Comparison of Four Provocative Tests for the Diagnosis of Gastrinoma

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In an attempt to determine the best provocative test for the diagnosis of gastrinoma, ten normal subjects, 13 patients with known gastrinoma, and one patient with presumed gastrinoma were administered four regimens: (1) rapid calcium infusion (2 mg Ca^{++}/kg/min), (2) secretin (2 clinical units (CU)/kg/bolus), (3) long calcium infusion (12 mg Ca^{++}/kg/3 h) and (4) a combination test consisting of a rapid calcium infusion followed immediately by secretin. Blood was drawn for serum gastrin levels before and following infusion of the test agents. The administration of rapid calcium followed by secretin provoked the greatest increases in serum gastrin above basal levels in both normals (29%) and patients (362%). Peak gastrin levels in patients were similar following the long calcium infusion (341%) but were less following the rapid calcium infusion alone (124%) and secretin alone (207%). There were no false-positive or false-negative tests with the calcium plus secretin when the criterion for diagnosis was either a 50% increase or a 200 pg/ml increase above the basal gastrin level. The distinct advantages (short test period, low patient morbidity, and relatively great potency) of the calcium plus secretin test make it an attractive alternative to other previously described provocative tests for the diagnosis of gastrinoma.

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IN 1955, ZOLLINGER AND ELLISON[1] described a clinical syndrome characterized by gastric hyperacidity and hypersecretion, fulminant peptic ulcer disease and pancreatic islet cell neoplasia. It was subsequently shown that the pancreatic islet tumors secreted the hormone gastrin[2] and that excess amounts of this polypeptide accounted, either directly or indirectly, for all of the pathophysiologic manifestations of the Zollinger-Ellison syndrome (ZES).[3] Sensitive radioimmunoassays,[4] which could measure serum gastrin levels in normal subjects,[5,6] were developed and, when used in concert with determinations of gastric secretory volume and basal and maximal output of gastric acid, markedly enhanced the diagnostic accuracy of patients with the ZES.

The diagnosis of ZES became relatively easy when the serum gastrin level was markedly elevated in patients with a characteristic clinical presentation. Difficulties were encountered when the serum gastrin level was borderline or low.[7] It was also realized that an increased gastrin level was not specific for ZES, since patients with atrophic gastritis and achlorhydria often had elevated levels.[8,9] A significant advance in the clinical diagnosis of the ZES was the observation that certain agents (calcium ion and secretin), when administered intravenously, were potent gastrin secretagogues in patients with gastrinoma.[10,11] Most investigators felt that an intravenous injection of secretin constituted a better provocative test for gastrinoma than a calcium infusion, even though the incidence of false-negative tests was 10%.[12] These agents also appeared to cause modest increases in serum gastrin in patients with duodenal ulcer disease but without ZES.[13-15]

In tests employing these agents, calcium was administered in a dose of 10–15 mg/kg/3–5 h[14-16] and secretin was administered in a dose of 1–3 unit/kg (depending on the source) as a bolus injection.[7,10,14,16,17]

Recent studies[18] in patients with medullary thyroid carcinoma (MTC) demonstrated that plasma calcitonin (CT) increased to higher levels more rapidly following

Presented at the Ninety-Fourth Annual Meeting of the Southern Surgical Association, December 6–8, 1982, Palm Beach, Florida.

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Supported by NIH Contract CB-63994 and by Grant RR-30 from the General Clinical Resources Center, Program of the Division of Research Resources, National Institutes of Health. Data were managed and analyzed with the Clinfo® computer system of the Duke University Medical Center Clinical Research Unit.

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Submitted for publication: December 13, 1982.

0003-4932/83/0500/0608 $01.30

TABLE 1. *Patient Characteristics*

Patient No.	Age	Sex	MEN I	Hist. Dx	Elevated G Post Gx	Diagnosis by Current Tests			
						RCI	SE	SECA	LCI
1	38	F	Y	Y	Y	++	++	++	++
2	63	M	Y	Y	Y	++	++	++	++
3	38	M	N	N	Y	++	++	++	++
4	48	M	N	N	Y	+0	+0	++	++
5	60	M	N	N	N.A.	+0	00	+0	+0
6	65	M	N	N	Y	++	++	++	++
7	42	M	N	N	Y*	++	N.D.	N.D.	++
8	68	M	N	Y	Y	++	++	++	++
9	60	F	Y	N	Y*	++	++	++	++
10	64	M	Y	N	Y	++	++	++	++
11	38	F	Y	N	Y	++	++	++	++
12	45	F	Y	N	Y	++	++	++	++
13	50	F	Y	N	Y	++	++	++	++
14	27	F	Y	N	N.A.	N.D.	++	++	N.D.

A positive diagnosis was determined by 2 separate criteria for each test: either an absolute basal to peak increase of 200 pg/ml or a basal to peak increase of 50%. Patients who met both criteria received ++, if only one criterion was met a +0 was given, and if neither criterion was met, a 00 was given. Actual basal and peak values are shown in Table 3. N.A.: not applicable. N.D.: not done.

* Only a partial gastrectomy was performed.

