Gastric Emptying and Secretion in Zollinger-Ellison Syndrome

ANDRE DUBOIS, PAUL VAN EERDEWEGH, AND JERRY D. GARDNER

From the Section on Gastroenterology, Digestive Diseases Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, and Laboratory of Theoretical Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

ABSTRACT Gastric emptying and secretion, as well as intragastric volume and composition, were determined simultaneously in three patients with Zollinger-Ellison syndrome and in seven normal subjects. Gastric hypersecretion was observed in patients with Zollinger-Ellison syndrome and in normal subjects receiving pentagastrin. In contrast, the fraction of gastric contents emptied per minute (fractional rate of emptying) was increased in Zollinger-Ellison patients and unchanged or decreased in normal subjects receiving pentagastrin. The increased fractional rate of gastric emptying in patients with Zollinger-Ellison syndrome persisted despite abolition of gastric hypersecretion by metiamide. Thus, the increased fractional gastric emptying seen in patients with Zollinger-Ellison syndrome is not attributable to hypergastrinemia, or to gastric hypersecretion per se. Instead, it appears to be caused by an undefined nervous or humoral factor.

INTRODUCTION

The characteristic abnormalities found in patients with the Zollinger-Ellison syndrome are generally considered to result directly or indirectly from increased circulating concentrations of gastrin (1). Administration of exogenous gastrin (or a functional equivalent such as pentagastrin) to normal human subjects (2) or laboratory animals (3) produces changes in gastrointestinal function similar and in most cases identical to those seen in patients with Zollinger-Ellison syndrome (4).

Insofar as gastric emptying is concerned there is an apparent discrepancy in the previously published literature. In one patient with Zollinger-Ellison syndrome, gastric emptying was reported to be increased (5) while administration of gastrin or pentagastrin to man or laboratory animals (6–8) has decreased gastric emptying. To explore this apparent discrepancy in greater detail we have simultaneously measured gastric emptying and secretion in normal subjects, normal subjects receiving pentagastrin, patients with Zollinger-Ellison syndrome, and patients with Zollinger-Ellison syndrome receiving metiamide.

METHODS

All patients and normal volunteers were studied as inpatients at the Clinical Center, National Institutes of Health, Bethesda, Md. The experimental procedure was explained to, and informed consent obtained from, each subject for each study performed. The seven normal subjects (aged 22–26 yr; three females, four males) were free of and had no previous history of gastrointestinal disease and had normal serum gastrin concentrations.[1] The patients with Zollinger-Ellison syndrome (aged 27, 47, and 48 yr; two females, one male) had fasting serum gastrin concentrations greater than 300 pg/ml, basal gastric acid secretion greater than 20 mq/h with a ratio of basal acid secretion to maximal acid secretion (determined by Histalog administration; Eli Lilly and Co., Indianapolis, Ind.) greater than 0.6, and at some time radiological evidence of gastrointestinal ulceration. Two of the subjects had metastatic islet cell pancreatic carcinoma (verified histologically). The third patient had not undergone abdominal surgery. At the time these studies were performed none of the patients with Zollinger-Ellison syndrome had an "active ulcer" by endoscopic or radiological examination, although each had abnormalities known to be associated with Zollinger-Ellison syndrome (e.g. scarred duodenal bulb and gastric rugal hypertrophy). The patient with endogenous hyperhistaminemia (10) had basophilic leukemia with increased whole blood and urinary histamine, normal serum gastrin, gastric acid hypersecretion, and duodenal ulcer.

Intragastric volume and rates of gastric emptying and secretion were determined with a dilution technique. During each study 150 mM sodium chloride was adminis-

Dr. Dubois' present address is: Department of Internal Medicine, Uniformed Services University of the Health Sciences, National Naval Medical Center, Bethesda, Md. 20014.

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[1] Normal serum immunoreactive gastrin activity in our laboratory is less than 150 pg/ml (9).

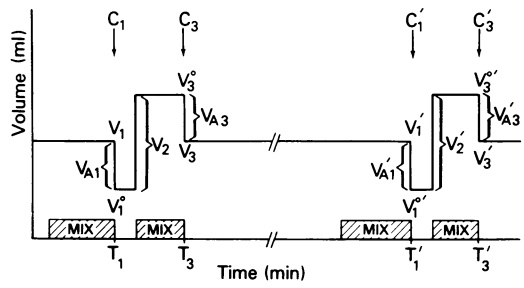

FIGURE 1 Dilution technique. Schematic illustration of the technique used to determine gastric emptying and secretion.

tered intravenously at a rate of 60 ml/h. When appropriate, pentagastrin and metiamide were infused at 5 μg/kg per h and 4 mg/kg per h, respectively. Studies were started 30 min after introducing a no. 12 French, double lumen polyethylene Salem sump tube (bore 4 mm, wall thickness 1 mm, Sherwood Medical Industries Inc., St. Louis, Mo.) in the stomach. Proper positioning of the tube in the most dependent part of the stomach was verified by demonstrating that immediately after injecting 20 ml of water at least 15 ml could be recovered.

