Secretin-Gastric Emptying and Motor Activity: Natural Versus Synthetic Secretin (36976)

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Secretin has been found to inhibit slow wave activity of the stomach of the dog (1) and to delay gastric emptying of liquid meals in man (2). In a previous study in dogs in which gastric emptying, electrical and motor activity of the antrum were measured simultaneously it was found that pentagastrin delayed gastric emptying (3). This occurred despite evidence of increased slow wave activity as well as increased force and frequency of antral contractions (3).

The purpose of this study was to study simultaneously the effect of secretin on gastric emptying as well as gastric electrical and motor activity to determine whether a correlation could be found for emptying and antral activity. Further studies were made to compare the gastric emptying and gastric acid inhibitory responses to synthetic and natural secretin.

Methods. Animal preparations. Studies were made in 7 unanesthetized healthy dogs weighing 15 to 18 kg.

In four dogs (Group 1) a Thomas cannula (4) was put into the most dependent part of the stomach to form a gastric fistula. During the same operation, electrodes and transducers were sewn to the gastric antrum and proximal duodenum to record contractile activity. Electrical activity was recorded by 2 electrodes; one on the stomach approximately 6 cm proximal to the gastroduodenal junction and one on the duodenum 4 cm distal to the junction. Mechanical activity of the stomach was recorded by two strain gauge transducers placed 4 and 8 cm proximal to the gastroduodenal junction. Details of construction and implanting the electrodes and transducers have been published previously (5, 6). Records of electrical activity were made on an Offner Type RM dynograph through AC couplers (9806) with a time constant of 1 sec. Records of contractile activity were made through the strain gauge couplers (9803).

In three dogs (Group 2) Thomas cannulas were put into the stomach to form a gastric fistula (GF) and these animals were used to study the effects of both secretins on gastric secretion.

Studies were started 3 wk after operation and the dogs remained healthy throughout the period of study.

Procedure. The animals were fasted for 18 hr before each test. A polyethylene catheter (PE-50) was inserted into a peripheral hindlimb vein and 154 m*M* NaCl was infused throughout the experiment using a peristaltic infusion pump (Harvard Apparatus, Millis, MA) set to deliver 25 ml/hr. A plastic adapter with a stopcock was connected to the gastric cannula through which the test meals were instilled and drained.

In the studies with the dogs of Group 1, three 10 min test meals were given in sequence with 20 min intervals in between each meal. The first and the third 10 min meals were controls and only saline was infused. Twenty minutes before and during the second 10 min test meal either synthetic (Squibb, New Jersey) or natural secretin (G.I.H., Sweden) was infused intravenously in doses of 1, 4 and 8 U/kg hr. Immediately before each test 100 ml of 154 m*M* NaCl was instilled in the stomach, immediately drained and discarded. This washout was done to clear the stomach of any accumulated secretions. The test meal of 300 ml of 154 m*M* NaCl with phenol red (40 mg/liter) was instilled at 37° via gastric fistula into the stomach in 45 sec. After 10 min the contents of the stomach were completely drained by gravity through the gastric

fistula. After gastric contents were collected, 200 ml of a "recovery" solution of 154 m*M* NaCl was instilled into the stomach to recover any residual contents. During the 20 min intervals between the tests the gastric fistula was opened and gastric secretions were allowed to drain by gravity.

In some experiments (4 U/kg hr natural secretin) data on contractile activity were recorded at the same time as the data for the gastric emptying. Recordings were begun 10 min before instilling the first test meal. The records were analyzed during the 10 min that each test meal was in the stomach. Slow waves of the distal antrum and the proximal duodenum were counted (cycles/min). Antral contractions were analyzed such that every phasic rise of 5 mm (approx 5 g force) or more above base line was counted as a contraction. All gauges had approximately the same sensitivity. The number of contractions in each 10 min period was counted, divided by 10, and expressed as contractions per minute. A motility index was determined by summing the peak height of each contraction (mm) over a 10 min period. A mean motility index was calculated by dividing the motility index of a given time period by the number of contractions that occurred during that period. This was a measure of the average force of contraction during that time period.