MEN = Multiple endocrine neoplasia; Hist. Dx. = Histologic Diagnosis; G = gastrin; Gx = gastrectomy; RCI = rapid calcium infusion; SE = secretin; SECA = secretin + calcium; LCI = long calcium infusion; Y = Yes; N = No.

a rapid calcium infusion (2 mg/kg/min) than following a 4-hour infusion (15 mg/kg). A combination of calcium (2 mg/kg/min) and pentagastrin (0.5 μg/kg/5 sec), another potent calcitonin secretagogue, stimulated even higher plasma CT levels than either agent alone.[18]

Medullary thyroid carcinoma cells are derived from the neural crest and embryologically are similar to pancreatic islet cells. Therefore, the possibility that a rapid calcium infusion (with or without secretin) might stimulate secretion from gastrinoma cells was considered, since there is uncertainty regarding both the best provocative agent(s) and the specific biochemical criteria required for the diagnosis of the ZES.[12,16,19,20] In the present study, we compared calcium and secretin as gastrin secretagogues. The agents were administered intravenously, either alone or in combination, to normal subjects and to patients with gastrinoma.

Materials and Methods

Patient Population

Fourteen patients with gastrinoma were studied. There were 6 women and 8 men, and their mean age was 51 years (range, 27–68 years). Nine patients had multiple endocrine neoplasia Type I (MEN I). In 3 patients, the gastrinoma was confirmed histologically while in 11 patients, it was not; however, basal serum gastrin levels remained elevated after total gastrectomy, giving strong presumptive evidence of gastrinoma. Two patients (Nos. 5 and 14) are receiving cimetidine. The characteristics of the patients are detailed in Table 1.

Ten normal control subjects (1 woman and 9 men) with a mean age of 31 years (range, 22–50 years) were studied also. The Clinical Investigations Committee of Duke University Medical Center approved protocols for this study in March 1978 and March 1981.

Provocative Tests

Rapid calcium infusion (RCI). Calcium gluconate (2 mg Ca^{++}/kg) was administered intravenously (I.V.) over 1 minute to 13 patients with gastrinoma and to 10 normal control subjects.

Long calcium infusion (LCI). Calcium gluconate (12 mg Ca^{++}/kg) in 300 ml of saline was administered I.V. over 3 hours to 13 patients with gastrinoma and to 7 normal control subjects.

Secretin (SE). Secretin in a dose of 2 clinical units (CU)/kg (not exceeding 150 CU/subject) was administered as an I.V. bolus to 13 patients with gastrinoma and to 5 normal control subjects. Purified secretin from the Gastrointestinal Hormone Laboratory (GIH), Karolinska Institute, Stockholm, Sweden was used (distributed by Pharmacia Piscataway, New Jersey).

Secretin and calcium (SECA). Calcium gluconate (2 mg Ca^{++}/kg) was administered I.V. over 1 minute and was immediately followed by a bolus injection of secretin (2 CU/kg) (not exceeding 150 CU/subject). This combination test was administered to 13 patients with gastrinoma and to 5 normal control subjects.

After the patients and subjects fasted overnight, all tests were performed in a random order, and there were always one or more days between tests. In three tests

TABLE 2. *Peak and Basal Serum Gastrin Levels in Normal Controls During Four Provocative Tests*

	RCI		SE		LCI*		SECA	
Subject	Peak/Basal	(%)	Peak/Basal	(%)	Peak/Basal	(%)	Peak/Basal	(%)
1	49/38	(29)	78/76	(3)	76/84	(−9)	71/64	(11)
2	71/68	(4)	85/79	(8)	99/101	(−2)	55/41	(34)
3	91/79	(15)	93/84	(11)	95/95	(0)	128/103	(24)
4	80/72	(11)	—	—	90/72	(25)	—	—
5	71/66	(8)	104/104	(0)	80/83	(−4)	136/97	(40)
6	114/113	(1)	—	—	63/75	(−16)	—	—
7	97/76	(28)	—	—	—	—	—	—
8	73/49	(49)	—	—	—	—	—	—
9	149/120	(24)	—	—	—	—	—	—
10	130/103	(26)	154/119	(29)	116/108	(7)	136/101	(35)
Mean		(19.5)		(10.2)		(0.1)		(28.8)

Peak and basal serum gastrin levels are expressed as pg/ml. % = percentage increase above basal.

* Peak and percentage increases for LCI are based on an average of the values achieved by each subject at 150 and 180 minutes, the time of peak calcium levels.

(RCI, SE, and SECA), blood samples were collected before (at −15 and −1 minutes) and then at 1, 2, 3, 5, 10, 15, and 30 minutes after the administration of the provocative agent(s). With the LCI, blood samples were collected before (at −15 and −1 minutes) and then at 5, 10, 15, 30, 60, 90, 120, 150, and 180 minutes after the infusion.