Gastric contents were mixed for 1 min by rapid, repeated aspiration and immediate reinsertion of 5 ml of gastric contents with a 50-ml syringe; 2.5 ml (V_{A1}) were sampled at time T_1 (Fig. 1). Immediately thereafter 5 ml (V_2) of a phenol red solution in distilled water (280 mg/liter, pH 7.4) was instilled into the stomach and mixed thoroughly with gastric contents for 50 s. A second 2.5-ml sample (V_{A3}) was then taken.

This 2-min mixing, sampling, and dilution procedure was performed at 10-min intervals for 30 min. 250 ml of a phenol red solution in distilled water ("meal"; 40 mg/liter, pH 7.4)[2] was then instilled into the stomach during 2.5 min with a constant infusion pump. The 2-min mixing, sampling, and dilution procedure was then repeated at 5 and 10 min after the start of the meal and subsequently at 10-min intervals for 40 min.

Each sample of gastric juice and the phenol red solutions were adjusted to pH 10 with 0.25% Na_3PO_4 and analyzed for the concentration of phenol red with a spectrophotometer at 560 nm (Gilford Micro-sample Spectrophotometer, Gilford Instrument Laboratories, Inc., Oberlin, Ohio). Hydrogen ion concentration was determined by endpoint titration to pH 7.4 with 0.01 N NaOH (Titration assembly, Radiometer Co., Copenhagen, Denmark).

The reason for using 5- or 10-min intervals was that the time should be long enough to allow for changes in phenol red and ion concentrations but short enough to permit the assumption that the fractional rate of emptying and secretory rates remained constant over the given interval. When the volume present in the stomach was greater than 10 ml, the size of the samples V_{A1} and V_{A3} was 10 ml, and the volume of test solution injected (V_2) was 20 ml, while, when it was less than 10 ml, volumes identical to the ones used during the fasting period were sampled and injected. Because the volume of test solution injected (V_2) was equal to the total of the volume aspirated ($V_{A1} + V_{A3}$), there was no net gain or loss of fluid resulting from the sampling and dilution procedure.

Several assumptions were needed to calculate intragastric volume at the times of the dilution procedure as well as the rates of emptying and secretion during the intervals between these dilution procedures. (*a*) Phenol red is not absorbed, secreted, or degraded by the human stomach (11). (*b*) A 5–20-ml phenol red solution injected into the stomach can be mixed completely with the gastric contents by aspirating and reinjecting 5–20-ml aliquots four times during a 1-min period (unpublished observations and 12). (*c*) Over a short interval of time, the rate of decline of intragastric phenol red (dP/dt) is proportional to the intragastric amount of phenol red (P). This assumption is expressed mathematically by

$$dP/dt = -g \cdot P,$$

where g is the fractional rate of emptying, i.e., the fraction of the intragastric contents leaving the stomach per unit of time. (*d*) Phenol red remains homogeneously mixed with the gastric contents during the intervals between samplings. A logical corollary of this assumption is that any element present in the stomach (water, ions) is emptied at a fractional rate identical to that for phenol red. That is, if the fractional rate of emptying for phenol red is 5% per min, 5% of the intragastric amount of water and ions will also leave the stomach per minute. (*e*) The fractional rate of emptying and the rates of secretion are constant during one 5- or 10-min interval but can vary between intervals.

From assumptions *a* and *b* an initial estimate of the intragastric volume was calculated from the equation (Appendix and Fig. 1):

$$V_1 = V_2 \cdot (C_2 - C_3)/(C_3 - C_1) + V_{A1},$$

where V_1 is the volume of fluid in the stomach before the dilution procedure, C_1 is the concentration of phenol red in the first aspirated sample, the volume of which is V_{A1}, V_2 is the volume of test solution instilled into the stomach, C_2 is the concentration of phenol red in this test solution (280 mg/liter), and C_3 is the concentration of phenol red in V_{A3} ml aspirated after mixing the test solution with the gastric contents. The amount of phenol red present in the stomach (P_1) was then calculated at the time of each sampling during the experiment. This initial estimate is obtained by neglecting the secretion and emptying occurring during the 1-min interval between the two samplings V_{A1} and V_{A3}.

From assumptions *a*, *c*, and *d*, fractional rate of emptying, g, was then calculated from the change in the amount of intragastric phenol red during any 5- or 10-min interval (Appendix). The amount of a particular substance (X) present at the end of any given interval reflects the amount of X present at the beginning of the interval plus the net difference between the amount secreted and the amount emptied. One can calculate the rate at which X is emptied. By determining the amounts of X present at the beginning and at the end of the interval one can then calculate the rate at which X was secreted during the interval (Appendix).

After rates of emptying and secretion were determined, intragastric volume was recalculated with an equation which includes a term for the emptying and secretion which occur during the 1-min mixing period (Appendix). The fractional rate of emptying and the rate of water secretion were then computed again and these new values were used to determine the intragastric volume. This iterative process (13) was repeated until the calculated value for intragastric volume changed by less than 1%. Calculations were performed with a locally developed program and a GE 265 computer (Call-

[2] A solution containing phenol red was used instead of distilled water to avoid the large relative errors which may result from spectrophotometric measurements of solutions containing low concentrations of phenol red.

a-Computer, Inc., Wellesley Hills, Mass.). For the 2.5-min interval corresponding to the instillation of the meal, we have calculated secretory and emptying rates with an equation which includes a term describing this infusion (Appendix).