In all the experiments only one dose of secretin was studied on each day. If the animal vomited the results of that day were discarded.

The volumes of recovered gastric contents were measured to the nearest 1 ml and samples were taken for the determination of the pH and phenol red concentration. The pH of the recovered contents (usually pH 6 or greater) was determined by a glass electrode (Radiometer, Copenhagen) and phenol red concentration was measured spectrophotometrically at a wavelength of 558 nm.

In the dogs with gastric fistulas only (Group 2) the potency of the natural and the synthetic secretin was tested to determine the relative activities on inhibition of gastric secretion. After two 15 min basal periods, pentagastrin (4 μg/kg hr) was infused intravenously. The gastric contents were collected from the gastric fistula at 15 min intervals. After an interval in which the volumes from the gastric fistula had reached a plateau, and this usually occurred at the sixth 15 min period, a 10 ml solution containing either synthetic or natural secretin in a dose of 0.5, 1 or 2 U/kg was rapidly injected intravenously over a period of 1 min. Different doses were injected on different days. The gastric secretions were continued to be collected for a minimum of three 15 min periods after the injection or until the level of gastric acid output had returned to that of the control period.

Gastric contents were measured to the nearest 0.1 ml and titratable acidity was measured using a 0.2 sample of juice and titrated against 0.2 *N* NaOH to a pH of 7 using a glass electrode and Autoburet (Autoburet, Radiometer, Copenhagen).

Calculations. Concentration of phenol red was measured in the meal ingested and in the gastric contents recovered. The volume of the original meal left in the stomach was used as the index of gastric emptying. In the study of the dogs of Group 1 this volume was calculated from the formula:

$$\left(V_n' + V_w \times \frac{P_w}{P_n} \right) \frac{P_n}{P_0}$$

in which V_n' and V_w are the volumes of the gastric contents collected at 10 min and the recovery solution, respectively. The concentration of phenol red in the solution instilled into the stomach is P_0, in the gastric contents recovered at 10 min is P_n and in the recovery solution is P_w.

Inhibition of acid output was calculated as the difference between the mean acid output for the two 15 min periods just prior to the injection of secretin and the 15 min period immediately following the injection. Acid output was expressed as a percentage of the preinjection acid output.

Statistics. Tests for significances of differences in gastric emptying with the three test periods in the dogs of Group 1 were made by one-way analysis of variance (7). Tests for significance of differences in gastric emptying with dose and type of secretin and for

TABLE I. The Effect of Secretin on the Gastric Emptying of 300 ml Saline Meals in the Gastric Fistula Dog.

Agent infused intravenously during period 2	Dose (U/kg hr)	Vol of the original meal remaining in the stomach at 10 min (ml) (mean ± SE)			Analysis of variance		
		Period 1	Period 2	Period 3	*dF*	*F*	*p*
Saline	0[a]	112 ± 10	117 ± 11	114 ± 7	23	0.07	>.05
Natural Secretin	1[a]	122 ± 10	153 ± 19	107 ± 10	23	3.01	>.05
	4[b]	121 ± 11	196 ± 13	90 ± 8	32	21.7	<.005
	8[c]	110 ± 31	254 ± 7	77 ± 2	5	29.7	<.005
Synthetic Secretin	1[a]	119 ± 11	116 ± 13	106 ± 11	23	0.32	>.05
	4[b]	138 ± 10	156 ± 11	109 ± 7	32	6.68	<.005
	8[c]	137 ± 7	212 ± 1	93 ± 33	5	10.5	<.005

[a] Eight experiments in 4 dogs.
[b] Eleven experiments in 4 dogs.
[c] Two experiments in 2 dogs.

percentage inhibition of acid output with dose and type of secretin were made by two-way analysis of variance (7). A *t* test was used to test differences in slow wave frequencies, number and force of antral contractions, and mean motility index with saline and secretin infusions (7).