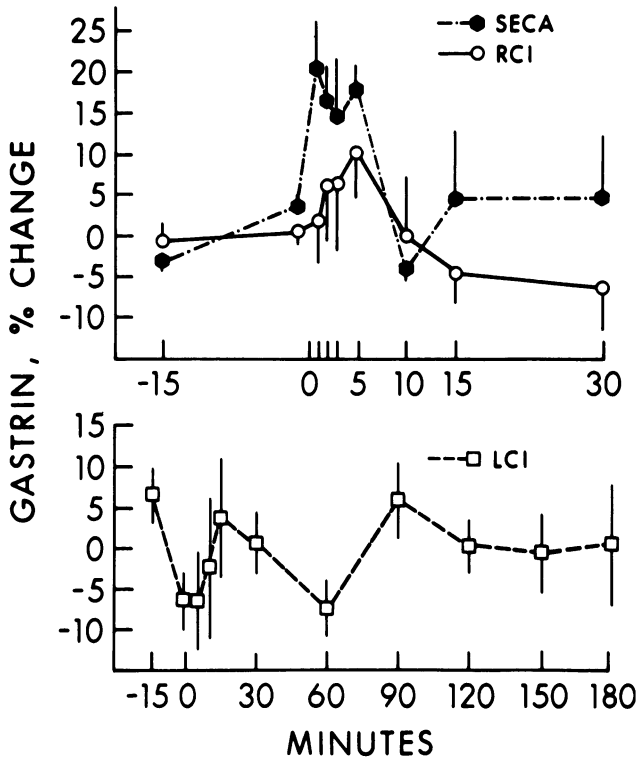

FIG. 1. Average percent increases (mean ± S.E.) of serum gastrin in normal controls. In all cases, the basal values were taken as the mean of the −15 and −1 minute values. Upper panel: RCI—rapid calcium infusion test (2 mg Ca^{++}/kg/min); N = 10. SECA—secretin plus calcium infusion test. A rapid infusion of calcium as above, followed by a bolus of secretin (2 CU/kg); N = 5. Lower panel: LCI—long calcium infusion test (12 mg Ca^{++}/kg/3 h); N = 5.

Laboratory Analysis

Total serum calcium concentration was determined by atomic absorption spectrophotometry (Model 151, Instrumentation Laboratory, Inc., Lexington, Massachusetts). The normal range of serum calcium in our laboratory, determined by evaluating 134 normal control subjects, was 8.5 to 10.2 mg/dl. Serum gastrin was determined by radioimmunoassay (Gastrin Radioimmunoassay Kit, Becton Dickinson, Orangeburg, New York), for which the upper limit of normal was 300 pg/ml. Some samples were measured by a radioimmunoassay method previously described.[4,5,21] The two assays yielded comparable results upon repeat testing of previously assayed, frozen (−70 C) specimens.

Statistical comparison of different tests results was by Wilcoxon signed rank test and by paired Student's t-test.

Results

Normals

The mean basal serum gastrin level before the 27 separate tests in ten normal subjects was 83.3 pg/ml (range, 38 to 122 pg/ml). The maximum gastrin level reached by any control subject during any test was 154 pg/ml. Definite increases in serum gastrin levels could be seen in most normal subjects in response to RCI and SECA, but not to LCI (Table 2). Following RCI, six (Nos. 1, 3, 7, 8, 9, 10) of ten normal subjects had a small but significant ($p < 0.05$) increase (mean, 28%; range, 15–

TABLE 3. *Peak and Basal Serum Gastrin Levels in Patients during Four Provocative Tests*

	RCI		SE		LCI		SECA	
Patient	Peak/Basal	(%)	Peak/Basal	(%)	Peak/Basal	(%)	Peak/Basal	(%)
1	1,675/460	(264)	2,152/453	(375)	4,747/422	(974)	3,730/360	(936)
2	5,752/3,325	(73)	7,944/4,248	(87)	9,531/3,971	(140)	8,340/2,144	(289)
3	4,907/3,086	(59)	4,128/2,472	(67)	10,243/3,231	(217)	7,642/2,884	(165)
4	1,024/711	(44)	754/530	(42)	1,351/538	(151)	1,324/788	(68)
5	1,804/1,240	(45)	248/212	(17)	444/281	(58)	384/226	(70)
6	558/338	(65)	1,106/432	(156)	1,239/410	(202)	1,372/356	(285)
7	2,099/748	(181)	—		3 300/1,174	(181)	—	
8	15,383/6,604	(133)	18,254/3,795	(381)	18,768/5,775	(225)	29,330/5,695	(415)
9	1,799/664	(170)	1,800/800	(125)	2,550/400	(538)	3,400/634	(436)
10	4,356/2,475	(76)	6,095/1,465	(316)	2,488/1,508	(65)	8,369/2,274	(268)
11	6,007/2,847	(111)	7,820/3,460	(126)	14,000/2,603	(438)	7,123/2,233	(219)
12	12,760/5,104	(150)	13,752/3,852	(257)	15,959/2,599	(514)	14,930/3,047	(390)
13	107,936/31,746	(240)	123,810/23,810	(420)	131,911/15,864	(732)	126,959/28,530	(345)
14	—		2,720/640	(325)	—		4,760/520	(418)
Mean		(124)		(207)		(341)		(362)

Serum gastrin values are expressed as pg/ml. % = percent increases above basal.