For each time interval between two sampling and dilution procedures, fractional rate of emptying and rates of secretion were determined from the changes in intragastric concentrations of phenol red and ions. The fraction of the test meal remaining in the stomach was calculated at the end of each interval. For each subject, one fasting value was calculated from the mean of the results obtained before the meal. In each group, values obtained in each subject before and for each interval after the meal were used to determine the mean (±SEM) given in Figs. 2–7. The change in each function (e.g., fractional emptying, water secretion, etc.) was evaluated using a two-factor (time and group of subjects) analysis of variance with repeated measures (14) and multiple *t* tests. These calculations were performed with the program LDUO 40 (K. L. Dorn) and an IBM 370 computer (Division of Computer Research and Technology, National Institutes of Health, Bethesda, Md.).

Two different techniques were used to test the validity of the dilution technique. (*a*) In dogs, fractional rate of emptying was measured simultaneously with the present dilution technique and by counting externally intragastric ^{99m}Tc-DTPA with a gamma camera interfaced with a computer. Results obtained with the two techniques were not significantly different (15). Furthermore, repeating the isotope study on a separate day without mixing yielded similar results, indicating that the mixing procedure does not affect gastric emptying. (*b*) In humans, the gastric contents were aspirated completely immediately before each dilution procedure during fasting and at the end of each experiment. In all instances, the aspirated volume was greater than 90% of that calculated with the dilution technique.

TABLE I

Intragastric Volume and Rates of Gastric Secretion and Fractional Emptying in Fasting Subjects

Subjects	Water secretion	Hydrogen ion secretion	Intragastric volume	Fractional rate of emptying
	ml/min	*meq/min*	*ml*	*%/min*
Normal (7)	0.9±0.2	0.031±0.006	24±5	4±2
Normal plus pentagastrin (7)	5.0±0.6	0.55±0.04	95±16	6±0.7
ZES* (3)	8.2±1.0	0.83±0.20	42±6	19±6
ZES plus metiamide (3)	1.3±0.4	0	10±0.4	16±2
Hyperhistaminemia (1)	3.5	0.59	94	3

Intragastric volume and fractional rates of gastric emptying and water secretion were determined at 10-min intervals during a 40-min fasting period. Pentagastrin (5 μg/kg per h or metiamide (4 mg/kg per h) were given intravenously in 150 mM NaCl at a rate of 60 ml/h. When these agents were used experimental determinations were begun 30 min after starting infusion of the drug. Values are means±1 SEM. The number of subjects is given in parentheses.

* Zollinger-Ellison syndrome.

TABLE II

Gastric Secretion of Water and Hydrogen Ion in Patients with Zollinger-Ellison Syndrome

Patient	Rate of water secretion		Rate of hydrogen ion secretion	
	Dilution technique	Aspiration technique	Dilution technique	Aspiration technique
	ml/min		*meq/min*	
J. G.	8.97	6.70	1.14	0.90
D. M.	6.27	4.12	0.45	0.46
P. R.	9.27	7.25	0.90	1.07
	$P < 0.05$*		NS*	

Gastric secretion of water and hydrogen ion was determined in three patients with Zollinger-Ellison syndrome with (*a*) the dilution technique described in Methods and (*b*) continuous aspiration of the gastric contents via a nasogastric tube. Results are means of four measurements.

* As calculated with an analysis of variance with repeated measures (14).

RESULTS

In seven normal fasting subjects administration of pentagastrin caused a 5-fold increase in water secretion, an 18-fold increase in acid secretion, no change in the fractional rate of gastric emptying, and a 4-fold increase in intragastric volume (Table I). In three fasting patients with Zollinger-Ellison syndrome secretory rates of water and acid were significantly greater than those in normal subjects (9- and 28-fold, respectively) and fractional rate of gastric emptying was three to five times greater than normal. In Zollinger-Ellison syndrome, intragastric volume was approximately twice that in normal subjects but approximately one-half of that of normal subjects receiving pentagastrin. Administration of metiamide to the patients with Zollinger-Ellison syndrome reduced the rates of water secretion to values that were not significantly different from those in normal subjects and abolished acid secretion but did not alter the fractional rate of gastric emptying. Thus, in patients with Zollinger-Ellison syndrome, metiamide reduced the volume of the intragastric contents to a value which was approximately one-half that obtained in normal fasting subjects. The patient with hyperhistaminemia had values for acid and water secretion, fractional rate of emptying, and intragastric volume which were the same as those in normal subjects given pentagastrin.

