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The role of secretin in the inhibition of gastric secretion by intraduodenal acid

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SUMMARY The effect of intraduodenal acid on pentagastrin-stimulated gastric secretion has been investigated in 12 normal subjects and 23 patients with chronic duodenal ulceration. Plasma secretin levels were monitored during each test using a highly sensitive radioimmunoassay.

Significant inhibition of gastric secretion occurred in the normal subjects and duodenal ulcer patients. A significant rise in plasma secretin was observed in both groups after intraduodenal acid though there was a complete lack of correlation between the magnitude of the secretin response and the degree of gastric inhibition. Ten subjects received intraduodenal acid and a subsequent intravenous infusion of exogenous secretin (0·125-0·25 units/kg over six minutes). Gastric inhibition occurred after the acid instillation but not after secretin infusion despite plasma secretin levels greatly in excess of those produced by intraduodenal acid.

These results suggest that release of secretin by itself cannot explain the gastric inhibitory response to intraduodenal acid in man.

The presence of acid in the duodenum is known to inhibit gastric secretion both in animals (Pincus, Friedman, Thomas, and Rehfuss, 1944; Sircus, 1958) and in man (Shay, Gershon-Cohen, and Fels, 1942; Johnston and Duthie, 1964). The mechanism of this response is, however, uncertain. The main possibilities (which may of course interact) appear to be either a vagal reflex or a humoral response particularly involving secretin. The evidence for each of these views is fully discussed elsewhere (Ward, 1974). The role of the vagus has been examined in detail and it appears likely that gastric inhibition is dependent on a vagal reflex in man (Ward, 1974). Strong claims, however, have been made that in dogs secretin is the mediator of gastric inhibition by intraduodenal acid (Johnson and Grossman, 1968) and the present study was therefore undertaken to examine the response with particular emphasis on the role of secretin.

Materials and Methods

The response to intraduodenal acid was investigated in 35 patients, 10 of whom also received an intravenous secretin infusion. There were 12 normal subjects (10m, 2f) and 23 patients (21m, 2f) with chronic duodenal ulceration. The average age of the normal subjects was 38 years (range 21-63) and their average weight 71 kg (range 55-83 kg). These subjects were awaiting minor inpatient surgery and all were free of gastrointestinal symptoms. The duodenal ulcer patients were awaiting gastric surgery and in all cases the pathology was confirmed subsequently at laparotomy. Their average age was 42 years (range 27-67) and their average weight 68 kg (range 52-82 kg).

A duodenal inhibitory test (Ward, 1973) was carried out on each of the normal subjects and duodenal ulcer patients. The gastric stimulus was an intravenous infusion of pentagastrin at a dose rate of 6 μg/kg/hr. Gastric samples were collected at 10-minute intervals throughout the test.

Once a secretory plateau had been reached 40 ml of 0·1N hydrochloric acid at 37°C and labelled with 2% polyethylene glycol was infused into the distal duodenum over a five-minute period. Gastric collection was continued for at least 50 minutes after commencing duodenal acidification. Blood samples were withdrawn from an antecubital vein at intervals throughout the test for secretin assay. The blood was taken into heparin-trasylol, rapidly centrifuged, and deep frozen. Samples were taken at 10-minute intervals before acidification then at minute intervals for 10 minutes after the start of the duodenal acid infusion. Further blood samples were taken at 12, 15, 20, and 40 minutes. The secretin

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levels were measured by a radioimmunoassay using an ^{125}I histidine tracer and antibodies raised to synthetic secretin. A charcoal separation method was used and changes in individual samples of 9 pg/ml plasma were detected with 95% confidence. Methodology is discussed more fully elsewhere (Bloom, 1974).

In four normal subjects and six duodenal ulcer patients an infusion of secretin (Karolinska Institute) was given 50 minutes after the start of the intraduodenal acid when the gastric secretory rate had returned to a plateau level. The effect of this secretin infusion on gastric output was observed for a further 50 minutes. The four normal subjects and three of the duodenal patients received 0·125 units/kg secretin over six minutes. The remaining three duodenal ulcer patients were given 0·25 units/kg again over six minutes. In a further seven duodenal ulcer patients an infusion of secretin was administered without a preceding duodenal acid infusion. Three of these patients received 0·5 units/kg over six minutes, two patients received 1·0 units/kg over nine minutes, and the remaining two patients 2·0 units/kg over nine minutes. Whenever exogenous secretin was administered, the dose was made up in 20 ml (50% plasma/saline). The plasma was added to stabilize the secretin and prevent surface adsorption. The solution was injected immediately after preparation. Blood samples were withdrawn for secretin assay at similar intervals to those taken during duodenal acid infusion.

