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A New *in Vivo* Method for Repeatedly Studying Gastric Acid Secretion and Other Secretory Parameters in Awake Guinea Pig

SHMUEL BATZRI,[1] JOHN W. HARMON, ANDRE DUBOIS, DEBBIE MOSKOWITZ, ROBERT WEICHBROD, AND NORMAN M. RICH

Departments of Surgery, Pharmacology, and Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814

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A new model for measuring gastric secretory parameters in awake guinea pigs is described. A chronic cannula was surgically implanted in the stomach of each guinea pig. The rates of gastric secretion and changes in intragastric volume were measured using a dye dilution technique. In contrast to previous techniques in small laboratory animals, there was no collection of gastric juice via drainage, no oral intubation for aspiration was involved, no special or sophisticated equipment was used, no anesthesia was employed, and there was no stress associated with acute surgery. This method offers a valuable advantage by combining the chronic gastric cannula with a dye dilution technique in that the same animal can be used several times and finally, several gastric secretory parameters can be measured simultaneously. The animals were used from 3 weeks to 10 months after surgery and as many as 15 studies were performed on the same guinea pig. Samples were collected at 10-min intervals and analyzed for acid and dye concentration from which the onset and kinetics of gastric secretion were followed. Basal gastric secretion (11.8 ± 1.6 μeq/kg/min; all mean ± 1 SEM) was increased within 20 min after subcutaneous infusion of histamine (30 μg/kg/hr) and peaked by 40–60 min at a mean acid output rate of 41 ± 3 μeq/kg/min. Histamine also increased the intragastric volume from 6.3 to 13.4 ml as it increased fluid output from 1.6 ± 0.1 ml/10 min to 3.4 ± 0.2 ml/10 min. The increase in acid output caused by histamine was inhibited by the H_2-antagonists cimetidine (3 μmole/kg) and ranitidine at 0.5 μmole/kg. Omeprazole (1.2 μmole/kg), an H-K-ATPase inhibitor, almost abolished acid output under both basal and histamine-stimulated conditions. Thus, the present method is simple and suitable to study the physiology and pharmacology of gastric secretion in the guinea pig with a particular emphasis on the action of histamine. Furthermore, because of the species involved, there is also a significant economical advantage and the guinea pig can also be used as a potential model for studying experimental ulcer.

INTRODUCTION

The guinea pig is widely used *in vivo* and *in vitro* for the study of gastric secretion and the pathogenesis of peptic ulceration. Since acid itself plays an important role in ulcer development, information regarding the guinea pig gastric secretory functions is very valuable. Several methods for studying *in vivo* gastric secretion in small laboratory animals have been reported. In most methods, gastric juice was collected by drainage or aspiration of the gastric contents, and the amount lost into the duodenum could only be estimated. Using a nonabsorbable radioactive marker in guinea pigs, Ragins and Wincze reported that 63% of the radioactivity was recovered during the 2 hr of collections [1]. In rats, Borella and Herr [2] estimated that only one-half of the acid production was recovered when the stomach was perfused via two implanted gastric cannulas.

Gastric fistulas have been used extensively in dogs and cats [3–6] and to lesser extent in rats [2, 7] and guinea pigs [1, 8]. Due to the small volume of gastric secretion in both rats and guinea pigs, it was necessary to use long collection periods in order to obtain mean-

[1] To whom all correspondence and reprint requests should be addressed at Uniformed Services University of the Health Sciences, Room A3014, 4301 Jones Bridge Road, Bethesda, MD 20814.

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ingful data. In guinea pigs, 5 ml of gastric juice was collected during a 3-hr period [1], whereas in rats, as little as 10 ml was collected during a 24-hr period [7]. To overcome this problem, Borella and Herr [2] perfused the stomach via two gastric cannulas implanted in the rat stomach. Studies in guinea pigs with gastric fistulas were also reported. In some studies the reported acid output was quite variable [1], while in others a relatively high dose of histamine was used [7]. In none of these reports, however, were data presented regarding the onset of acid secretion or any other gastric secretory parameters during the onset of secretion.

Gastric secretory studies in small laboratory animals are usually performed in an acute model. In those studies, there is only one experimental point in the life of the animal and usually the animal undergoes a significant stress which may lead to postsurgical changes in gastric secretion. The use of anesthesia to minimize stress in guinea pigs and rats results in reduction in gastric secretion [2]. Attempts to use awake guinea pigs with gastric intubation via the esophagus caused stress to the animals and required prolonged quantitative collection of gastric juice which was quite difficult [7, 8].