In the three patients with Zollinger-Ellison syndrome we compared values for gastric secretion ob-

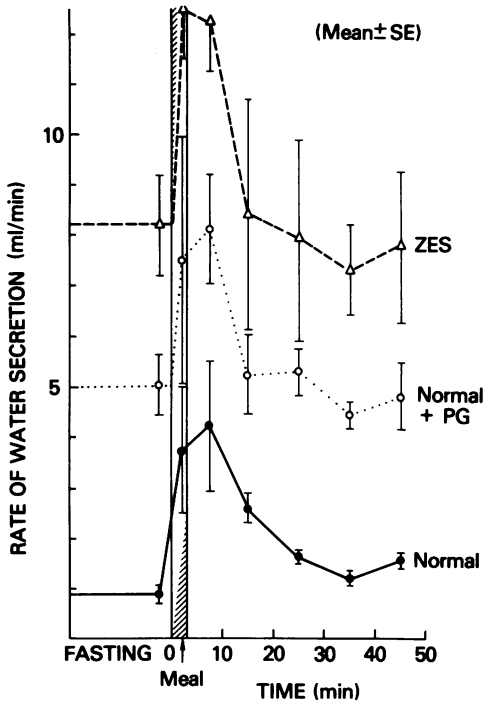

FIGURE 2 Rate of water secretion before and after administration of a liquid meal in three groups of subjects. Rate of gastric secretion was determined during fasting. The test meal (250 ml) was administered and water secretion was determined at 5- or 10-min intervals for the subsequent 50 min. Results shown are means (±SEM) from experiments in seven normal subjects (●), seven normal subjects receiving pentagastrin (PG) (○), and three patients with Zollinger-Ellison syndrome (ZES) (△).

tained with the dilution technique to those obtained with the more conventional technique of continuously aspirating the gastric contents. Rates of water secretion determined with the dilution technique were significantly higher ($P < 0.05$) than those determined with continuous aspiration (Table II). The two techniques gave similar values for rates of gastric acid secretion.

After administering a 250-ml water meal to normal subjects the rate of gastric water secretion increased fourfold during the first 10 min after the meal, was still significantly elevated compared to fasting from 20 to 30 min, returned to fasting values from 30 to 40 min, and increased again significantly ($P < 0.05$) from 40 to 50 min (Fig. 2). In normal subjects receiving pentagastrin and in patients with Zollinger-Ellison syndrome the magnitude of the increase in the rate of water secretion after the water meal was the same as in normal subjects; however, in both groups the secretory rate returned to basal values more rapidly than it did in normal subjects. In patients with Zollinger-Ellison syndrome, metiamide reduced the fasting rate of water secretion but did not alter the increase in water secretion induced by the meal (Fig. 3). The water meal produced a significant increase in the rate of hydrogen ion secretion in normal subjects but not in normal subjects receiving pentagastrin or in patients with Zollinger-Ellison syndrome (Fig. 4). Although pentagastrin did not alter fractional rate of gastric emptying in normal fasting subjects (Table I), it significantly slowed fractional rate of emptying after administration of the meal (Fig. 5). In patients with Zollinger-Ellison syndrome, fractional rate of gastric emptying was significantly greater than that in normal subjects both during fasting (Table I) and after administration of the liquid test meal (Fig. 5).

The net effect of the meal-induced changes in gastric secretion and emptying determines the intragastric volume after administration of a 250-ml liquid meal (Fig. 6). In normal subjects the volume of the gastric contents was 150 ml at the end of the instillation, did not change during the subsequent 5 min, and then decreased progressively to basal values by 40 min. In normal subjects receiving pentagastrin, intragastric volume was 200 ml at the end of the instillation and then decreased steadily (but more slowly than that in normal subjects) during the subsequent 45 min. In pa-

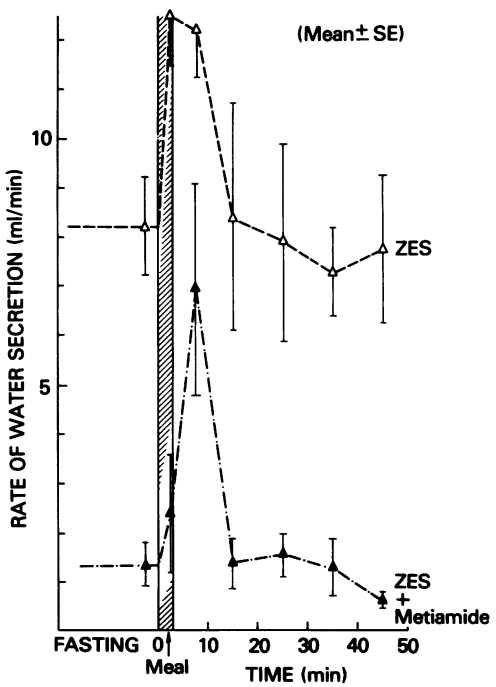

FIGURE 3 Rate of water secretion during fasting and after administration of a 250-ml water meal in three Zollinger-Ellison (ZES) patients. Rate of water secretion was determined during fasting. The test meal was administered and water secretion was determined at 5- or 10-min intervals for the subsequent 50 min. Results shown are means (±SEM) from three Zollinger-Ellison patients (△) or three Zollinger-Ellison patients receiving metiamide (▲).