PYLORIC LOSSES

Phenol red (15 g/l) was instilled into the stomach via a proximal side hole in the Salem sump tube to allow estimation of pyloric losses (Hobsley and Silen, 1969). Measurements were undertaken in six normal subjects and six duodenal ulcer patients.

DUODENOGASTRIC REFLUX

Spontaneous reflux was measured by means of an infusion of 0·9% saline labelled with 2% polyethylene glycol (PEG) given at a rate of 21·5 ml/hr into the distal duodenum. This infusion was commenced at the beginning of each test and continued until 10 minutes before duodenal acidification. Reflux during this period was then estimated on the basis of PEG recovery in gastric samples.

Reflux after duodenal acidification was estimated in a similar fashion by the PEG 'label' on the instilled acid.

In those patients who were given a secretin infusion following intraduodenal acid the initial saline infusion (with 2% PEG) was recommenced 10 minutes before the secretin to allow reflux to be monitored during this additional part of the study.

Although PEG recovery in gastric samples was used as the main means of detecting reflux an additional check was provided by studying the changes in concentration and volume of the gastric aspirate. In all cases where reflux occurred on the basis of PEG recovery there was an increase in volume with a reduction in acid and chloride concentration of the gastric juice and an attendant rise in sodium concentration.

CONTROL STUDIES

1 Forty ml 0·9% saline was instilled into the distal duodenum during a pentagastrin plateau in four normal subjects and four duodenal ulcer patients. There was no effect on gastric acid output or on plasma secretin levels.

2 A continuous pentagastrin infusion (6μg/kg/hr) was administered on its own to five normal subjects and four duodenal ulcer patients for a period of three hours. The purpose of this infusion was to detect any spontaneous decrease in gastric acid output with time. None was noted.

3 An intravenous infusion of 20 ml 0·9% saline/plasma was given over a six-minute period during pentagastrin stimulation in six normal subjects and six duodenal ulcer patients. There was no effect on gastric acid output or on plasma secretin levels in any of these patients.

MEASUREMENTS ON THE GASTRIC ASPIRATE

1 Volume, pH, and hydrogen ion concentration by titration to pH 7 with 0·1N NaOH (Radiometer equipment).

2 Sodium, potassium, and chloride concentration (AutoAnalyzer)

3 Polyethylene glycol concentration in all samples by a turbidimetric method (Malawer and Powell, 1967).

4 Phenol red concentration by a colorimetric method.

Results

EFFECT OF INTRADUODENAL ACID ON GASTRIC ACID OUTPUT AND SECRETIN RELEASE

Normal subjects (table I)

Plasma secretin levels were measured during gastric testing in 12 normal subjects. In three cases a satisfactory gastric collection was not obtained due to duodenogastric reflux (1), hypochlorhydria (1), and inability to achieve a secretory plateau before duodenal acidification (1).

Inhibition of gastric secretion was assessed by comparing the mean of the three 10-minute collections which constitute the pentagastrin plateau with the mean of the three lowest consecutive

No.	*Plateau Acid Output (m-equiv/10 min)*	*Acid Output after Intraduodenal Acid (m-equiv/10 min)*	*Inhibition (m-equiv/10 min)*	*Prestimulation Plasma Secretin (pg/ml)*	*Peak Plasma Secretin (pg/ml)*
1	3·80	3·99	+0·19	23	51
2	5·22	2·50	2·72	19	53
3	8·66	6·66	2·00	25	70
4	5·38	1·97	3·41	21	46
5	3·25	2·76	0·49	18	80
6	6·57	2·35	4·22	17	61
7	3·30	0·40	2·90	17	59
8	4·32	2·80	1·52	17	59
9	2·50	2·55	+0·05	17	48
10	U[1]	—	—	15	39
11	U[1]	—	—	14	52
12	U[1]	—	—	26	82
Mean	4·77	2·88	1·91	19·1	58·3
SE	0·64	0·55	0·48	1·0	3·8

Table I *The effect of intraduodenal acid on gastric acid output and secretin release in normal subjects*

[1]U = Unsatisfactory gastric collection

collections after duodenal acidification. The mean plateau acid output in nine normal subjects was 4·77 ± 0·64 m-equiv/10 min and this was reduced to 2·88 ± 0·55 m-equiv/10 min following intraduodenal acid. Mean inhibition was 1·91 ± 0·48 m-equiv/10 min which is significant ($P < 0·01$). Gastric inhibition was due to a reduction in volume and acid concentration in most instances.