A chronic gastric cannula overcomes most of these problems. It offers an animal model which is more economical than the dog by requiring far less space for housing and maintenance. Combined with a dye dilution technique [9, 10], the changes in intragastric volume and rates of gastric secretion can be easily determined. A chronic animal model allows one to perform multiple studies in the same animal and thus minimizes experimental variation. The effect of anesthesia can be eliminated by studying the animal awake. In guinea pigs, studies of gastric secretory functions *in vivo* can be compared to *in vitro* gastric gland/cell studies [11, 12]. In addition to measurement of acid secretion, such models can be used to study the secretion of enzymes, ions, mucus, and other macromolecules. Finally, a guinea pig model can be used as a research tool for comparison with other animal species and to further our basic knowledge of gastric acid secretion.

In the present communication, we report the surgical procedure for preparing the chronic gastric fistula in guinea pig and the various gastric secretory parameters basally and with histamine stimulation [13].

MATERIAL AND METHODS

Male Hartley albino guinea pigs (200–250 g) were obtained from Camm Research Center (Wayne, NJ). Histamine was from Sigma Chemical Co. (St. Louis, MO). Cimetidine was a gift from Dr. Ganellin, Smith, Kline & French Laboratories (Welwyn Garden City, Hertfordshire, England). Ranitidine was a gift from Dr. F. N. Eshelman, Glaxo Group Research, Ltd. (Fort Lauderdale, FL) Omeprazole was a gift from Dr. Hakan Larson, AB Hassle (Molndal, Sweden). The dye solution contained phenol red (sodium salt, Fisher Scientific Co., Fair Lawn, NJ) at 560 mg/liter. The solution was filtered to remove any undissolved particles and diluted 1:2.5 with water before use. Other chemicals were analytical grade and solutions were prepared in our laboratory.

Surgery for gastric cannulation. Guinea pigs were anesthetized by inhalation of methoxyflurane. Following a midline laparotomy, the stomach was isolated and a plastic cannula (35 mm long × 6 mm o.d.; Fig. 1A) was implanted ventrally in the antrum

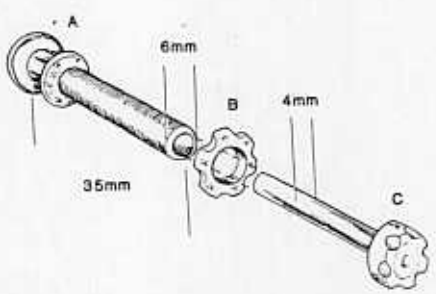

FIG. 1. Components of the gastric cannula showing the body of the cannula (A), the washer (B), and the plug (C). The length of the plug was such that when screwed in it was flush with the inner part of the cannula.

near the pylorus through a 2-mm incision in the stomach wall. The edge of the incision was then tightened around the cannula by purse-string suture. The cannula was then exteriorized via a stab wound in the abdominal wall, to the side of the midline incision. A small plastic washer (Fig. 1B) was then screwed down into the cannula so that it would not slip back into the abdomen. The cannula was then plugged (Fig. 1C) to avoid any loss of gastric contents. The abdomen was closed and after 24 hr the guinea pig was allowed free access to water and chow. After a period of 2–3 weeks recovery the animals were used for gastric function studies at a frequency of no more than once per week. The mortality of the animals postoperatively was between 10 and 20%. The weight and general health of the guinea pigs were monitored on a daily basis and any animal that showed a sign of illness was discarded from future studies. On the average, approximately one out of every 15–20 animals was discarded even though it survived the operation.

