Methoxyflurane (Penthrane) Anesthesia Effect on Histamine Stimulated Gastric Secretion in the Chicken[1] (36358)

C. A. KESSLER, B. I. HIRSCHOWITZ,[2] P. G. BURHOL,[3] AND G. SACHS

Division of Gastroenterology, Department of Medicine, University of Alabama in Birmingham, Birmingham, Alabama 35233

In studying gastric secretion in chickens with chronically implanted gastric cannula, several anesthetics were used in the operations in which the cannulas were implanted. Urethane (ethyl carbamate), barbiturates and ether were all found to be less satisfactory surgical anesthetics than methoxyflurane (Penthrane or Metofane) a volatile inhaled anesthetic (1). Because of the need for acute experiments to study aspects of gastric secretion under anesthesia, we studied the effect of Metofane on secretion in chickens already equipped with a cannula and previously studied without anesthesia. Like other anesthetics, metofane only partly inhibits secretion, though *in vitro* it is capable of completely inhibiting secretion by amphibian gastric mucosa (2).

Methods. Four adult (av weight 1.7 kg) White Leghorn hens with gastric cannulas implanted 6–8 months previously (1, 3) were studied after an 18 hr fast with water allowed. The birds were suspended in a canvas sling and the stomach washed with 5–10 ml aliquots of warm water followed by free drainage for 15–30 min. Thereafter, observations were made for twenty 15-min periods (5 hr). After the first 30-min basal secretion period, histamine was given in saline (125 μg base/ml) by sc infusion in the thigh at the doses of 75, 150, 300, 750, and 1500 mg histamine base/kg body wt/hr. Each dose was given in the above sequence for 45 min.

The above procedure was also followed while the birds were maintained under surgical anesthesia with methoxyflurane delivered with 100% O_2 from a model 96 Pittman–Moore veterinary anesthetic machine.

Anesthesia was induced by administering a 2% methoxyflurane vapor in oxygen via a specially designed face mask employing a semiclosed carbon dioxide absorption system (96 Pittman–Moore). The bird was allowed to breathe spontaneously while inhaling the methoxyflurane–oxygen vapor. While being induced, a painful stimulus (crushing of the skin with a hemostat) was presented in one minute intervals to which the bird responded by withdrawal of the legs. The response to this stimulus faded while the bird entered the analgesic state and completely disappeared with the establishment of surgical anesthesia (third stage, first plane). At this time the concentration of methoxyflurane was reduced to 0.5% and anesthesia maintained with this concentration of methoxyflurane throughout the procedure. Methoxyflurane administration was discontinued when the procedure was completed and the bird was allowed to breathe room air. Emergence from anesthesia was associated with spontaneous movement of the legs and wings. The bird regained consciousness within 1 hr following discontinuing of methoxyflurane administration and was returned to the cage.

Volumes of gastric juice were measured to 0.1 ml, H^+ by electrometric titration with 0.04 *N* NaOH to pH 7.4, Cl by Coulombetric

[1] This work was supported by Grants AM09260 and TIAM05286 from the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service. The authors acknowledge the technical assistance of Robert Harris and Patrick Campbell.

[2] Address reprint requests to: B. I. Hirschowitz, M.D., 1919 Seventh Avenue South, Birmingham, AL 35233.

[3] International Postdoctoral Fellow, Fogarty International Center, U.S. Public Health Service, IF05 TWO 1426. Present address: Department IX, Ulleval Hospital, Oslo, Norway.

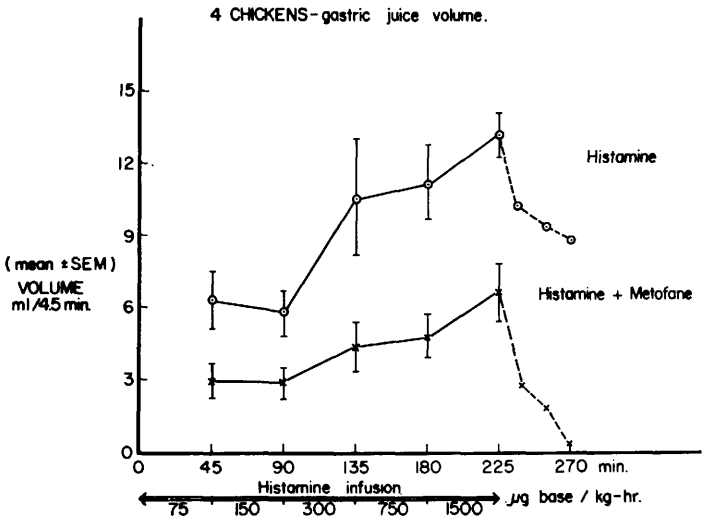

FIG. 1. Volume output in four chickens at increasing doses of histamine given in sequence, each dose for 45 min while conscious and while under Metofane anesthesia. The dotted lines (225–270 min) gives the rates of secretion after histamine infusion was stopped (the 15 min rates were multiplied by 3).

measurement and pepsin by hemoglobin digestion using an autoanalyzer modified for this measurement (1 μg Sigma pepsinogen = 4 peptic units) (1, 3).