The plasma secretin level before duodenal acid infusion has been represented by the mean of the three values taken at 10 < minute intervals during the pentagastrin plateau. This level has been termed the 'prestimulation plasma secretin'. After duodenal acidification a peak plasma secretin level was recorded in each subject. The mean prestimulation secretin level in the 12 normal subjects was 19·1 ± 1·0 pg/ml and this increased to a mean peak value of 58·3 ± 3·8 pg/ml following intraduodenal acid, a highly significant response ($P < 0·001$). This peak occurred at a mean time of six minutes from the start of the acid infusion (fig 4).

There was no correlation between the magnitude

No.	*Plateau Acid Output (m-equiv/10 min)*	*Acid Output after Intraduodenal Acid (m-equiv/10 min)*	*Inhibition (m-equiv/10 min)*	*Prestimulation Plasma Secretin (pg/ml)*	*Peak Plasma Secretin (pg/ml)*
1	10·58	6·59	3·99	6	16
2	9·93	6·65	3·28	2	33
3	5·94	5·10	0·84	12	59
4	6·62	4·62	2·00	17	28
5	3·23	3·54	+0·31	17	39
6	6·13	3·85	2·28	16	82
7	8·10	5·93	2·17	15	17
8	4·03	3·85	0·18	4	36
9	6·61	5·95	0·66	12	28
10	5·87	5·51	0·36	11	82
11	10·68	10·29	0·39	15	34
12	5·82	5·85	+0·03	11	30
13	8·50	6·01	2·49	8	40
14	9·56	9·70	+0·14	18	44
15	5·37	4·66	0·71	14	49
16	5·75	2·50	3·03	18	57
17	7·91	4·75	3·16	19	25
18	11·15	3·81	7·34	18	48
19	9·04	5·99	3·05	16	78
20	U[1]	—	—	15	35
21	U[1]	—	—	21	42
22	U[1]	—	—	10	61
23	U[1]	—	—	9	25
Mean	7·41	5·53	1·89	13·2	42·9
SE	0·52	0·43	0·41	1·0	4·0

Table II *The effect of intraduodenal acid on gastric acid output and secretin release in duodenal ulcer patients*

[1]U = Unsatisfactory gastric collection

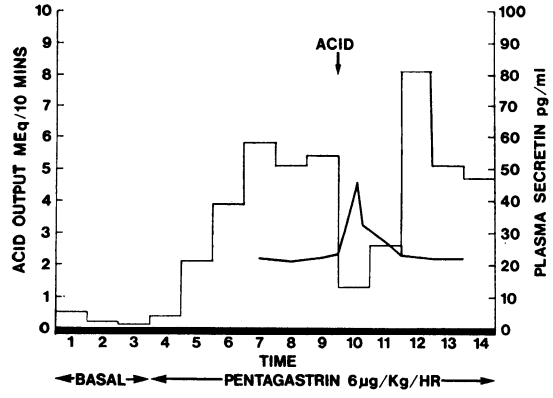

Fig 1a

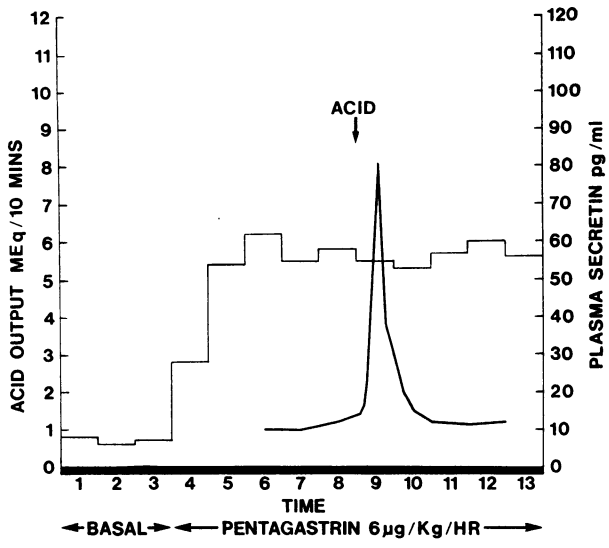

Fig 1b

Fig 1 *The effect of intraduodenal acid on gastric acid output and secretin release.* (a) *Normal subject.* (b) *Duodenal ulcer patient.*