49%) in serum gastrin levels at 1 to 5 minutes. One (No. 10) of five normal subjects had a clear increase (29%) in serum gastrin at 3 minutes following SE. There was a significant ($p < 0.025$) increase (mean, 33%; range, 24–40%) in the serum gastrin levels of four (Nos. 2, 3, 5, 10) of five patients at 1 to 5 minutes following SECA. During LCI, there were fluctuations in serum gastrin about the basal level, but no consistent pattern of change. The average pattern of response in normal subjects to RCI, SECA, and LCI are shown in Figure 1.

Patients with Gastrinoma

Basal levels of serum gastrin in the 14 patients ranged from 212 to 31,746 pg/ml, with a mean of 3,736 pg/ml (Table 3). Only one patient (No. 5), in three tests, had basal levels less than 300 pg/ml, the upper limit of normal. In contrast to normal controls, there was a clear increase in serum gastrin in response to each of the provocative regimens. The responses of 3 patients to each of the four tests are shown in Figure 2. These patients were selected to demonstrate the range and pattern of response observed when the basal serum gastrin was less than 1000 pg/ml. Patient 1 had a marked response to each of the tests. Patient 4 responded best to SECA and LCI, but poorly to RCI and SE. Patient 6 had a marked response to LCI, SECA and SE but a weak response to RCI. Because of the wide range in basal values, the gastrin levels in the total population of patients are best expressed as percentage increases above basal. The patterns of the average per cent changes in gastrin are shown in Figure 3. RCI, SE and SECA all provoked similar patterns of response: a rapid increase in serum gastrin peaking at 1 to 5 minutes, occasionally as late as 15 minutes following infusion. The levels then fell rapidly during the following 10 minutes, and then more slowly in the subsequent 15 minutes. In contrast, the LCI test provoked a gradual linear increase of serum gastrin which did not peak until the calcium infusion was completed at 150 to 180 minutes.

The magnitude of increase achieved was dependent on the test regimen (Table 3). The SECA test achieved the highest mean percentage increase followed by LCI, SE and RCI. Although the mean serum gastrin response following SECA was not significantly greater than that following LCI, it was significantly greater than the response following SE ($p = 0.009$) or RCI ($p = 0.003$). The gastrin response following LCI was also significantly greater than that following SE ($p = 0.043$) and RCI ($p = 0.008$). The gastrin response following SE was significantly greater ($p = 0.035$) than that following RCI. Therefore, the tests could be placed in the following ranking in terms of peak gastrin levels achieved: SECA = LCI > SE > RCI. In 11 of 12 patients who received all four tests, LCI or SECA provoked the greatest increases in serum gastrin levels. It was also found in individual patients that the sum of ones peak gastrin increases following SE and RCI was not significantly different from ones peak increase following SECA.

Since following stimulation, the highest serum gastrin increase in any normal was 49%, above basal the value of 50% was chosen as that increase above basal representing a positive response. This value has been recommended by other investigators,[15] and is close to the mean maximum per cent increases +2 S.D. value of 52% achieved by our normals in response to SECA stim-