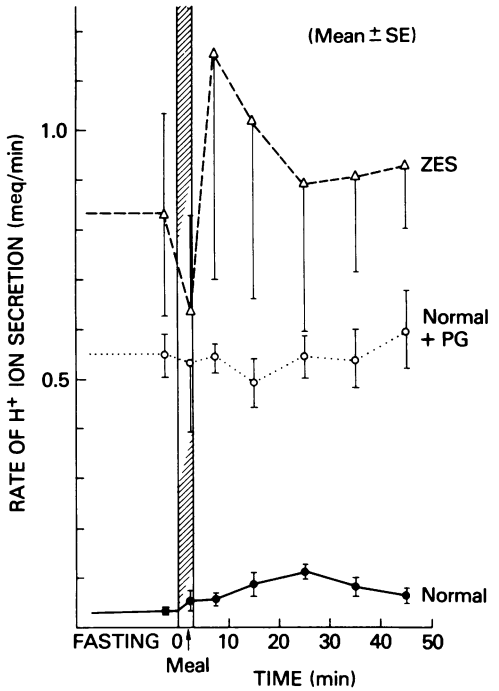

FIGURE 4 Rate of acid secretion before and after administration of a liquid meal. The rate of gastric secretion was determined during fasting. The test meal (250 ml) was administered and acid secretion was determined at 5- or 10-min intervals for the subsequent 50 min. Results shown are means (±SEM) from seven normal subjects (●), seven normal subjects receiving pentagastrin (PG) (○), and three patients with Zollinger-Ellison syndrome (ZES) (△).

tients with Zollinger-Ellison syndrome, the volume of the gastric contents increased to 120 ml at the end of the infusion and then returned to basal values by 20 min. After metiamide was given to patients with Zollinger-Ellison syndrome intragastric volume was significantly decreased during fasting ($P < 0.01$), increased after the meal to values similar to those observed without metiamide, and decreased to fasting volume by 30 min (Fig. 7). Since fractional rate of emptying was unaffected by metiamide in these patients, these changes can be accounted for completely by differences in secretory rates.

DISCUSSION

In the present studies we determined intragastric volume and rates of gastric emptying and secretion simultaneously with a modification of a dye dilution technique originally proposed by Mathieu and Remond (16) and subsequently improved by Hildes and Dunlop (17). Others have also measured gastric emptying and secretion simultaneously; however, the techniques used for these studies were only applied after administration of a liquid meal (17–20), required separate studies on separate days (19), or involved duodenal intubation (20, 21) or the use of radioisotopes (20).

Initially, dilution techniques were used to measure the decline of intragastric volume after administration of a liquid meal (16). This decline was often interpreted as reflecting the rate of emptying (12), although, in fact, it reflects the net result of concurrent secretion and emptying (22, 23). We have developed equations (see Appendix) which enable one to use a dilution technique to determine secretory and emptying rates during fasting as well as during and after administration of a liquid meal. Our computational procedure involves iterative fitting (13) and requires a digital computer. Others (12, 16–18, 24) have tried to avoid this computational procedure by assuming that no secretion or emptying occurs during the 1-min dilution procedure. The present method permits an evaluation of the error produced by this assumption (see Appendix). At relatively low rates of emptying and secretion, values computed with and then without this assumption differed by less than 5%, but at relatively high rates of secretion or emptying values differed by as much as 30%. These findings indicate that one cannot neglect emptying and secretion which occur during the dilution procedure, particularly when

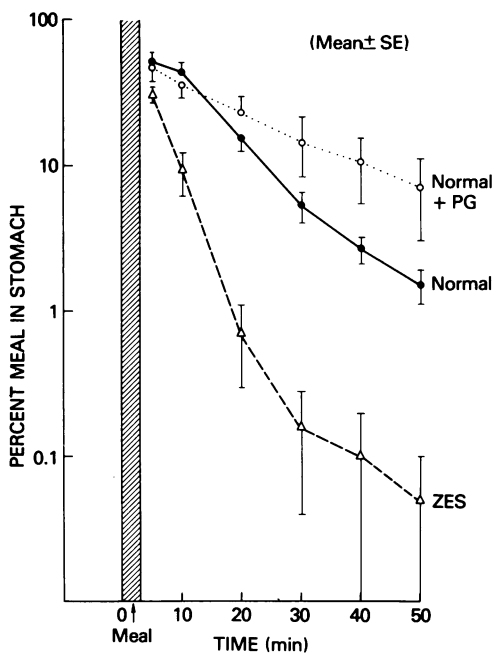

FIGURE 5 Percent of meal remaining in stomach during 50 min after intragastric administration of a 250-ml water meal. The slope of this decline, plotted on a semilogarithmic scale, is the fractional rate of emptying. Results shown are means (±SEM) from seven normal subjects (●), seven normal subjects receiving pentagastrin (PG) (○), and three patients with Zollinger-Ellison syndrome (ZES) (△).

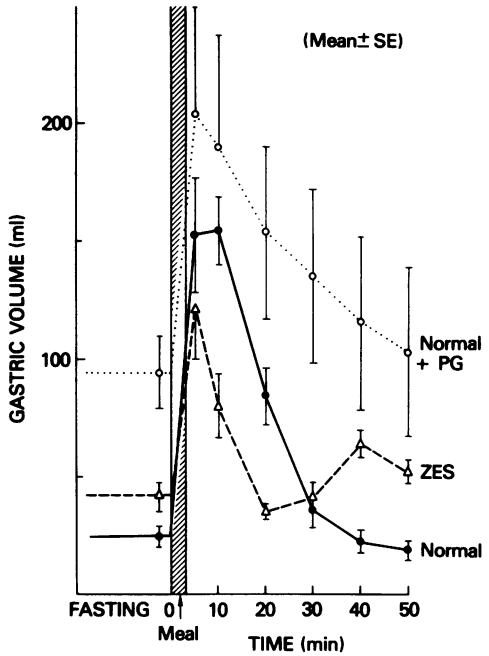

FIGURE 6 Volume of the intragastric contents in the fasting state and after administration of a 250-ml water meal. Intragastric volume was determined during fasting. The test meal was administered and intragastric volume was determined at 5- or 10-min intervals for the subsequent 50 min. Results shown are means (±SEM) from seven normal subjects (●), seven normal subjects receiving pentagastrin (PG) (○), and three patients with Zollinger-Ellison syndrome (ZES) (△).