Results. Gastric emptying and contractile activity with secretin (Group 1). The volume of the original meal remaining in the stomach did not change significantly ($p > .05$) with the control intravenous infusion of saline or in response to 1 U/kg hr of either synthetic or natural secretin (Table I). In response to greater doses of natural or synthetic secretin (4 and 8 U/kg hr) the volume of the original meal remaining in the stomach increased significantly ($p < .005$) (Table I). By the third period, emptying was about the same as that found during the control period (Table I). The delay in gastric emptying in response to synthetic and natural secretin increased linearly with increasing dose ($p < .001$, $F(2, 22) = 12.95$) (Fig. 1). Natural secretin was more effective than synthetic secretin ($p < .003$, $F(1, 22) = 11.39$) (Fig. 1 and Table I).

Unsatisfactory recordings were obtained in one dog. In the three dogs in which emptying, slow wave and motor activity were measured simultaneously, only 1 dose of natural secretin (4 U/kg hr) was tested. This dose delayed significantly the emptying of the saline meals (Table II). Accompanying the delay in gastric emptying was a decrease in the frequency and the force of antral contractions (Fig. 2 and Table II). Contractile activity returned to control values 20 min after secretin was stopped (Table II). Secretin had no effect on the frequency of the antral or of the duodenal slow waves (Table II). No differences were found for the mean frequency of antral slow waves whether the stomach was empty or a test meal present (Table III).

Effect of both secretins on pentagastrin stimulated acid secretion (Group 2). The percentage inhibition of pentagastrin stimulated

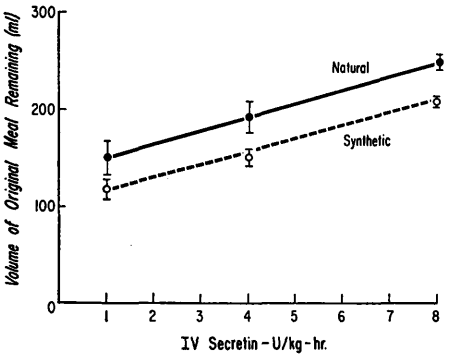

FIG. 1. Effect of secretin on gastric emptying of 300 ml saline meal. The vertical bars represent the SE. Each point is the mean of 8 experiments in 4 dogs at 1 U/kg hr, 11 experiments in 4 dogs at 4 U/kg hr, and 2 experiments in 2 dogs at 8 U/kg hr.

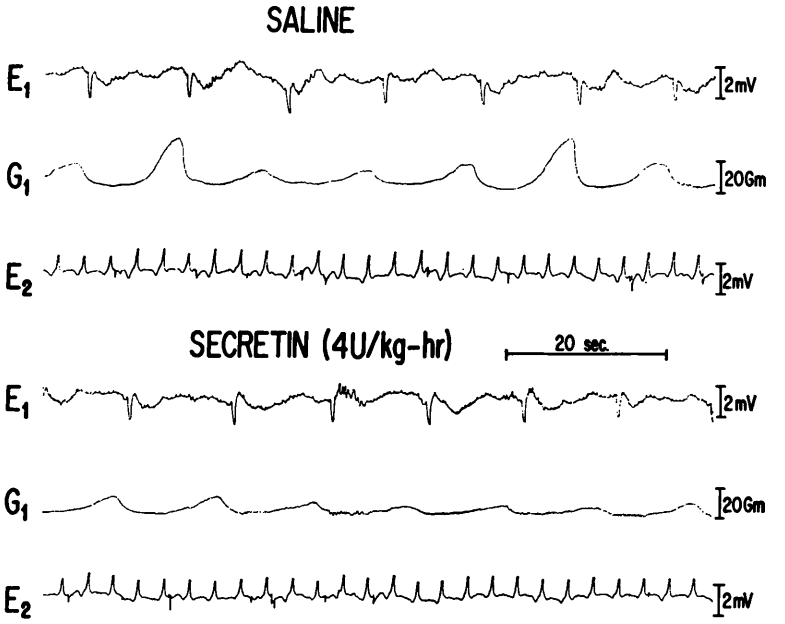

FIG. 2. Contractile pattern of the gastroduodenal area in response to a saline meal with an intravenous infusion of saline or natural secretin (4 U/kg hr). Note the decreased amplitude and frequency of antral contractions in response to secretin. Records were obtained 5 min after instillation. (E_1) electrode placed 6 cm proximal to the gastroduodenal junction; (G_1) strain gauge 4 cm proximal to the junction; (E_2) electrode 4 cm distal to junction.

acid output by secretin increased with increasing dose of secretin (Table IV). There was no significant difference ($p > .05$) between the percentage inhibition of acid output by natural and that by synthetic secretin (Table IV). Acid outputs in response to pentagastrin were similar before each dose of natural or synthetic secretin was tested (Table IV).