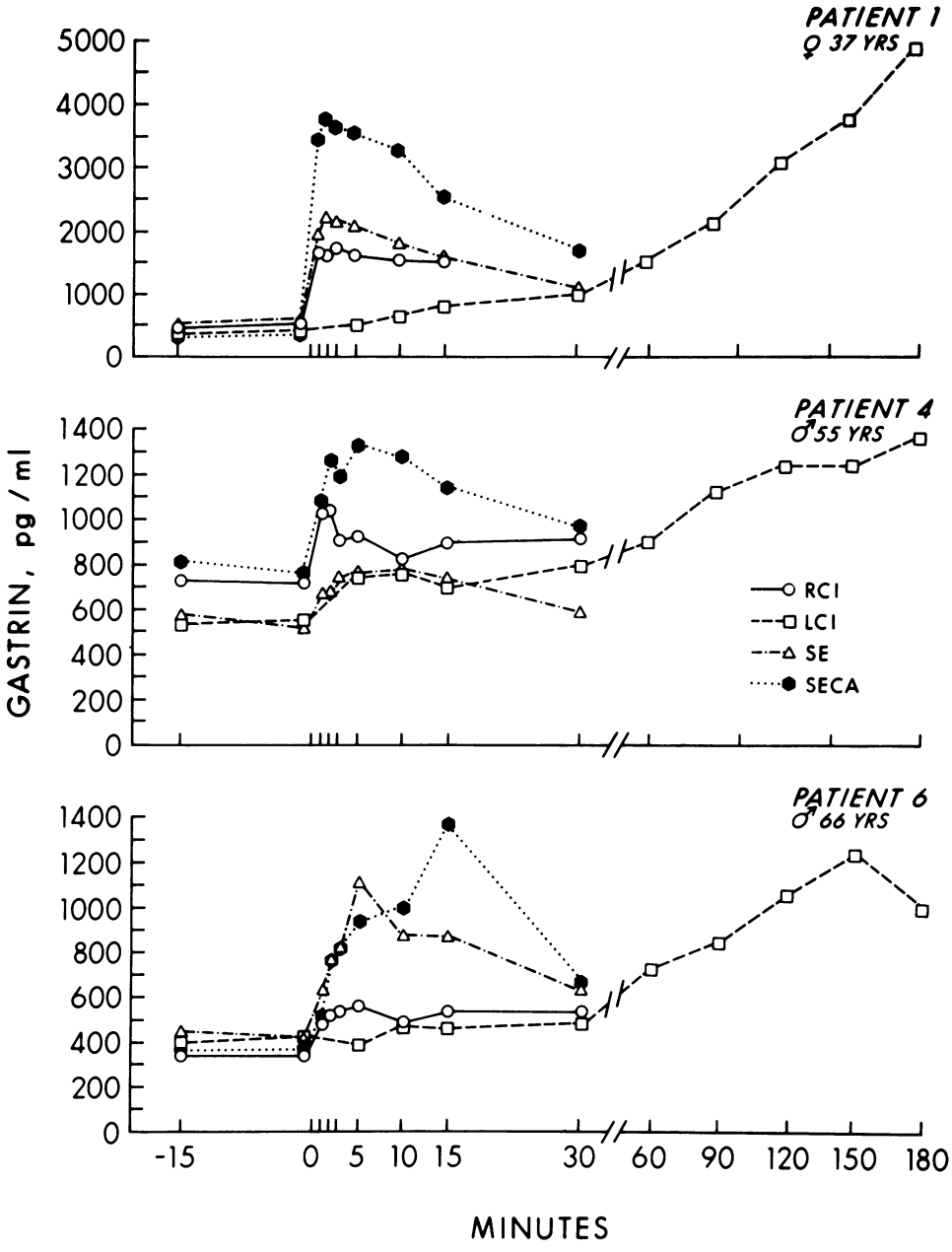

FIG. 2. Gastrin levels in three patients with gastrinoma during four provocative tests. Tests regimens as in Figure 1; SE—secretin infusion (2 CU/kg).

ulation, the most potent test. Utilizing this criterion, there were two patients (Nos. 4 and 5) (Table 3) who failed to develop significant increases in serum gastrin following either SE or RCI. These two patients also responded weakly to LCI and SECA, but had gastrin increases greater than 50% above basal. Using the criterion of a minimal 200 pg/ml increase from basal to peak, as suggested by McGuigan and Wolfe,[12] the SE, LCI, and SECA tests were negative in patient No. 5. Among all patients, the peak gastrin response in one test was linearly correlated with the peak response in each of the other tests. The linear regression equations relating all tests to each other are listed in Table 4 together with the correlation coefficients, and the significance levels.

Calcium Levels in Patients and Controls

The mean basal and peak serum calcium levels in the normal subjects were lower, but not significantly so, than the levels in the patients. Since the pattern of change in the two groups was identical, only a description of the patients will be given (Fig. 4).

During the SE test in patients, there was a slight increase in serum calcium of 0.2 mg/dl, which occurred during the first few minutes and peaked at 5 minutes. This increase was significant ($p < 0.05$) at 3 and 5 minutes by paired t-test. A similar pattern was seen in the normal subjects.

The average changes in serum calcium during RCI and SECA were not significantly different from each other. There was an immediate increase of 1.9 mg/dl to a level of 11.3 mg/dl. There was then a fairly rapid drop of 0.8 mg/dl during the next 2 minutes. The levels continued to drop, but more slowly, so that at 30 minutes, they were an average of 0.7 mg/dl above their basal levels.