the rate of either is relatively high. In our computations, in contrast to others (18), the fractional rate of emptying is not assumed to be constant from one interval to the next. By avoiding their restrictive assumption we found that fractional rate of emptying is modified by administration of a water meal. This finding indicates that gastric emptying cannot be described completely in terms of half-life. This is especially critical when the study of emptying is not confined to the early phase after a meal but extends into the transition period when a fasting situation is progressively reestablished.

The validity of the rates of gastric emptying and secretion determined in the present study depends in turn on the validity of five assumptions. The assumption that phenol red is not absorbed, adsorbed, secreted, or degraded by the stomach and that the dye is mixed completely with gastric contents during the 1-min period of aspiration and reinjection have been verified experimentally (7, 11, and unpublished observations). Previous observations by others (18, 19, 25) led us to the assumption that during a given interval phenol red leaves the stomach at a rate which is proportional to the intragastric amount of phenol red (exponential emptying); in contrast, Hildes and Dunlop (17) assumed that the rate of emptying is independent of the amount of intragastric contents (constant emptying). The assumptions that gastric contents remain homogeneously mixed during the interval between sampling procedures and that secretion and fractional emptying remain constant during this interval have not been verified with independent experimental techniques; therefore, it should be kept in mind that the present results are estimates and will be in error to the extent that these assumptions are invalid.

The usual technique for measuring gastric secretion involves continuous aspiration of the gastric contents and, consequently, is applicable only to subjects during fasting. In addition, it is usually assumed that, with aspiration, pyloric losses are negligible, although they have been found to be as great as 50% of fasting secretory rates (26). To overcome these limitations, rates of hydrogen ion secretion have been determined by intragastric titration of acid (27). This titration method, however, precludes determination of secretory rates for other ions and water. In addition, each of these techniques precludes simultaneous measurement of gastric emptying and interferes with duodenogastric regulatory processes by preventing acid from coming in contact with antroduodenal mucosa. In pa-

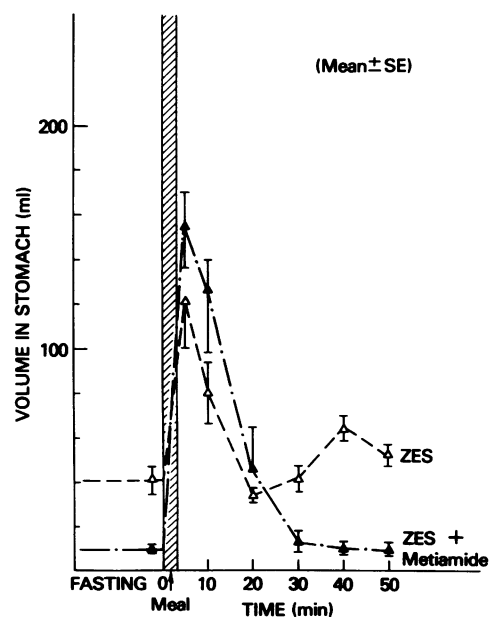

FIGURE 7 Volume of the intragastric contents during fasting and after administration of a 250-ml water meal. Intragastric volume was determined during fasting. The test meal was administered and intragastric volume was determined at 5- or 10-min intervals for the subsequent 50 min. Results shown are means (±SEM) from experiments in three Zollinger-Ellison patients (ZES) (△) or three Zollinger-Ellison patients receiving metiamide (▲).

tients with Zollinger-Ellison syndrome, we found a consistent discrepancy between rates of water secretion obtained with the dye dilution technique and those obtained by continuously aspirating the gastric contents. Our finding that the two techniques gave similar values for rates of gastric acid secretion argues against the discrepancy being due to incomplete recovery caused by loss of gastric juice through the pylorus. The lower rates of water secretion obtained with continuous aspiration may reflect differences in intragastric pH and volume between the two techniques. That is, the dilution technique is accompanied by a larger volume of intragastric contents and a higher intragastric pH and one or both of these may stimulate water secretion more than acid secretions, thereby accounting for the greater rates of water secretion found with the dilution technique. Additional observations which are consistent with this possibility are that, in patients with Zollinger-Ellison syndrome, administration of a 250-ml water meal increased gastric water secretion but did not alter gastric acid secretion and metiamide abolished gastric acid secretion but not water secretion.