Measurement of gastric function. In well-fed guinea pigs the stomach contents during most of the daytime is a semisolid mass of food. Under those conditions, washing and sampling of gastric content becomes a prolonged procedure, difficult and sometimes impossible. In the fasted animals (16 hr or more) the stomach content is fluid and although not totally free of food, it is possible to wash the stomach clear. Therefore, guinea pigs were fasted for 18–24 hr in mesh-bottomed cages to minimize coprophagy with water *ad libitum.* Each animal was studied awake resting quietly in a Bowman restrainer for the duration of the experiment of up to 4 hr. Prior to starting the sampling, the stomach was repeatedly washed through the gastric cannula with 5–7 ml of water to remove any solid contents and a No. 10 French, double lumen polyvinyl nasogastric Levin tube (National Catheter Co., Argyle, NY) was introduced into the stomach. Proper positioning of the tube in a dependent part of the stomach was verified by demonstrating that

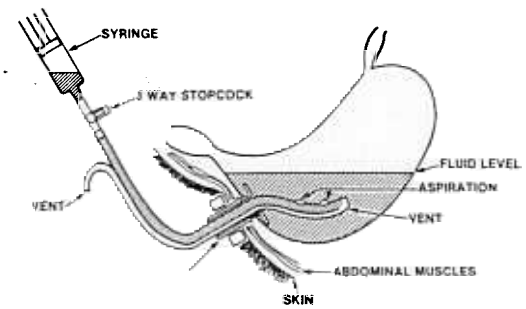

FIG. 2. Schematic representation of the chronic model system. Changes in intragastric volume were calculated from the dilution factor of a known dye solution instilled into the stomach. The intragastric volume did not change by the repeated instillation and aspiration of gastric samples because attempt was made to keep the aspirated volume equal to the instilled volume.

immediately after injecting 10 ml of water, at least 9 ml could be recovered. After the tube was positioned, 5 ml of water was injected into the stomach followed by a 60-min stabilization period before the start of the study.

Changes in intragastric volume and the rates of gastric secretion were determined with a dye dilution technique [9, 10] which allows concurrent measurements of these parameters. The technique is based on the principle that a volume of unknown solution can be determined from the dilution factor of a known dye solution. Repeated determination of the dye concentration at preset time intervals during the process allows calculation of the intragastric volume and from that, the changes in gastric volume. Generally, secretion of fluid into the stomach results in a dilution of the gastric dye solution while the total amount of dye remains unchanged, whereas the exit of fluid from the stomach into the duodenum (emptying) results in a reduction in the total amount of dye in the stomach. It is this difference that allows the distinction between changes in intragastric volume due to secretion and changes due to emptying. Gastric sampling was carried out via the gastric cannula by instillation and aspiration of phenol red (0.022%, w/v) at 10-min intervals (Fig. 2). The amount of dye instilled was 3 ml and

aspirations of gastric juice were 1.5 ml each occurring 1 min before and 1 min after each dye instillation. Each sample of gastric juice and phenol red solution was adjusted to pH 10.0 with 0.25% Na_3PO_4 and absorption was determined at 560 nm with a spectrophotometer (Stasar III, Gilford Instrument Laboratories, Inc., Oberlin, OH). Hydrogen ion concentration was determined by endpoint titration to pH 7.0 with 0.01 *N* NaOH using an Auto burette/pH-stat system (Radiometer Co., Copenhagen, Denmark). Histamine or saline was given as a continuous subcutaneous infusion. Cimetidine, ranitidine, and omeprazole were given as a bolus subcutaneous injection after 1 hr infusion of histamine. The changes in the intragastric concentrations of phenol red were used to determine the rate of secretion for each time interval between instillation and sampling. Results were computed and analyzed as described in detail elsewhere [9, 10] using a locally developed computer program and a PDP10 computer (DCRT, NIH, Bethesda, MD). Acid output was calculated as the mean ± 1 SEM for each group of animals at each time point in the experiment and was expressed, unless otherwise indicated, as microequivalents per minute. Differences between means were analyzed by analysis of variance or by Student's *t* test, as appropriate, at probability of $P < 0.05$. The correlation coefficient was calculated by the least-squares method.

RESULTS

Gastric acid output in unstimulated awake guinea pigs was 10.2 ± 1.3 μeq/kg/min and remained unchanged for the 150-min duration of the experimental procedure (Fig. 3). Infusion of histamine increased gastric acid output in a time- and dose-dependent manner. A significant increase in acid output was seen within 20–30 min, it leveled off by 50–60 min, and it remained unchanged for the remainder of the 90–100 min of histamine infusion. At the plateau, the acid output with 30 μg/kg/hr histamine was 30–38 μeq/kg/min, approximately three- to four-fold higher than basal. Increasing the rate of histamine infusion to 60 μg/kg/min did not change the shape of the time course, but caused a further increase in acid secretion to 44–55 μeq/kg/min (Fig. 3). Decreasing the concentration of histamine to 15 μg/kg/hr lowered the acid output to 20–30 μeq/kg/min (results not shown). These results demonstrate that the guinea pig responds to histamine infusion with an increase in gastric output in a time- and dose-dependent manner.