of the secretin release and the extent of gastric inhibition among these subjects nor between plasma secretin levels before duodenal acid infusion and plateau acid output.

The response to intraduodenal acid in a normal subject is shown in figure 1a. There is clear-cut gastric inhibition after intraduodenal acid but relatively little rise in plasma secretin in this patient.

Duodenal ulcer patients (table II)

Plasma secretin levels were measured in 23 duodenal ulcer patients. In four patients the secretory data were unsatisfactory due either to duodenogastric reflux (3) or inability to achieve a plateau before duodenal acidification (1).

The mean plateau acid output in 19 patients was 7·41 ± 0·52 m-equiv/10 min and this was reduced to 5·53 ± 0·43 m-equiv/10 min after duodenal acid infusion. The mean inhibition was 1·89 ± 0·41 m-equiv/10 min which is highly significant ($P < 0·001$). As in the normal subjects, inhibition was usually due to a combined volume and acid concentration reduction.

The mean prestimulation plasma secretin level in the 23 duodenal ulcer patients was 13·2 ± 1·0 pg/ml. After intraduodenal acid a mean peak level of 42·9 ± 4·0 pg/ml was reached at a mean time of six minutes. This increase in plasma secretin is highly significant ($P < 0·001$). There was again no correlation between the magnitude of secretin release and the degree of gastric inhibition nor between prestimulation secretin values and plateau acid output.

The response to intraduodenal acid in a duodenal ulcer patient is shown in figure 1b. Gastric secretion in this patient remained unchanged after intraduodenal acid despite an appreciable rise in plasma secretin.

NORMAL SUBJECTS V. DUODENAL ULCER PATIENTS

The gastric inhibitory response to intraduodenal acid was almost identical in the two groups though the mean plateau acid output in the duodenal ulcer patients was significantly higher than that of the control subjects ($P < 0·01$).

The mean prestimulation plasma secretin level in the duodenal ulcer patients was significantly lower than in the normal subjects ($P < 0·01$). A similar difference was observed in the mean peak secretin levels ($P < 0·02$). This aspect is more fully discussed elsewhere (Bloom and Ward, to be published).

INTRADUODENAL ACID V. EXOGENOUS SECRETIN

Normal subjects (table III)

Four normal subjects were given intraduodenal acid followed 50 minutes later by an intravenous infusion of secretin 0·125 units/kg over six minutes. After intraduodenal acid the mean acid output decreased from 4·17 ± 0·87 m-equiv/10 min to 2·02 ± 0·54 m-equiv/10 minutes. Mean inhibition was 2·25 ± 0·89 m-equiv/10 min which does not quite reach significance at the $P < 0·05$ level due to the small numbers in this group. After the

No.	*Stimulus*	*Plateau Acid Output (m-equiv/10 min)*	*Acid Output after Intraduodenal Acid or Secretin (m-equiv/10 min)*	*Inhibition (m-equiv/10 min)*	*Prestimulation Plasma Secretin (pg/ml)*	*Peak Plasma Secretin (pg/ml)*
1	Intraduodenal acid	3·30	0·04	2·90	17	59
	Secretin 0·125 u/kg	3·10	3·23	+0·13	18	284
2	Intraduodenal acid	4·32	2·80	1·52	17	59
	Secretin 0·125 u/kg	4·53	3·96	0·57	17	176
3	Intraduodenal acid	6·57	2·35	4·22	17	61
	Secretin 0·125 u/kg	6·16	4·04	2·12	18	289
4	Intraduodenal acid	2·50	2·55	+0·05	17	48
	Secretin 0·125 u/kg	2·71	2·60	0·11	10	242

Table III *Intraduodenal acid v. exogenous secretin in four normal subjects*

secretin infusion mean acid output decreased from 4·12 ± 0·78 m-equiv/10 min to 3·45 ± 0·33 m-equiv/10 minutes. Mean inhibition was 0·67 ± 0·46 m-equiv/10 min, which is not a significant response.