In the present studies we found that during fasting and after a liquid meal fractional gastric emptying in patients with Zollinger-Ellison syndrome was approximately four times greater than that in normal subjects. This observation is consistent with the report by Lawrie et al. (5) who found that gastric emptying was increased in a patient with Zollinger-Ellison syndrome. However, complete remission during anticholinergic therapy raises doubts about the diagnosis in this patient. The increased gastric emptying in Zollinger-Ellison syndrome does not appear to be attributable to hypergastrinemia per se since gastric emptying did not increase in normal subjects given pentagastrin. It is possible, however, that chronic hypergastrinemia may in some unknown way be able to increase fractional gastric emptying. Although pentagastrin did not alter fractional gastric emptying in fasting normal subjects, the peptide caused a significant decrease in gastric emptying after these subjects were given a water meal. This latter observation agrees with previous studies in man (6) and dogs (7, 8).

The increased gastric emptying seen in patients with Zollinger-Ellison syndrome cannot be attributed to gastric hypersecretion, since pentagastrin, which in normal subjects increased gastric secretion to rates approaching those in the patients with Zollinger-Ellison syndrome, decreased or did not alter fractional gastric emptying. Furthermore, the rate of fractional gastric emptying was normal in a patient with endogenous hyperhistaminemia and gastric secretory rates comparable to those in the Zollinger-Ellison syndrome. This latter finding, although based on studies in a single patient, also argues against the increased gastric emptying in patients with Zollinger-Ellison syndrome being due to chronic gastric hypersecretion. Additional evidence against gastric hypersecretion being the cause of increased gastric emptying in Zollinger-Ellison syndrome is our finding that metiamide reduced gastric secretory rates to normal but did not alter the fractional rate of gastric emptying. Our finding that metiamide did not alter the rate of gastric emptying agrees with the report by Richardson et al. (28) who found that metiamide did not significantly alter gastric emptying in normal subjects or in patients with duodenal ulcers.

The increased fractional rate of gastric emptying in patients with Zollinger-Ellison syndrome may be attributable to decreased inhibition of gastric emptying by intragastric acid (29), increased stimulation of emptying by intragastric volume (25), chronic hypergastrinemia, or to the presence of a nervous or humoral factor which directly stimulates gastric emptying. Additional studies will obviously be required to elucidate the basis for this increased gastric emptying.

APPENDIX

(*a*) *Intragastric volume and amount of phenol red.* The dye dilution technique used for the present studies is based on the assumptions that mixing with the gastric contents is complete and that the dye, phenol red, is not absorbed, degraded, or secreted by the stomach. Initially, one also assumes that there is no loss or gain in the volume of distribution of the marker during its mixing (Fig. 1). $V_1°$ and $V_3°$ are the unknown volumes present in the stomach, respectively, before and after the addition of a known volume of the marker solution, V_2. The corresponding measured concentrations of the marker are C_1, C_2, and C_3.

$$V_1°C_1 + V_2C_2 = V_3°C_3; \quad (1)$$

$$V_1° + V_2 = V_3°. \quad (2)$$

These equations can be solved for $V_1°$ and $V_3°$:

$$V_1° = V_2 \cdot (C_2 - C_3)/(C_3 - C_1);$$

$$V_3° = V_2 \cdot (C_2 - C_1)/(C_3 - C_1).$$

C_1 and C_3 are measured on samples aspirated from the stomach, the volumes of which are V_{A1} and V_{A3}, respectively. The calculated intragastric volumes before (V_1) and after (V_3) the dye dilution procedure are

$$V_1 = V_1° + V_{A1}; \quad (3)$$

$$V_3 = V_3° - V_{A3}. \quad (4)$$

The intragastric amounts of phenol red at those two times are

$$P_1 = V_1 \cdot C_1, \quad (5)$$

$$P_3 = V_3 \cdot C_3, \quad (6)$$

and, for the subsequent dilution procedures, volumes of water and amounts of phenol red will be V_1',P_1',V_3',P_3'; V_1'',P_1'',V_3'', P_3''; etc. We selected a value for V_2 which was directly pro-

portional to V_1 and V_3 so that

$$C_1 \leq 0.7\ C_3 \leq 0.6\ C_2.$$

Thus, the relative error on V_1 and V_3 was of the same order of magnitude as the relative error on C_1, C_2, and C_3.

(*b*) *Fractional rate of emptying between the dilution procedures.* Assuming that the rate of emptying of phenol red is proportional to its intragastric amount, P:

$$dP/dt = -g \cdot P. \quad (7)$$

If g, the fractional rate of emptying, is assumed to be constant over a time interval t ($= T_1' - T_3$), one can integrate this equation to obtain

$$P_1' = P_3 \cdot \exp(-g \cdot t), \quad (8)$$

where P_1' and P_3 are the amounts of marker at times T_1' and T_3, respectively. This equation can then be solved for g.

If phenol red is instilled into the stomach at a constant rate, Up (expressed in milligrams per minute), during the time t', starting at T_3 and ending at T_4 ($T_4 < T_1'$), the relation is

$$P_1' = P_3 \cdot \exp(-g \cdot t) + \int_{T_3}^{T_4} Up \cdot \exp(-g \cdot [T_1' - \tau])d\tau. \quad (9)$$

$[T_1' - \tau]$ is the time interval between any time τ ($T_3 < \tau < T_4$) and T_1' or by evaluating the integral,

$$P_1' = P_3 \cdot \exp(-g \cdot t) + Up \cdot [\exp(-g \cdot [t - t']) - \exp(-g \cdot t)]/g. \quad (10)$$

This equation cannot be solved analytically for g, but g can be evaluated by successive iterations (Ref. 13).