One of the major potential advantages in developing this animal model was the ability to carry out several experiments on the same animal. Figure 4 illustrates this point in two individual guinea pigs. The weight of the guinea pigs, as expected, was progressively increased with age. Concomitantly, peak acid output in response to histamine also increased with age. There was a positive correlation between the increase in acid output and the weight of the animal (Fig. 4). For example, in one guinea pig weighing 495 g, the peak acid output was 24 μeq/min and when the same animal reached 910 g, peak

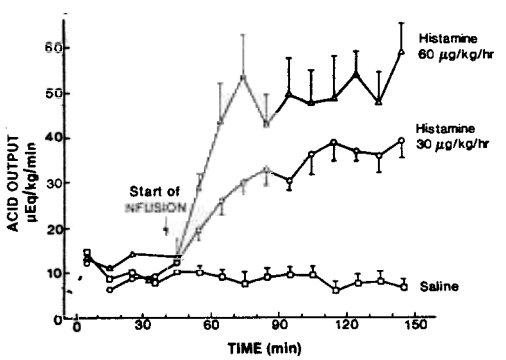

FIG. 3. Time course of histamine-stimulated increase in acid output in guinea pig *in vivo*. Awake animal was held in a Bowman restrainer and gastric samples were collected every 10 min for acid and dye determination. Histamine or saline was administered as indicated by sc infusion at 40 min (arrow). Gastric acid output was normalized for the weight of the animal and is expressed as μeq/min/kg. Values are the mean from at least six experiments for each treatment. Compared to no histamine, both concentrations of histamine increased significantly acid output after 20 min infusion ($P < 0.05$).

acid output was increased to 33 μeq/min. This positive correlation was observed over the range of guinea pig weight from 300 to 1200 g. Once the animals matured, however, there was no further increase in weight or in peak acid output (Table 1). In one mature guinea pig, for instance, the peak acid output ranged from 34 to 44 μeq/min over the span of 2 months, with a correlation coefficient of $R = 0.091$ between the weight and acid.

In addition to gastric acid output, this technique allows the evaluation of changes in other parameters of gastric secretion. Histamine infusion (30 μg/kg/hr) caused approximately a fourfold increase in acid output but only a twofold increase in fluid output (Table 2). Under basal conditions, the hydrogen ion concentration in the secreted fluid was approximately 70 m*M* and with histamine it was increased to 127 m*M*. The increase in fluid output from 0.16 to 0.34 ml/min with histamine (i.e., increment 0.18 ml/min) probably reflects secretion from the parietal cells. This increase is also reflected by the rise in intragastric volume from 6.3 ml under basal to 13.4 ml with histamine stimulation (Table 2).

TABLE 1

REPEATED MEASUREMENTS OF GASTRIC ACID OUTPUT IN ADULT CHRONIC GUINEA PIG

	Days after surgery	Weight (g)	Acid output (μeq/min)
Guinea pig 1	254	1164	44.0 ± 4.3
	266	1166	36.5 ± 2.9
	275	1180	35.5 ± 8.0
	287	1210	39.5 ± 2.1
	299	1164	37.2 ± 2.6
	307	1164	34.9 ± 2.4
	320	1175	41.9 ± 3.4
Guinea pig 2	294	1260	56.6 ± 7.2
	312	1250	68.8 ± 6.7
	332	1285	78.9 ± 5.7
	340	1279	75.6 ± 11.2
	349	1300	75.5 ± 12.8

Note. Guinea pigs received sc infusion of histamine (30 μg/kg/hr). Acid output was measured between 50 and 100 min after the start of infusion. Results are expressed as the mean ± 1 SD of four gastric samples taken during that period.