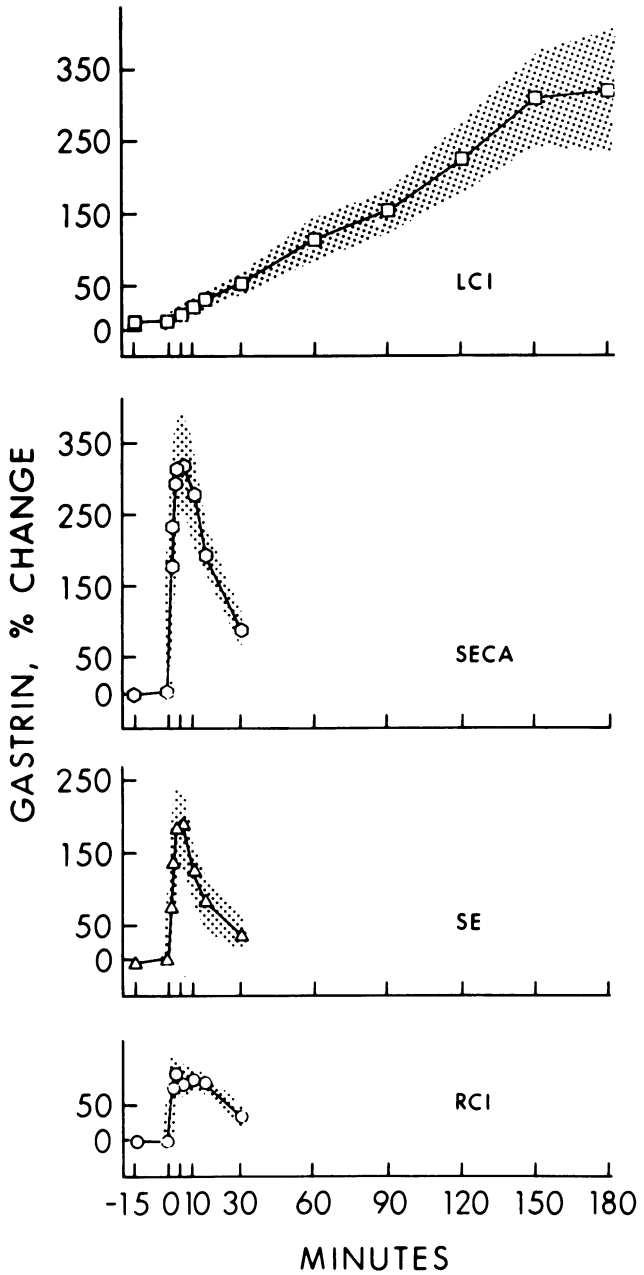

FIG. 3. Average percentage increases in serum gastrin in 13 patients with gastrinoma during four provocative tests. Test regimens as described in Figures 1 and 2.

TABLE 4. *Correlations Between Tests*

Single Regressions	Correlation Coefficient (r)	Significance (p)
SE = 0.37 SECA + 72	0.67	0.012
SE = 0.285 LCI + 96	0.57	0.05
RCI = 0.39 SE + 43	0.75	0.005
RCI = 0.23 LCI + 46	0.87	0.001
SECA = 0.63 LCI + 99	0.80	0.002
SECA = 2.53 RCI + 22	0.83	0.001

All equations represent the least-squares best fit of the peak percentage increase data from 13 patients with gastinoma.

During LCI, there was a gradual and linear increase of 3 mg/dl in serum calcium from 9.2 mg/dl to a peak of 12.2 mg/dl at 180 minutes.

It was found in all patients who received a calcium infusion that the average level of calcium in the serum at any time was linearly correlated with the average level of gastrin at that time LCI ($r = 0.92$; $p = 0.003$), RCI ($r = 0.68$; $p = .02$) and SECA ($r = 0.65$; $p = 0.003$). These relationships are shown in Figure 5 for 2 separate patients.

Subjective Response to Tests

There seemed to be no qualitative difference in response to any test regimen when comparing normal subjects to patients with gastrinoma. Patients and controls had fewest complaints with SE, experiencing slight epigastric pain for only a few seconds after the secretin was administered. More discomfort was described following RCI. Most test subjects felt heat in the back of the throat, lips, tongue, chest, and torso. With SECA, the epigastric pain of SE was superimposed on the heat sensations of RCI. The greatest discomfort to controls and patients was experienced during LCI. The most frequent symptoms were nausea and headache. Fatigue during the latter part of the test was a prominent feature. A diuresis was usually induced, and patients and controls often urinated several times during the test period. After the test was completed, there was usually a generalized fatigue which lasted for several hours. Some individuals went through all four tests with no complaints and only minimal symptoms, whereas others were clearly symptomatic. The LCI had to be terminated early (at 150

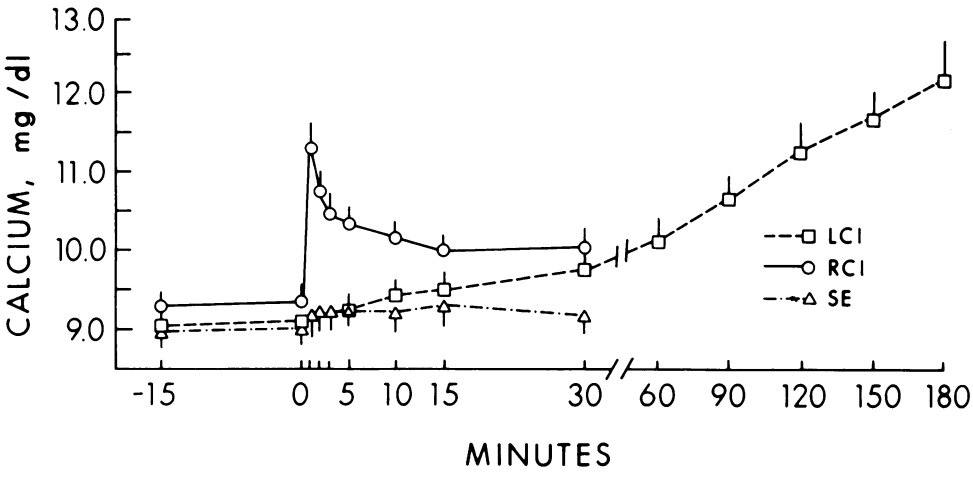

FIG. 4. Calcium levels in 13 patients during 3 provocative tests. Test regimens as described in Figures 1 and 2.

minutes) in three patients because of nausea, sweating and restlessness.