Results. The output of water (Fig. 1), H and Cl, was reduced 40–60% by Metofane at all five doses of histamine and the decline of the rate of secretion after histamine was stopped was much faster with the anesthetic (Fig. 1). Table I gives the values for each component of gastric juice measured. Total output of juice for the 3 3/4 hr of histamine infusion in each chicken was reduced 40–80% by Metofane. Pepsin was not measured in two birds under anesthesia because of very low volumes (20–25% of control) in which it was elected to measure electrolytes rather than pepsin. In the two remaining birds, pepsin was reduced in one and unchanged in the other.

Kinetic analysis. As previously reported, the gastric secretory response of the chicken to stimuli such as histamine can be described in terms of the law of mass action by fractional linear transformation of the data (1, 3). From such calculations estimates may be made of V_{max} (the theoretical maximum rate of secretion) and of S_{50} or the dose necessary to stimulate secretion at 50% of the V_{max} rate. For volume rate secreted in response to 5 doses of histamine, $r = .997$ for the equation $S/V = aS + b$; (Fig. 2), (where $S =$ dose of histamine and $V =$ output per unit time, ml/45 min) and $V_{max} = 13.6$ ml/45

TABLE I. Total Output in Each Chicken During Histamine Infusion (225 min) While Conscious (Control) and While Under Metofane Anesthesia.

Chicken	Body wt (g)	Volume (ml)		H^+ (mEq)		Cl^- (mEq)		Pepsin (PU)	
		Control	+Metof.	Control	+Metof.	Control	+Metof.	Control	+Metof.
1	1900	43.3	10.8	3.23	1.26	5.64	1.55	38,800	—
2	1600	40.7	23.9	2.76	3.50	5.02	3.88	92,300	41,700
3	1600	31.0	6.1	2.84	.47	4.35	1.79	33,000	—
4	1800	94.7	51.7	14.05	6.81	13.86	7.79	115,000	111,000
Mean	1725	54.4	23.1	5.7	3.0	7.2	3.8		

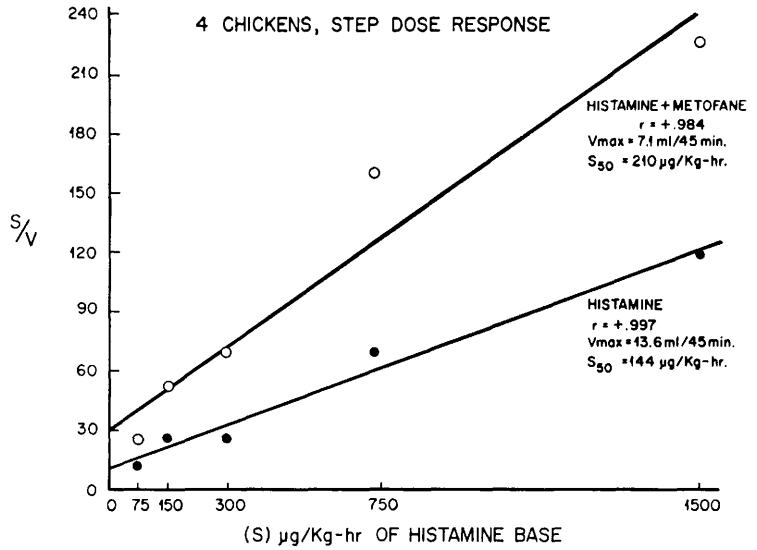

FIG. 2. The data of Fig. 1 transformed to the equation $S/V = aS + b$, where S = dose of stimulant and V = volume output per unit time. For this calculation for H, Cl and pepsin, see Table II.

min or 10.7 ml/kg hr and S_{50} = 144 µg base/kg hr.