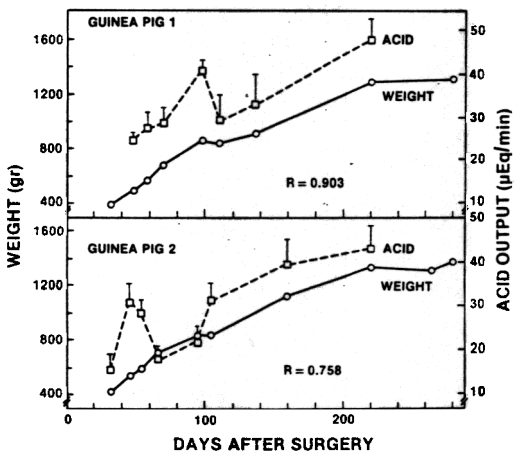

FIG. 4. Gastric acid output under peak histamine stimulation in the same guinea pigs at different ages. In each animal acid output was measured between 50 and 90 min after the start of histamine infusion (30 μg/kg/hr). Each value represents the mean ± 1 SD of samples taken at 10-min intervals during that period and each of the guinea pigs is shown. Correlation analysis of the results for these guinea pigs revealed that not only the weight and the acid output progressively increased with age of the animal but also there was positive correlation between gastric acid output and the weight of the animal. For guinea pig No. 1, this correlation coefficient was 0.901 and for guinea pig No. 2 it was 0.758.

We next examined the ability of various hyposecretory agents to inhibit the histamine-stimulated acid secretion. Guinea pigs received a continuous sc infusion of histamine and after 1 hr antisecretory drugs or saline was administered by a bolus sc injection. In control guinea pigs with histamine stimulation, acid output peaked after 50–60 min, remained unchanged between 60 to 120 min, and slowly but steadily declined thereafter (Fig. 5). After 3 hr stimulation the acid output was 75 to 80% of peak acid output observed between 60 and 100 min stimulation with histamine. The H_2-antagonists cimetidine (3 μmole/kg) and ranitidine (0.5 μmole/kg)—given as a bolus sc injection after 1 hr infusion of histamine—inhibited gastric acid output in guinea pigs (Fig. 5).

TABLE 2

VARIOUS GASTRIC SECRETORY PARAMETERS UNDER BASAL AND HISTAMINE STIMULATION IN AWAKE GUINEA PIG

Parameter	Basal	Histamine (30 μg/kg/hr)
Acid output (μeq/kg/min)	11.8 ± 1.6	41.2 ± 3.4
Fluid output (ml/kg/10 min)	1.6 ± 0.14	3.4 ± 0.23
Acid concentration (m*M*)	69.4 ± 7.2	127.0 ± 4.0
Intragastric volume (ml/kg)	6.3 ± 0.5	13.4 ± 1.1

Note. Animals were treated as described in the legend to Fig. 3. Basal was defined as the period of 30–40 min prior and up to the start of histamine infusion. Values with histamine represent the period between 60 and 100 min after the start of histamine infusion. Each value is the mean ± 1 SEM of 14 experiments (basal) and of 16 experiments (histamine). Acid concentration represents the concentration of acid in the secreted fluid. It was calculated separately for each experiment, and the mean was then calculated. Since some of the parameters changed with the age/weight of the animal (see Fig. 4 and unpublished observation), values were normalized where applicable and are expressed per kilogram weight. All values under histamine stimulation were significantly different from values under basal conditions ($P < 0.05$).

With both antagonists an inhibition was observed within 20–30 min and a maximum effect was observed within 30–40 min after drug injection. Ranitidine was more potent than cimetidine in that at a dose of 0.5 μmole/kg ranitidine caused 60–70% inhibition whereas 3 μmole/kg cimetidine (sixfold higher) caused only 40 to 50% inhibition. Similarly, the substituted benzimidazole, omeprazole, which has been reported to inhibit the gastric H-K-ATPase [14], also inhibited gastric acid output in guinea pigs (Fig. 5). At 1.2 μmole/kg, omeprazole inhibited acid output by 50% within 30 min and 90% by 60 min after drug injection. These results demonstrate that stimulation of acid output in the guinea pig is mediated by histamine via the H_2-receptor because both H2-antagonists inhibited the action of histamine.

DISCUSSION

The present method is simple and appears to be suitable for studying the physiology and pharmacology of gastric secretion in the guinea pig. In contrast to previous techniques in small laboratory animals, there was no collection of gastric juice via drainage, no oral intubation for aspiration was involved, no special or sophisticated equipment was used, no anesthesia was employed, there was no stress associated with acute surgery, and finally, several gastric secretory parameters could be measured simultaneously. In addition, the same animal could be used repeatedly and because of the species involved, there is also a significant economical advantage [25].