Discussion

The gastrin response to the four provocative tests was generally modest in normal subjects. The highest increase was 49% and the maximal gastrin level reached was 154 pg/ml. As others,[11,16] we did not find any pattern in the gastrin response to LCI in normals.

Following SE, only one of five normal subjects had a clear increase in serum gastrin. Previous reports of changes in serum gastrin following SE in non-ZE patients and normal subjects are contradictory.[13,22-25] Hansky et al.[22] and Korman et al.[23] reported in normals an immediate and gradual drop in gastrin from 60 to 14 pg/ml, with the nadir occurring at 20 to 25 minutes after the secretin injection. Conversely, a maximum increase of 28% at 5 minutes among 34 normal subjects was reported by Lamers et al.[24]

Following RCI, the average gastrin peak of 19% above basal levels was significant and showed that normal G cells were responsive to a pulse infusion of calcium. Other investigators reported no change in serum gastrin following calcium infusion in normals.[10,13] Data from a study of duodenal ulcer patients[25] showed an average increase in serum gastrin of 27% (range, 0–80%) immediately after calcium injection. There was a subsequent decrease of 18% at 30 to 60 minutes.

In the present study, when calcium and secretin were combined (SECA), we found a significant elevation above basal levels in serum gastrin in four out of five normal subjects. Thus, secretin appears to provoke gastrin release from G cells in normal individuals if calcium is injected concomitantly.

The basal and peak serum calcium levels were slightly higher in the patients than in the normal subjects, but not significantly so. We recorded an increase in calcium (0.2 mg/dl at 3 minutes) after SE which, although small, was significant ($p < 0.05$). Similar changes in serum calcium following secretin have been reported by others,[10,26] but the mechanism of the increase is unknown.

Because basal gastrin levels of patients varied widely, we, as Lamers and Tongeren,[16] normalized the data by expressing peak responses as percentage increases above basal. Based upon our results in normals and patients, our acceptance of a 50% increase above basal level should, on statistical grounds, provide a low incidence of false-positive and false-negative results. This criterion will differentiate patients with gastrinoma from normal subjects, but may or may not discern them from patients with other causes of hypergastrinemia such as atrophic gastritis.

Some investigators have defined a positive response as a specific absolute increase in serum gastrin following provocative stimulation. Increases in serum gastrin levels of 110 pg/ml[17] and 200 pg/ml,[12] following secretin administration, have been proposed as dividing points separating patients with gastrinoma from those without.

In the current study, four provocative tests have been used in 14 patients with gastrinoma. Twelve of the 14 patients received all four tests and, therefore, paired analyses were used. With all tests serum gastrin levels were elevated (range, 17%–974%) following injection. Gastrin levels were significantly higher following SECA than following either SE or RCI. Two of 13 patients failed to make the 50% increase for positivity with both RCI and SE. By the 200 pg/ml absolute criterion, suggested by McGuigan and Wolf,[12] one of these patients (No. 5) also failed SE, LCI, and SECA. No surgery has been performed on this patient, and there has been no histologic diagnosis of gastrinoma.

In agreement with other reports,[10,11,16,17] our patients responded well to the LCI test, with peak gastrin responses ranging from 65 to 974% (162–117,000 pg/ml) above basal levels. Although the average peak response following LCI was less than that following SECA, the difference was not significant. There have been reports of false-negative results with LCI;[16,19] indeed, one of our patients (No. 5) did not achieve the positive response criterion of 395 pg/ml, suggested by Deveny et al.,[17] for LCI tests. However, more serious disadvantages are the morbidity and patient discomfort associated with this regimen. Among our 14 patients, we had to terminate the test earlier than planned in three because of untoward symptoms. The calcium dose given during LCI is 6 times greater than that used in SECA and requires extra precautions. In patients with heart disease, renal failure, or hyperparathyroidism, a common entity in patients with MEN I, LCI should be performed with great caution if at all. RCI has been used by a few investigators,[11,20,27] and distinct increases in serum gastrin levels have been reported[20,27] however, it has not been previously proposed as a diagnostic procedure.

For SECA (and SE), we used GIH secretin at a dose of 2 CU/kg, administered as a bolus, as recommended by McGuigan and Wolf.[12] The SECA resulted in significantly higher average peak gastrin levels than either SE or RCI. The mean increase in serum gastrin after SECA was 362% above basal levels; no patient responded with less than a 68% increase. In absolute values, this test also clearly separated normals from patients with gastrinoma. The highest increase in a normal was 39 pg/ml, and the lowest increase for a patient was 158 pg/ml. The results in some patients suggested an additive effect of calcium and secretin (No. 1) (Figure 2), while in others, there was more of a synergism than a simple additive effect (Nos. 1, 2, 9) (Table 3). Lamers and Tongeren[16] noted potentiation of the secretin response by calcium in one patient when secretin was given at the end of a long calcium infusion. The serum gastrin rose 2.5 times the already elevated level. This influence of serum calcium on the secretagogue potential of secretin has been investigated further by Jansen et al.[28] When the serum calcium was either decreased (EDTA infusion) or increased (calcium infusion) in patients with gastrinoma, the response to secretin was diminished or augmented respectively.