Under Metofane anesthesia the points are somewhat more erratic ($r = +.984$, $n = 5$), and V_{max} = 7.1 ml/45 min or 5.6 ml/kg hr, a reduction of almost 50% while S_{50} for this V_{max} was increased to 210 µg/kg hr. The pepsin output data for the controls can also be well linearized ($r = .997$, $V_{max} = 18{,}100$ PU/45 min, $S_{50} = 162$ µg/kg hr) but the data are inadequate for similar analysis of the two Metofane experiments.

The data for H and Cl output, especially under Metofane do not linearize quite as well (Table II), suggesting that the model may not be very appropriate to describe the effect of Metofane or the action of histamine when given during Metofane anesthesia. Thus the $S/V = aS + b$ transformation tends to a curve rather than a straight line, suggesting

TABLE II. Calculated Parameters for Outputs with 5 Doses of Histamine in 4 Chickens while Conscious (control) and under Metofane Anesthesia.

	Volume (ml)[a]		H (mEq)		Cl (mEq)		Pepsin (PU)	
	Control	Metof.	Control	Metof.	Control	Metof.	Control	
Observed max. output (V_{obs})	12.6	6.6	1.82	1.01	1.98	1.07	16,500	[b]
Calculated max. output (V_{max})	13.6	7.1	2.16	1.14	2.22	1.18	18,100	—
S_{50} (µg/kg hr)	144	210	352	330	212	251	162	—
Correlation coefficient, r	.997	.984	.969	.952	.993	.975	.997	—
Calculated concentrations at V_{max}, H, Cl, mEq/liter, PU/ml	—	—	159	160	163	166	1330	—

[a] Per 45 min.
[b] Insufficient data.

that at higher doses secretion is disproportionately higher than at low doses.

Discussion. Penthrane has been shown to inhibit H^+ secretion in the isolated frog gastric mucosa at effective anesthetic concentrations (0.6–1.5%) (2), and Na^+ transport in toad bladder at somewhat higher concentrations (2–8%) (4). Besides the direct effect of the anesthetic on the gastric mucosa, it is also possible that other effects, *e.g.*, on blood flow or other homeostatic mechanisms might apply in the intact animal. The same was true in our previous report on the effect of Nembutal anesthesia on histamine and insulin stimulated secretion in dogs (5), compared to the effects of amytal on isolated frog gastric mucosa (6).

Thus the inhibition was incomplete *in vivo* despite effective anesthesia, while *in vitro* dose responsive inhibition of H^+ secretion was found between 0.2 and 1.0%, being total at $\geqq$ 1% and nearly so at levels of 0.6%, the concentration for moderately deep anesthesia *in vivo* (7). Thus though this agent could be used for acute experiments, the results may be difficult to interpret. The same is probably true of other anesthetics as well.

Though the S_{50} is almost the same for volume, the calculated rate of maximum water secretion (V_{max}) by the consecutive dose doubling technique used here is about 40% smaller than that obtained by calculation from separate dose histamine infusion experiments (3). This may be explained by the marked fade noted previously with single dose experiments (1). The major change in secretion is related to volume, since the calculated maximal concentration of H and Cl remain unchanged under Penthrane (Table II).

The tendency for the transformation of the data to be curvilinear rather than linear is a reminder that interpretations of modification of gastric secretion by inhibitors can not always be accurately described in terms of enzyme kinetics. Thus one would hesitate to apply any of the conventional labels such as "competitive" or "noncompetitive" to the effects of methoxyflurane in these experiments.

Summary. In four White Leghorn hens with chronically implanted gastric cannulas, a step-dose–response was done with histamine (75–1500 μg base/kg hr) given by subcutaneous infusion. The dose–response was repeated under Penthrane anesthesia. V_{max} for gastric juice volume calculated from linear transformation of the data was reduced from 10.7 ml/kg hr to 5.6 ml/kg hr but S_{50} was only slightly increased.

1. Burhol, P. G., and Hirschowitz, B. I., Amer. J. Physiol. **218**, 1671 (1970).

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

3. Burhol, P. G., and Hirschowitz, B. I., Amer. J. Physiol. **222**, 308 (1972).

4. Anderson, N. B., Anesthesiology **27**, 304 (1966).

5. Powell, D. W., and Hirschowitz, B. I., Amer. J. Physiol. **212**, 1001 (1967).

6. Sachs, G., Shoemaker, L. L., and Hirschowitz, B. I., Biochim. Biophys. Acta **143**, 522 (1967).

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

Received Sept. 1, 1971. P.S.E.B.M., 1972, Vol. 139.