The mean peak plasma secretin level after intraduodenal acid was 56·7 ± 2·9 pg/ml whereas after the secretin infusion the mean peak plasma level was 247·7 ± 26·1 pg/ml which is a significantly higher level ($P < 0·01$).

Figure 2 illustrates a change in gastric acid output and in plasma secretin levels recorded in a normal subject receiving intraduodenal acid followed by an infusion of 0·125 units/kg secretin.

Duodenal ulcer patients (table IV)

Six duodenal ulcer patients were given intraduodenal acid followed by a secretin infusion. The dose of secretin used in three was 0·125 units/kg given over six minutes and in the remaining three 0·25 units/kg again over six minutes. After intraduodenal acid the mean acid output (all six patients) fell from 6·70 ±0·78 m-equiv/10 min to 4·70 ± 0·50 m-equiv/10 minutes. Mean inhibition was 1·99 ± 0·55 m-equiv/10 min which is significant ($P < 0·02$). After secretin infusion (all six patients) a reduction in mean acid output from 6·15 ± 0·72 m-equiv/10 min to 5·68 ± 0·61 m-equiv/10 min was observed. This difference is not of statistical significance.

The mean peak plasma secretin level after intraduodenal acid (six patients) was 43·7 ± 9·1 pg/ml whereas after exogenous secretin 0·125 units/kg (three patients) a mean peak plasma level of 321·7 pg/ml was reached. After infusion of 0·25 units/kg secretin (three patients) the mean peak plasma level was 434·3 pg/ml. The plasma secretin levels after secretin infusion are greatly in excess of those seen after intraduodenal acid, though the small number of patients in each individual group precludes statistical analysis.

Figure 3 illustrates the change in gastric acid

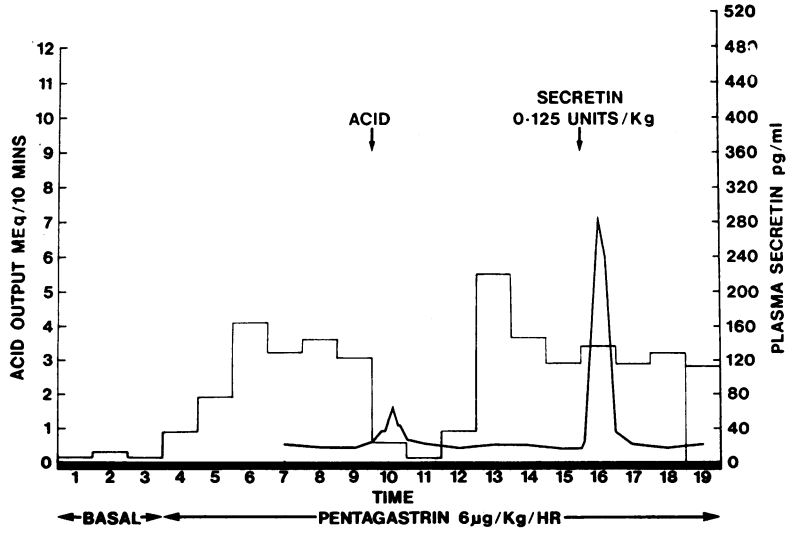

Fig 2 *The effect of intraduodenal acid and exogenous secretin infusion on gastric acid output and plasma secretin levels in a normal subject.*

No.	Stimulus	Plateau Acid Output (m-equiv/10 min)	Acid Output after Intraduodenal Acid or Secretin (m-equiv/10 min)	Inhibition (m-equiv/10 min)	Prestimulation Plasma Secretin (pg/ml)	Peak Plasma Secretin (pg/ml)
1	Intraduodenal acid	5·75	2·72	3·03	18	57
	Secretin 0·125 u/kg	5·21	5·24	+0·03	19	394
2	Intraduodenal acid	7·91	4·75	3·16	19	25
	Secretin 0·125 u/kg	7·53	7·08	0·45	20	311
3	Intraduodenal acid	9·04	5·99	3·05	16	78
	Secretin 0·125 u/kg	8·06	7·50	0·56	17	260
4	Intraduodenal acid	8·10	5·93	2·17	5	17
	Secretin 0·25 u/kg	7·63	6·23	1·40	5	332
5	Intraduodenal acid	4·03	3·85	0·18	5	36
	Secretin 0·25 u/kg	3·38	3·63	0·20	5	439
6	Intraduodenal acid	5·38	4·98	0·40	14	49
	Secretin 0·25 u/kg	4·67	4·43	0·24	8	532