(*c*) *Rate of water secretion.* The rate of change dV/dt of the intragastric amount of water (V) can be described by

$$dV/dt = -g \cdot V + Rw, \quad (11)$$

where Rw is the rate of water secretion.

If a time interval t($= T_1' - T_3$) is considered, the relation becomes

$$V_1' = V_3 \cdot \exp(-g \cdot t) + \int_{T_3}^{T_1'} Rw \cdot \exp(-g \cdot [T_1' - \tau]) \cdot d\tau. \quad (12)$$

V_3 and V_1' are the volumes of water present in the stomach at the times T_3 and T_1' respectively. The integral can then be evaluated if Rw is assumed to be constant over the interval t.

$$V_1' = V_3 \cdot \exp(-g \cdot t) + Rw \cdot [1 - \exp(-g \cdot t)]/g. \quad (13)$$

Rw can then be calculated.

If water is instilled into the stomach at a constant rate, Uw (expressed in milliliters per minute) during the time t', starting at the time T_3 and ending at T_4, the relation is

$$V_1' = V_3 \cdot \exp(-g \cdot t) + Rw \cdot [1 - \exp(-g \cdot t)]/g + Uw \cdot [\exp(-g \cdot [t - t']) - \exp(-g \cdot t)]/g. \quad (14)$$

Similar equations can be derived for the ions whose concentrations have been measured in the gastric contents, thus allowing the calculation of the secretory rates of ions.

(*d*) *Correction for secretion and emptying occurring during the dilution procedure (Fig. 1).* Initially, the emptying and secretory rates are assumed to be negligible over the 1-min sampling and dilution period (T_1 to T_3). If the fractional rate of emptying (g) and secretory rate (Rw) are known for the time interval T_3 to T_1' it can be assumed that these rates are also valid for the sampling intervals T_1 to T_3 and T_1' to T_3'. Therefore, equations (1) and (2) can be transformed to:

$$V_1^\circ C_1 \cdot \exp(-g \cdot [T_3 - T_1]) + V_2 \cdot [C_2 \cdot K + (C_3 - C_2) \cdot K'] = V_3^\circ C_3; \quad (15)$$

$$V_1^\circ \cdot \exp(-g \cdot [T_3 - T_1]) + V_2 \cdot K + \int_{T_1}^{T_3} Rw \cdot \exp(-g \cdot [T_3 - \tau]) \cdot d\tau = V_3^\circ. \quad (16)$$

$[T_3 - T_1]$ is the time interval between the samplings that permits the measurements of C_3 and C_1. $[T_3 - \tau]$ is the time interval between any time τ and T_3 ($T_1 < \tau < T_3$). K is a factor accounting for the fact that, due to four aspirations and four reinjections of volume V_2 during mixing, the injected phenol red test solution is in the stomach, available for emptying, only during a fraction of the 1-min dilution interval [$K = (1 + \exp(-g \cdot 3/4))/(1 + \exp(-g/12))$]. K' accounts for the progressive change in concentration of the injected phenol red from C_2 to C_3 [$K' = (1 - \exp(-g/12)) \cdot (4 + 3 \cdot \exp(-g/6) + 2 \cdot \exp(-g/3) + \exp(-g/2))/4$].

These equations can be solved for V_1° and V_3° to give:

$$V_1^\circ = [V_2 \cdot (C_2 - C_3) \cdot (K - K') - C_3 \cdot Rw \cdot [1 - \exp(-g \cdot [T_3 - T_1])]/g]/[(C_3 - C_1) \cdot \exp(-g \cdot [T_3 - T_1])]; \quad (17)$$

$$V_3^\circ = [V_2 \cdot [K \cdot (C_2 - C_1) - K' \cdot (C_2 - C_3)] - C_1 \cdot Rw \cdot [1 - \exp(-g \cdot [T_3 - T_1])]/g]/(C_3 - C_1). \quad (18)$$

By analogy with equations (3), (4), and (5), the intragastric volumes and amounts of phenol red before and after the dye dilution procedure can be calculated as follows:

$$V_1 = V_1^\circ + V_{A1} \text{ and } P_1 = V_1 \cdot C_1;$$

$$V_3 = V_3^\circ - V_{A3} \text{ and } P_3 = V_3 \cdot C_3.$$

A new estimate of the rates of gastric emptying and secretion can then be calculated. This two-step calculation is repeated, which gives alternatively over- and underestimated values for the intragastric volumes and the secretory and emptying rates. The solutions converge and the iterations are stopped when the fractional change of the calculated volume becomes less than 0.01. The initial, uncorrected value for intragastric volume was always significantly different from the final value. The absolute difference between these two values was directly related to the volume of the gastric contents and varied between 1.5 and 30 ml. The fractional difference was a function of the rates of emptying and secretion, and varied from 10% at low rates to up to 30% at higher rates. Similar differences were observed during computation of the rates of emptying and secretion.

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