Potency of Compound 347 (Ethrane) in Inhibition of Frog Gastric Secretion (35201)

MANUEL SCHWARTZ AND THOMAS N. MACKRELL
(Introduced by Warren S. Rehm)
Departments of Physics and Anesthesiology, University of Louisville, Louisville, Kentucky 40208

In an investigation to determine a standard of equipotency for volatile anesthetics, Saidman *et al.* (1) found a correlation between anesthetic potency and lipid solubility as defined by the oil/gas partition coefficient. Their measure of potency was the MAC, *i.e.*, the minimum anesthetic concentration required in man to prevent a muscular response to a skin incision in 50% of the subjects to whom the anesthetic is administered. A relationship between potency and lipid solubility was also reported earlier by Carpenter (2). Moreover, it has been shown (3) that the percentage of anesthetic required to produce a given decrease of the H^+ secretory rate in frog is essentially proportional to the MAC in man. Hence lipid solubility is indicated as a factor in the potency of anesthetics inhibiting acid secretion in the gastric mucosa.

Recently, a new inhalation agent, a halogenated liquid (CHF_2–O–CF_2–CHFCl) designated as Compound 347 (Ethrane), was developed (4). It was, therefore, of interest to study its potency in the inhibition of frog gastric secretion and to see how it compared in this respect with methoxyflurane, chloroform, halothane, and fluroxene. It is the purpose of this paper to present the results of this study. A preliminary report of this work appears elsewhere (5).

Methods. A well-known *in vitro* method was used in which frog gastric mucosae of *Rana pipiens* were mounted between cylindrical chambers. Details of the method are described elsewhere (6). Three electrophysiological parameters were measured: namely, the transmucosal potential difference (PD), the transmucosal resistance and the H^+-secretory rate. 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 (7). The pH of the secretory solution 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 bathing 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 Compound 347, the oxygen content was correspondingly reduced and the CO_2 content was maintained essentially at 5%. In all experiments reported here, both sides of the mucosa were washed with solutions, preequilibrated with anesthetic for over 30 min, prior to their use. A peristaltic pump bubbled the gas mixture through the chambers, thereby reducing the effects of back pressure upon the anesthetic vaporizer.

Results. In each experiment, to determine the potency of Compound 347, a fixed percentage of this anesthetic was used. In the experiment depicted in Fig. 1, 7.5% anesthetic was employed. During a period of about 20 min, as indicated in Fig. 1, the parameters were essentially constant, in particular the H^+ rate. Here the H^+ rate decreased some 86% while the resistance increased to a marked extent (about 175%). In general the decrease in H^+ rate with 7.5% Ethrane was 92%. Removal of the anesthetic restored the parameters to near control levels. Similar experiments were performed with 1.5, 3.0, 4.5, and 6.0% anesthetic and for each percentage of anesthetic, six experiments were performed. Table I gives the respective mean decreases in H^+ rate together with their SEM values.

Previously the data and the curves relating the percentage decrease in H^+ rate to

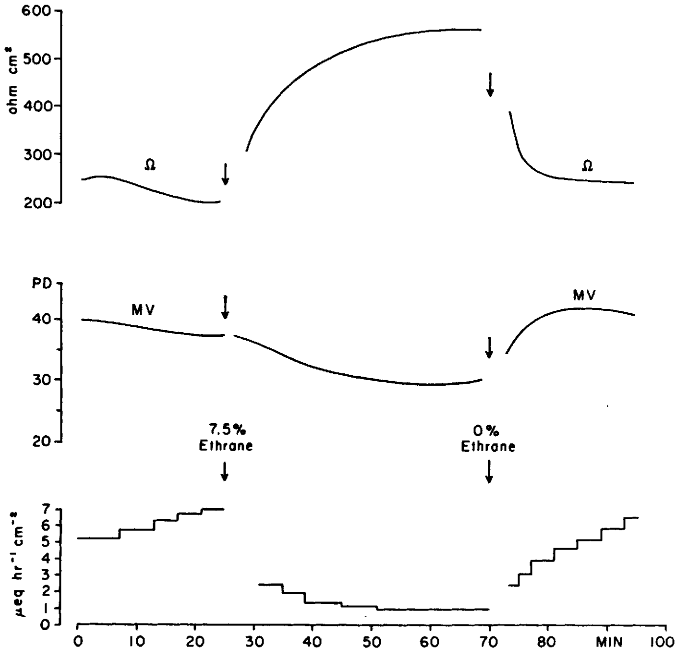

FIG. 1. A study of the potency of Compound 347 (Ethrane) in inhibiting the H^+-secretory rate of frog gastric mucosa in chloride solutions. At the time indicated by the first arrow, 7.5% Ethrane bubbled through the solutions on both sides of the mucosa and at the time indicated by the second arrow, no Ethrane bubbled through the solutions. Resistance, PD, and H^+-secretory rate are plotted versus time.