Table IV *Intraduodenal acid v. exogenous secretin in six duodenal ulcer patients*

output and in plasma secretin levels recorded in a duodenal ulcer patient receiving intraduodenal acid followed by an infusion of 0·125 units/kg secretin.

The change in mean plasma secretin level during testing in the four normal subjects and three duodenal ulcer patients who received 0·125 units/kg secretin infusion is shown in figure 4. This has been compared with the mean plasma secretin level produced by intraduodenal acid in the same subjects. The mean incremental area under the curve calculated for the interval 0-15 minutes from the start of the secretin infusion was 1705 ± 87 pg/ml. After intraduodenal acid the mean 15-minute incremental area was 231 ± 53 pg/ml which is 13·6% of the response produced by the secretin infusion. This difference between endogenous and exogenous secretin release is highly significant ($P < 0·001$).

THE EFFECT OF HIGHER DOSES OF SECRETIN ON GASTRIC ACID OUTPUT

Secretin infusions (0·5-2·0 units/kg) were given to seven duodenal ulcer patients undergoing pentagastrin stimulation. The gastric secretory data were disappointing in that copious duodenogastric reflux occurred in six of the seven patients following secretin infusion, though one patient did show some degree of inhibition, affecting both volume and concentration of the gastric juice. Very high levels of plasma secretin were recorded during these infusions (760-1320 pg/ml).

DUODENOGASTRIC REFLUX

Spontaneous reflux before intraduodenal acid infusion was assessed by means of the PEG-labelled saline infusion. Polyethylene glycol was not re-

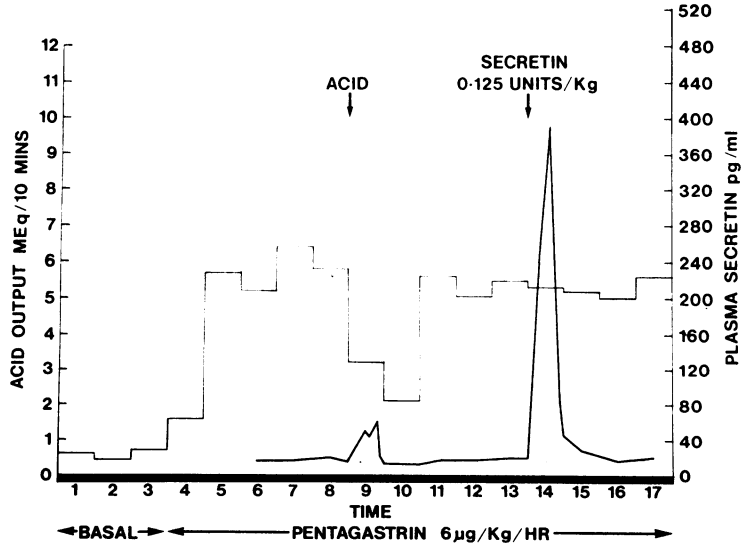

Fig 3 *The effect of intraduodenal acid and exogenous secretin infusion on gastric acid output and plasma secretin levels in a duodenal ulcer patient.*

