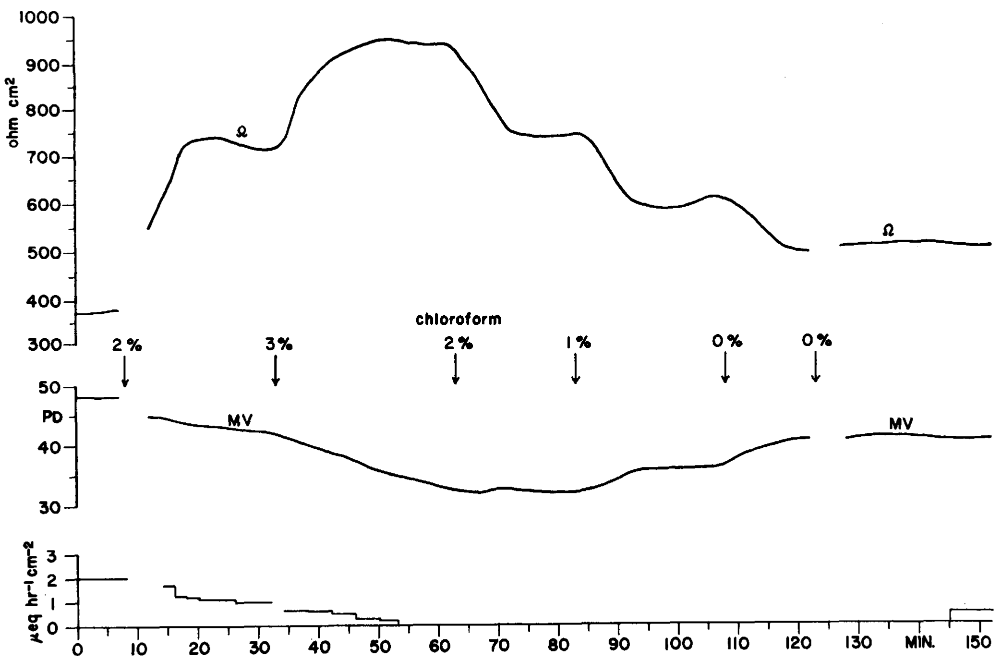

FIG. 1. Effects of chloroform on resistance, PD, and H^+ secretory rate in chloride bathing solutions for varying percentages of chloroform as a function of time.

tory rate. Washing both sides of the mucosa with chloroform-free solutions caused a measurable H^+ rate some 20 min later. It was observed, in long experiments with chloroform, that the resistance and PD did not recover as completely as with other anesthetics and that the recovery of the H^+ rate was at best only partial.

In Table I, the data are based on experiments involving a single percentage of anesthetic in any one experiment. In each experiment a steady state was attained in which the H^+ rate and the resistance attained essentially constant levels over a period of about 20 min. The PD in about 75% of the experiments also remained almost constant. In those experiments in which the percentage of anesthetic was sufficient to reduce the H^+ rate to zero and was permitted to continue bubbling through the chambers, the PD generally continued to decrease and the resistance also decreased to some extent (1). Figure 2 depicts the decrease in H^+ secretory rate in percentage as a function of $x + 1$, where x is the percentage anesthetic for methoxyflurane, chloroform, halothane, and fluroxene.

Discussion. Of prime significance is the fact that the data can be related to the MAC. The MAC values are available for methoxyflurane, halothane, and fluroxene (3). These are respectively, 0.16, 0.765, and 3.4%. Table II gives the ratios respectively for 25, 50, 75, and 95% decrease in the H^+ rate.

By interpolation in Fig. 2, an average value of 1.20% chloroform produced a decrease of the H^+ secretory rate of 25%; 1.92%, a decrease of 50%; 2.45%, a decrease of 75%; and 3.12%, a decrease of 95%. If these values are divided by the mean values of the ratios in Table II, respectively 2.2, 3.5, 4.5, and 6.3, then the MAC for chloroform is determined. The MAC computed for a 25%

TABLE I. Anesthetic Potency of Frog Gastric Secretion in Cl^- Solutions.[a]