We used the dye dilution technique for determining intragastric volume and gastric acid and fluid output. This technique has been validated and used extensively in human and monkey [9, 10]. It has been established that the method can be successfully used to determine gastric secretion and emptying rates under a variety of conditions, provided that certain assumptions are employed for the use of phenol red as a marker (e.g., the dye is neither absorbed nor causes by itself any changes in the secretion process) [10, 15].

The present method involved the continuous sampling of gastric juice and as such offers advantages over other techniques. Since there is no gastric drainage, the need for long collection periods to obtain volume sufficient for analysis was eliminated. The technique does not alter intragastric volume

and the use of short time intervals between samplings becomes possible. This allows one to follow the time course of drug effects on the secretory process. We observed for example, that histamine caused a significant increase in acid output by 20 min after infusion. Ranitidine or omeprazole inhibited acid output by 20 min after their administration and the inhibition persisted for at least 2 hr.

Basal acid output was approximately 10 μeq/kg/min (or 0.6 meq/kg/hr) and increased three- to fourfold after histamine. This illustrates that the guinea pig stomach responds to histamine by secreting acid. Histamine also increased gastric fluid output, intragastric volume, and acid concentration in the secreted fluid. The rise in acid concentration in the secreted fluid rose to 127 m*M*, an indication of increased secretion from the parietal cells.

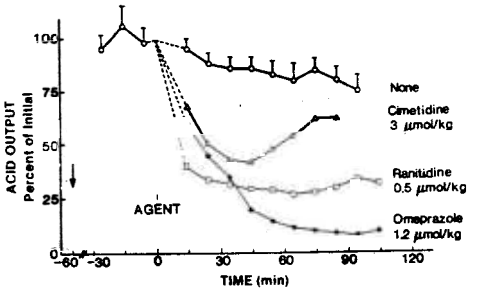

FIG. 5. Effect of various hyposecretory agents on histamine-stimulated gastric acid output in guinea pig. Awake animals were subcutaneously (sc) infused with histamine for 1 hr and gastric samplings were started (−30 min). At the arrow, animals received a bolus sc injection of either ranitidine (0.5 μmole/kg), cimetidine (3.0 μmole/kg), or omeprazole (1.2 μmole/kg). To minimize individual sample variations a moving average was calculated for all sample values after drug administration; an average from samples 1, 2, and 3 was calculated (AVR 1), then an average of samples 2, 3, and 4 (AVR 2), then samples 3, 4, and 5 (AVR 3), etc. The time at which a half-maximal inhibition was observed was 15 min with cimetidine and ranitidine and 20 min with omeprazole. The results represent the mean ± SEM of six animals for each antagonist and are expressed as the percentage of the mean acid output prior to the drug administration. For clarity, the standard errors of the mean (SEM) for the antagonists were omitted from the figure. However, these values did not exceed 10% of the indicated means. Analysis of these results using analysis of variance revealed that acid output in the presence of each antagonist was significantly different ($P < 0.05$) from control (None) values.

The increase in fluid output from 0.16 to 0.34 ml/min with histamine (i.e., increment of 0.18 ml/min) probably reflects secretion from the parietal cells. Since the corresponding increase in acid output was from 12 to 41 μeq/min (i.e., increment 29 μeq/min; Table 2), we calculated that the secreted fluid contained 161 m*M* acid (29 μeq in 0.18 ml). This is the expected concentration of acid from pure parietal cell secretion. Furthermore, using the same assumption that the increase in fluid output reflects increased secretion primarily from the parietal cells, we calculated the basal secretion of nonparietal cells. If the acid concentration in the secreted fluid from the parietal cells was 161 m*M*, only 0.07 ml/min of fluid has to be secreted under basal conditions in order to account for a hydrogen ion secretion rate of 12 μeq/min. Thus, under basal conditions fluid output was 0.16 ml/min of which 0.07 ml/min was parietal secretion and 0.09 ml/min (59%) was from nonparietal cell secretion. Under histamine stimulation, nonparietal cell secretion represented only 20–25% of the total fluid output. Likewise, the observed lower concentration of acid in the secreted fluid can be explained by the contribution of the fluid secreted from nonparietal sources.