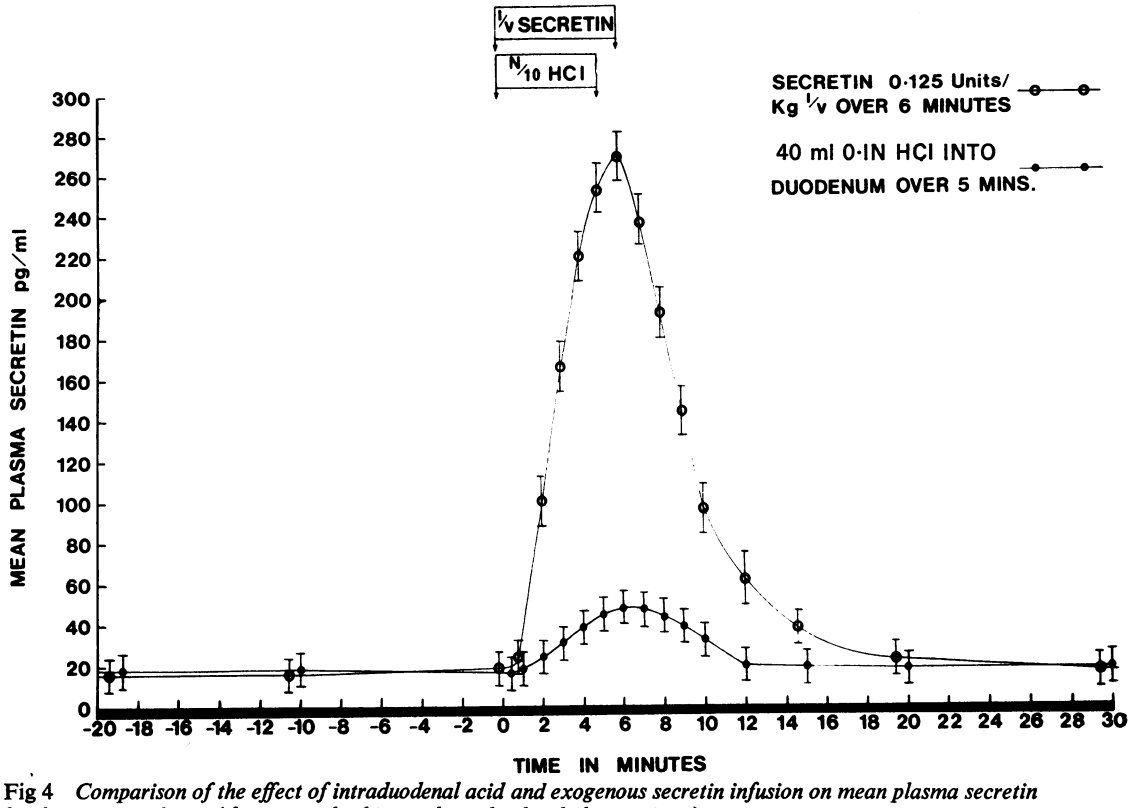

Fig 4 *Comparison of the effect of intraduodenal acid and exogenous secretin infusion on mean plasma secretin levels in seven subjects (four normal subjects, three duodenal ulcer patients).*

covered in any of the gastric samples before acidification suggesting that spontaneous reflux was not a problem in our series.

Reflux following delivery of acid into the duodenum was similarly assessed on the basis of PEG recovery in postacidification gastric samples. Recovery of more than 5% of the total PEG infused was deemed unsatisfactory and the test discarded for the purposes of gastric analysis. Tests in one normal subject and three duodenal ulcer patients were discarded on these grounds. An increase in volume of the gastric sample with a decrease in acid concentration was apparent in each of these cases as confirmation that reflux had occurred.

Reflux after secretin infusion was monitored as in the early part of the test by means of a slow saline infusion labelled with PEG. Reflux occurred in six duodenal ulcer patients following infusion of secretin in the range 0·5-2·0 units/kg.

PYLORIC LOSSES

Pyloric losses during plateau and postacidification inhibitory periods have been calculated for each patient using the method of Hobsley and Silen (1969). Mean pyloric loss during the plateau in six normal subjects was 5·36 ± 1·64 ml/10 min and mean loss during the inhibitory period 5·16 ± 0·76 ml/10 min. These means are not significantly different. (The mean volumes recovered during the plateau and inhibitory periods were 54·2 ml/10 min and 42·1 ml/10 min respectively.) Mean pyloric loss during the plateau period in six duodenal ulcer patients was 5·26 ± 2·40 ml/10 min and during inhibition 5·12 ± 1·06 ml/10 min; again these figures are not significantly different. (The mean volumes recovered during plateau and inhibitory periods were 68·4 ml/10 min and 58·2 ml/10 min in this group.)

These results suggest that inhibition of acid output cannot be attributed to changes in pyloric losses consequent upon duodenal acidification; the observed changes in gastric acid output appear to be a direct response to intraduodenal acid.