The average response in our patients with gastrinoma to SECA was 2.7 times higher than to SE and 2.5 times higher than to RCI. Furthermore, the sum of the percentage increases to RCI plus SE were essentially the same as the percentage increase to SECA. These data are consistent with an additive response between calcium and secretin. The response pattern to SECA seems to be similar in normal subjects and in patients with gastrinoma. However, the reaction of normal G cells to a bolus of porcine secretin is controversial[22,24] and may differ from the reaction in a physiologic feedback system. The mechanism behind the contrasting stimulatory effect of secretin on gastrinoma cells is not understood. Our observation that normal and tumor G cells can respond in a similar manner to the combination of secretin and calcium suggests common secretagogue mechanism(s) for these cells.

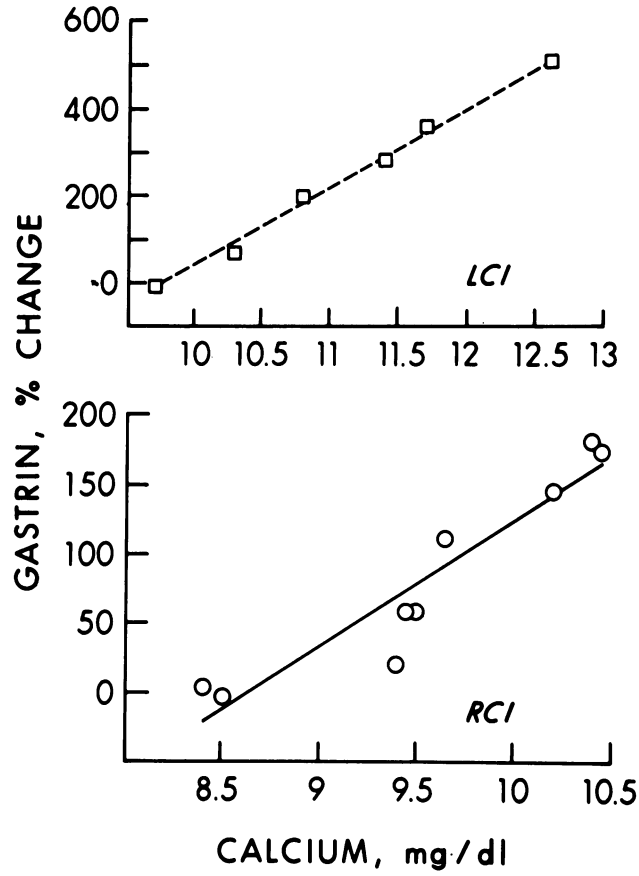

FIG. 5. Linear correlation between calcium and percentage change in serum gastrin during calcium infusion tests in 2 separate patients. Upper panel: LCI—long calcium infusion test (12 mg Ca^{++}/kg/3 h). Lower panel: RCI—rapid calcium infusion test (2 mg Ca^{++}/kg/min).

There are advantages with SECA other than its highly stimulatory effect on serum gastrin. Patient discomfort and morbidity are minimal with SECA, compared with LCI, and the test is rapid with peak serum gastrin levels usually occurring within 5 minutes.

The treatment of choice (second to cimetidine) in patients with gastrinoma is total gastrectomy, a procedure associated with a certain morbidity and mortality.[29]

The establishment of a firm, preoperative diagnosis of gastrinoma is, therefore, of the utmost importance. Our data suggests that the combination of secretin and calcium, SECA, is a potent gastrin secretagogue test. Since our test populations represented the extremes (normal subjects and patients with gastrinoma), the value of SECA in the differential diagnosis of patients with peptic ulcer disease and hypergastrinemia must be established in prospective studies.

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Discussion

DR. JAMES C. THOMPSON (Galveston, Texas): One of the problems that I have with this, and I do not know how to evaluate it, is: How many of these gastrinoma patients were tested before operation, and how many were tested afterwards? The reason I believe that the question is a cogent one is the changes in gastrin levels that we have observed after total gastrectomy. I alluded to one of them; after total gastrectomy, the release of gastrin to food is markedly enhanced. In addition, we find that the response to secretin after operation is about two and a half times greater than it is before operation.

In addition, we notice that basal gastrin values alone, taken all by themselves, unchallenged or unstimulated, are higher after total gastrectomy than they were before. This is not simply a matter of tumor growth, because it occurs in the immediate post-total gastrectomy period. The change in basal serum gastrin is not great, but it is real.

I do not know what happens to the sensitivity of the gastrin mechanism to calcium after operation, but I would not be surprised if it were increased also. And if some of these people are preoperative and some postoperative, Dr. Wells, I wonder if you could tell us if there is a difference between them in your testing. If they are all postoperative, have you tested any preoperative? Do you know if this works in them? I just wonder if this may vitiate somewhat the value of the differences that you have shown.

Now, if all these people are preoperative, I want to retract everything I say, and say this is a wonderful test, but the mechanism is still not yet clear to me.

What does the combination of the two do to specificity?

I cannot help but also observe that in the manuscript there is a statement that total gastrectomy is the procedure of choice in the