the percentage anesthetic were reported for methoxyflurane, chloroform, halothane, and fluroxene (3). In Fig. 2, the curve for Compound 347 (Ethrane) is included so that the relative potency of these five different anesthetics might be clearly exhibited. The decrease in H^+ rate (%) was plotted versus $x + 1$ where x is the percentage of anesthetic. The uppermost point determined for Compound 347 was for a 92% decrease in H^+ rate using 7.5% anesthetic. This curve was extrapolated to the 95% mark for purposes of comparison, as required below in the discussion section. The relative potency is as follows: The most potent is methoxyflurane; next, in order, chloroform, halothane, and Compound 347; and finally the least potent, fluroxene.

Discussion This work supports further the finding (3) that the % anesthetic required to produce a given percentage decrease in H^+ rate divided by the MAC for that anesthetic is essentially a constant for volatile anesthetics, *i.e.*, $x/\text{MAC} = \text{constant}$ (3). The ratios were previously computed for 25, 50, 75, and 95% decreases in the H^+ rate and were, respectively, 2.2, 3.5, 4.5, and 6.3 (3). The ratios were determined from the data for methoxyflurane, halothane, and fluroxene as indicated in Fig. 2 and their respective MAC values which are 0.16, 0.765, and 3.4% (1).

If now we assume that these ratios hold essentially for chloroform and Compound 347, in which cases the MAC values have not been determined directly, it is possible to com-

TABLE I. The Potency of Compound 347 in the Inhibition of the H^+-Secretory Rate in Frog Gastric Mucosa in Cl^--Solutions.

% Compound 347	1.5	3.0	4.5	6.0	7.5
% Mean H^+ rate decrease	14 ± 4[a]	38 ± 4	61 ± 4	79 ± 5	92 ± 3

[a] In each case this number denotes the mean decrease ± SEM (*i.e.*, the standard error of the mean).

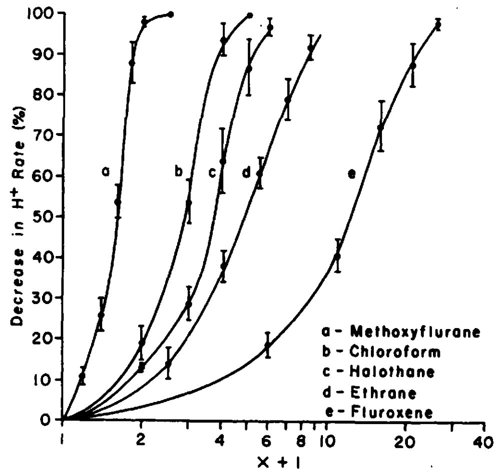

FIG. 2. Decrease in H^+-secretory rate (%) as a function of $x + 1$, where x is the percentage of anesthetic for five anesthetics as designated.

pute their MAC values. We use the relation MAC $= x/\text{constant}$. Previously the MAC for chloroform was thus estimated to be 0.535% (3). Making use of the 25, 50, 75, and 95% decreases in the H^+-secretory rate in Fig. 2, we arrive at estimates of the MAC for Compound 347 of, respectively, 1.1, 1.1, 1.3, and 1.3 with an average value of 1.2%.

For Compound 347, the oil/gas partition coefficient is 98.5 at 37° (4). An examination of the straight line correlating the MAC values with the oil/gas partition coefficients on a log–log plot (1) shows that Compound 347, like chloroform, fits the line reasonably well. Hence MAC values can be predicted with reasonable confidence from the gastric data.

Conclusion. Based on the finding that anesthetic potency in the inhibition of gastric secretion in frog is linearly related to the MAC in man, the MAC for Compound 347 (Ethrane) was predicted to be 1.2%.

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