Discussion. In previous studies the effects of secretin on gastric motor activity have been concerned only with gastric emptying in man (2, 8), slow wave activity in dog (1), motor activity in isolated pouches in dogs (9, 10) or *in vitro* studies of muscle strips (11). To date, there have been no studies in which gas-

TABLE II. Effect of Natural Secretin (4 U/kg hr) on Emptying and Gastroduodenal Activity.

Measurement	Period (10 min) Saline (1)	Secretin (2)	Saline (3)
Vol of original meal remaining (ml)	113 ± 21[a]	171 ± 19[b]	97 ± 11
waves (cycles/min)			
Frequency of antral slow	4.7 ± 0.1	4.8 ± 0.2	4.8 ± 0.2
Frequency of antral contractions (contractions/min)	3.5 ± 0.4	2.0 ± 0.7[b]	3.4 ± 0.6
Motility index of antrum	379 ± 84	159 ± 87[b]	474 ± 102[b]
Mean motility index of antrum	12.3 ± 3.0	7.4 ± 1.3[b]	16.3 ± 3.6[b]
Frequency of duodenal slow waves (cycles/min)	18.1 ± 0.3	18.1 ± 0.7	18.2 ± 0.7

[a] Each value in the mean ± SE of 8 experiments in 3 dogs.

[b] Indicates $p < .05$ when compared to period 1.

TABLE III. Mean Frequency of Antral Slow Waves Under Various Conditions (cycles/min).

Infusion	Test meal in stomach	Frequency
Saline	Absent	4.8
	Saline	4.7
Secretin	Absent	4.9
	Saline	4.8

tric emptying, slow wave and motor activity have been measured simultaneously in response to secretin.

Secretin delayed gastric emptying but at doses considered greater than those thought to be physiological (12). Thus, doses greater than 1 U/kg hr delayed emptying and this response was dose related (Fig. 1 and Table I). Natural secretin caused greater delay in emptying than synthetic secretin but both were equipotent for inhibition of gastric acid secretion (Tables II and IV). Furthermore, 50% inhibition of acid secretion was found in response to a dose of 0.5 U/kg.

The findings suggest that the sensitivity of the stomach to secretin differs for secretion and emptying. Why the two secretins differ in potency for gastric emptying is unclear since Vagne *et al.* (13) found no difference for pancreatic and gastric secretion and gastric motility. It is possible that the effects represent different properties of the two secretins or the presence of another inhibitory factor for gastric emptying only able to be demonstrated for natural secretin at large doses.

An interesting finding was that coincident with a delay in gastric emptying was a decrease in the force and frequency of antral contractions without changes in duodenal and antral slow wave activity (Fig. 2, Tables II and III). These findings for the slow wave are similar to those reported by Kelly, Woodward and Code (1). Those workers found that the percentage of action potentials accompanying the antral slow wave decreased in response to secretin. The present studies are the first in which all parameters (emptying, slow wave and motor activity) were measured simultaneously. The delay in gastric emptying associated with decreased force and frequency of antral contraction is not unexpected on the basis of the classical concept that the antrum regulates gastric emptying. In a previous study, however, pentagastrin was found like secretin to delay gastric emptying, but this delay was associated with increased force and frequency of antral contractions (3). These different results with secretin and pentagastrin raise questions concerning the role of the antrum in regulating the emptying of liquid meals. From the present study and the previous one (3) two possibilities exist. Firstly, the antrum does regulate gastric emptying. This would explain the secretin studies but not the findings with pentagastrin. Second, the antrum does not regulate gastric emptying of liquid meals. Support for this hypothesis comes from the pentagastrin studies (3), from those of Weisbrodt and co-workers (14) and Dozois, Kelly and Code (15). Weisbrodt and co-workers suggested that it is the coordinated movements of the antrum and duodenum that determine emptying (14). Dozois, Kelly and Code (15) found that resection of the terminal antrum had no effect on gastric emptying of liquid meals but accelerated gastric emptying of solids. Whatever is the true state of affairs, the role of the antrum in regulating gastric emptying of liquid meals is open to question but obviously further data are needed.