Anesthetic	No. of expts.	Anesthetic (%)	Av decrease in H^+ rate (%)	SEM[b]
Penthrane	4	0.2	11	±2
	6	0.4	26	4
	5	0.6	54	4
	6	0.8	88	5
	7	1.0	98	1
	16	1.5	100	0
Chloroform	4	1.0	19	±4
	4	2.0	54	5
	10	3.0	94	4
	6	4.0	100	0
Halothane	3	1.0	13	±1
	4	2.0	29	4
	7	3.0	64	8
	8	4.0	87	7
	9	5.0	97	2
Fluroxene	7	5.0	19	±3
	12	10.0	41	4
	7	15.0	73	6
	9	20.0	88	5
	8	25.0	98	1

[a] Column 3 indicates the percentage of anesthetic bubbling through the chambers. Column 4 gives the percentage decrease in H^+ rate compared to the control level and column 5 gives the SEM for each set of experiments for a fixed percentage of anesthetic.

[b] SEM = the standard error of the mean of the values in the preceding column.

decrease in H^+ rate is 0.55; for a 50% decrease, 0.55; for a 75% decrease, 0.54; for a 95% decrease, 0.50. The average value of these four determinations yields 0.535 for the MAC of chloroform.

TABLE II. The Ratio of the Percentage of Anesthetic for a Specific Percentage Decrease in H^+ Secretory Rate to the MAC.

Anesthetic	Ratio for percentage decrease (%): 25	50	75	95
Methoxyflurane	2.4	3.6	4.4	5.8
Halothane	2.3	3.5	4.4	6.2
Fluroxene	1.9	3.3	4.7	6.8
Mean	2.2	3.5	4.5	6.3

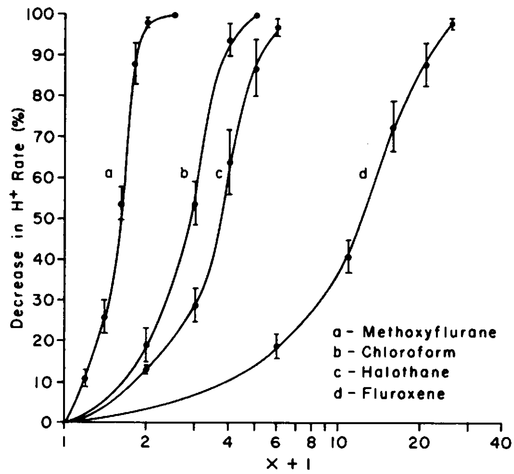

FIG. 2. Decrease in H^+ secretory rate (%) as a function of $x+1$, where x is the percentage of anesthetic for methoxyflurane, chloroform, halothane, and fluroxene.

For chloroform, the oil/gas partition coefficient is 370 at 37°. An examination of the straight line correlating the MAC values with the oil/gas partition coefficients (3) shows that chloroform fits this curve reasonably well. Since the percentage of anesthetic is related to the MAC and since the MAC for chloroform can be predicted with reasonable confidence from the gastric data, to this extent the present work lends support to that of Saidman *et al.* (3).

Since the inhibition of gastric secretion is related to the MAC and since the MAC, in turn, correlates with the oil/gas partition coefficient, lipid solubility, as indicated by Saidman *et al.* (3), suggests itself as a factor in anesthetic potency in the gastric mucosa. Other alteratives such as the Pauling hydrate hypothesis (5) or the inhibitory effects of anesthetics on a proton pump which is directly coupled into ATP synthesis (6) are, however, not excluded.

Conclusion. The inhibition of gastric secretion in frog was related to the MAC in man for methoxyflurane, halothane, and fluroxene. Based on these data, the MAC for chloroform was predicted to be 0.535%.

1. MacKrell, T. N. and Schwartz, M., Am. J. Physiol. **216**, 572 (1969).

2. Rehm, W. S., Am. J. Physiol. **203**, 63 (1962).

3. Saidman, L. J., Eger, E. I., II, Munson, E. S., Babad, A. A., and Muallem, M., Anesthesiology **28**, 994 (1967).

4. Durbin, R. P. and Heinz, E., J. Gen. Physiol. **41**, 1035 (1958).

5. Pauling, L., Science **134**, 15 (1961).

6. Rottenberg, H., Sci. Res. (April 28, 1969), 13.

Received May 29, 1969. P.S.E.B.M., 1969, Vol. 132.