Discussion

Previous work on the importance of secretin in gastric inhibition by intraduodenal acid has suffered

from the disadvantage that an accurate method of measuring plasma secretin was not available, reliance being placed instead on circumstantial methods such as pancreatic bicarbonate response. The present results are based on a radioimmunoassay for secretin which has a high sensitivity.

There have been many claims, largely on an experimental basis, that inhibition by intraduodenal acid is mediated by secretin. Preshaw (1969) acidified the duodenum of dogs with Heidenhain pouches at various rates and observed a very close correlation between gastric inhibition and pancreatic stimulation, the latter being taken to reflect endogenous secretin release. He concluded that the two responses were mediated by the same mechanism. Johnson and Grossman (1969) produced inhibition of gastrin-stimulated secretion in Heidenhain pouch dogs using a secretin infusion and compared the response with that produced by intraduodenal acid. They observed an almost identical effect in time, duration, and magnitude and concluded that secretin was the enterogastrone mediating gastric inhibition by intraduodenal acid. Not all studies have agreed with this view and the existence of a secretin-independent inhibitory mechanism in the duodenum has been noted by Way and Grossman (1971) and Konturek, Tasler, and Obtulowicz (1971). In man, Wormsley (1970) has shown that the gastric response to exogenous secretin and to intraduodenal acid differ sufficiently to suggest that secretin may not be the sole mediator of gastric inhibition.

The results of the present study provide direct evidence that secretin is not significantly involved in the inhibitory response to intraduodenal acid in man. Gastric secretion was significantly inhibited after intraduodenal acid in both normal subjects and duodenal ulcer patients. The rise in plasma secretin levels following duodenal instillation, however, was small in both groups compared with the levels produced by exogenous secretin infusion. Moreover in individual patients there was no correlation between the magnitude of the secretin response and the degree of gastric inhibition. Exogenous secretin in doses of 0·125-0·25 units/kg for six minutes was without significant effect on gastric acid output in normal subjects and duodenal ulcer patients despite plasma secretin levels many times in excess of those produced by intraduodenal acid. A study of the data on patients receiving both intraduodenal acid and exogenous secretin reveals that the secretin response to acid was only 13·6% of that observed after exogenous secretin 0·125 units/kg. Such comparisons may in future enable the total amount of secretin in clinical units to be correlated with the amount of acid in milliequivalents placed in the duodenum.

The relative absence of gastric inhibition after exogenous secretin in our patients requires comment. Secretin has been shown to inhibit pentagastrin-stimulated gastric secretion on many occasions in the past though large dose intravenous infusions and low dose gastric stimulation have proved the best background against which to demonstrate this effect (Brooks and Grossman, 1970; Chey, Hitanant, Hendricks, and Lorber, 1970). The method of administration of the secretin is also important since an intravenous infusion produces a greater inhibition than the same dose given as a single intravenous injection (Peterson and Berstad, 1972). An infusion time of six minutes was chosen in our patients in an attempt to produce a secretin release curve comparable in timing with that observed after intraduodenal acid. The doses of secretin infused per minute were in agreement with those of earlier studies (Brooks and Grossman, 1970; Konturek, 1970). It seems likely that more marked gastric inhibition could have been achieved with a longer period of secretin infusion and submaximal gastric stimulation.

If the results of this study are correct an alternative to secretin must be sought to account for gastric inhibition by intraduodenal acid. There is good evidence for the existence of a separate humoral mechanism in the duodenal bulb, at least in experimental animals (Andersson, Nilsson, Sjodin, and Uvnäs, 1973), and an inhibitory factor ('bulbogastrone') has been extracted from the porcine duodenal bulb mucosa (Uvnäs, 1971). This mechanism is unlikely to be involved in our cases, however, as the distal duodenum was selectively acidified, and although hydrogen ions may have diffused back to the duodenal bulb, this is unlikely to have made a significant contribution to the response. A vagal reflex is a possible alternative and this has been suggested in several previous reports (Code and Watkinson, 1955; Konturek and Johnson, 1971). In a recent report (Ward, 1974), using the same experimental technique as in the present series, the response to intraduodenal acid in man was examined before and after truncal, selective, and highly selective vagotomy. Gastric inhibition was found to be abolished by all three procedures suggesting that the mechanism is based on a vagal reflex. The finding of the present study that inhibition by intraduodenal acid is based on factors other than secretin lends support to this view.

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