Summary. Studies were made in four dogs with gastric fistulas to compare the effects on gastric emptying of natural and synthetic secretin. In some experiments gastric electrical and motor activity using electrodes and strain gauges was studied simultaneously with

TABLE IV. Effect of Secretin on Acid Output in Response to Pentagastrin (4 μg/kg hr).

Dose of secretin (U/kg)	Inhibition (%) of acid output (mean ± SE)[a]		100% Inhibition (mEq/15 min; mean)[a]	
	Synthetic	Natural	Synthetic	Natural
0.5	54.2 ± 5.0	62.6 ± 2.4	5.86	5.38
1.0	67.0 ± 6.5	69.9 ± 5.0	6.66	6.25
2.0	78.0 ± 0.4	72.1 ± 1.0	6.23	5.75

[a] Each value mean of 3 experiments in 3 dogs for 0.5 and 2.0 U/kg and 6 experiments in 3 dogs for 1.0 U/kg.

emptying. In three other dogs with gastric fistulas the acid inhibitory effects of the two secretins were tested against a continuous intravenous infusion of 4 μg/kg hr of pentagastrin.

Natural and synthetic secretin in doses greater than 1 U/kg hr (4 and 8 U/kg hr) delayed significantly the gastric emptying of 0.15 *M* saline meals and natural secretin was more potent than synthetic secretin. Associated with the delay in gastric emptying was a decrease in the force and frequency of antral contractions. Antral and duodenal slow waves were unchanged. Natural and synthetic secretin were equipotent as inhibitors of pentagastrin-stimulated acid secretion and the doses were less than those required for delay of gastric emptying.

These studies suggest that (a) inhibition of gastric emptying by secretin requires much larger doses of secretin than those for inhibition of gastric acid secretion, (b) natural secretin was more potent that synthetic secretin for gastric emptying and that (c) delay in gastric emptying was associated with decreased force and frequency of antral contractions.

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1. Kelly, K. A., Woodward, E. R., and Code, C. F., Proc. Soc. Exp. Biol. Med. **130**, 1060 (1969).

2. Chey, W. Y., Hitanant, S., Hendricks, J., and Lorber, S. H., Gastroenterology **58**, 820 (1970).

3. Cooke, A. R., Chvasta, T. E., and Weisbrodt, N. W., Amer. J. Physiol. **223**, 934 (1972).

4. Thomas, J. E., Proc. Soc. Exp. Biol. Med. **46**, 260 (1941).

5. Carlson, G. M., doctoral dissertation, Univ. of Michigan, 1969.

6. McCoy, E. J., and Bass, P., Amer. J. Physiol. **205**, 439 (1963).

7. Snedecor, G. W., and Cochran, W. G., "Statistical Methods." Iowa State Univ. Press, Ames (1967).

8. Vagne, M., and Andre, C., Gastroenterology **60**, 421 (1971).

9. Sugawara, K., Isaza, J., Curt, J., and Woodward, E. R., Amer. J. Physiol. **217**, 1633 (1969).

10. Chey, W. Y., Kosay, S., Hendricks, J., Braverman, S., and Lorber, S. H., Amer. J. Physiol. **217**, 848 (1969).

11. Cameron, A. J., Phillips, S. F., and Summerskill, W. H. J., Gastroenterology **59**, 539 (1970).

12. Hubel, K. A., Gastroenterology **62**, 318 (1972).

13. Vagne, M., Stening, G. F., Brooks, F. P., and Grossman, M. I., Gastroenterology **55**, 260 (1968).

14. Weisbrodt, N. W., Wiley, J. N., Overholt, B. F., and Bass, P., Gut **10**, 543 (1969).

15. Dozois, R. R., Kelly, K. A., and Code, C. F., Gastroenterology **61**, 675 (1971).

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