We compared the acid output observed with histamine with the output values reported by others. We found that 41 and 51 μeq/kg/min or an hourly rate of 2.4 and 3.1 meq/kg/hr of acid was secreted with infusion of 30 and 60 μg/kg/hr of histamine, respectively. These values are higher than those reported for human (24–40 meq/hr) [16–18], monkey (8meq/hr) [19, 20], or dog (35–45 meq/hr) [2, 4], when the reported acid output was adjusted per kilogram weight of the species. For instance, the calculated output would be 0.34–0.57 meq/kg/hr in 70-kg men and 1.7–2.2 meq/kg/min in 20-kg dogs. In the monkey, when acid output was expressed per kilogram, the stimulated value was

0.4–1.6 meq/kg/hr [20]. These reported values are below ours for the guinea pig, using the dye dilution technique. The acid lost into the duodenum in those studies, however, is unknown and thus cannot be accounted for. In contrast, in small laboratory animals, maximal acid outputs were higher. In the guinea pig 1.6 meq/kg/hr of acid was secreted in response to a maximal effective dose of betazol [1] and a lower rate of 0.63 meq/hr in response to histamine [8] and 2.4–3.1 meq/kg/hr in the present studies. Cats secrete acid at the rate of 2.8–3.2 meq/hr [5], which when adjusted to weight (2 kg; i.e., 1.4–1.6 meq/kg/hr), is somewhat lower than the guinea pig values.

In the rat with gastric fistula, prolonged infusion of histamine at 100 mg/kg/24hr, a dose that is almost 100-fold higher than the dose we used, yielded 3 meq of acid over a 24-hr collection period [7]. This secretion rate (0.125 meq/hr) is much lower than that in the guinea pig. It should be noted, however, that in some of these studies, the dose of histamine used was extremely high compared to the range of doses reported for human monkey dog, and cat. The infusion of 4.1 mg/kg/hr histamine [7] or its injection at 2 mg/kg histamine [1] to the rat is suggestive that the rat stomach is relatively insensitive to histamine stimulation.

Fluid output generally represents fluid secretion from both parietal and nonparietal cells. A significant portion, if not all, of the increase in fluid output caused by histamine is due to increased secretion from the parietal cells. The previously reported gastric fluid output from the guinea pigs under basal conditions were lower by several fold than our values. Kowalewski collected 5.0 ml from guinea pig during 3 hr drainage (i.e., 1.67 ml/hr) [8] compared with our value of 9.6 ml/hr. He also reported that with infusion of 520 μg/kg/hr of histamine (i.e., 10-fold higher than the dose we used), the fluid output was increased to 5 ml/hr, compared with our value of 20.4 ml/hr. These differences are probably due in part to the method of collection used. Estimation of fluid output by drainage does not account for the lost fluid into the duodenum. Using a nonabsorbable radioactive marker in the guinea pig, Ragins and Wincze reported that 63% of the radioactivity was recovered during a 2-hr collection period [1].

The stimulation of acid output by histamine peaked by 40–60 min and remained almost unchanged for the subsequent 60 min. We observed that after 2 hr of histamine infusion, there was a small but steady decline in acid output which by the end of the third hour reached the value of 75% of the mean peak acid output. The reason for this decline is not clear and cannot be determined from the present studies. Similar findings were observed by Kowalewski who reported that after infusion of histamine into guinea pigs bearing permanent gastric cannula, the acid output during the second 3-hr collection period declined 30–50% from the first 3-hr collection [8].

In agreement with other *in vivo* and *in vitro* studies [21–24], gastric acid output in the guinea pig was significantly inhibited by H_2-antagonists and by omeprazole, an H–K-ATPase inhibitor [14]. Ranitidine was a more potent inhibitor than cimetidine because lower doses of 0.5 μmole/kg caused a larger inhibition than 3 μmole/kg cimetidine. These results are supported by *in vitro* studies regarding the ability of cimetidine and ranitidine to inhibit the action of histamine in guinea pig gastric cells [11, 21] and are in agreement with other studies which support the hypothesis that the H_2-receptor located on parietal cells mediate acid secretion [23]. Finally, the finding that omeprazole abolished the acid output under both basal and histamine stimulation supports the hypothesis that as in other species, secretion of acid in the guinea pig is mediated by the gastric H–K-ATPase.

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