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CLINICAL TRENDS AND TOPICS

Secretin Injection Test in the Diagnosis of Gastrinoma

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Nearly 25 years have elapsed since Zollinger and Ellison described a syndrome characterized by a severe form of peptic ulcer, accompanied by marked gastric acid hypersecretion and non-beta islet cell tumors of the pancreas (1). A gastric acid secretagogue was extracted from these tumors in 1960 (2). Subsequent biochemical isolation of gastrin from the tumors (3) and detection of elevated serum gastrin concentrations by radioimmunoassay in patients with the Zollinger-Ellison syndrome (4) established gastrin-secreting tumors (gastrinomas) as the hallmark of the disease.

The clinical manifestation of the Zollinger-Ellison syndrome, or gastrinoma, have been well-described in several recent reviews (5–9). Ninety to ninety-five percent of patients with gastrinoma develop ulcer during the course of their disease. Most patients have symptoms which are similar to those of patients with common peptic ulcer. However, symptoms are usually more persistent, progressive, and less responsive to therapy (9).

Optimal therapy for patients with gastrinomas is in a state of evolution (10). Treatment must be selected which corrects gastric acid hypersecretion. However, it must also take into consideration the lethal malignant potential of these tumors (7,9). Until recently total gastrectomy was accepted uniformly as the procedure of choice for treatment of those patients (11). This decision was based on evidence that mortality was lowest among gastrinoma patients in whom total gastrectomy was the initial surgical procedure (11–13). With the development of histamine H_2-receptor antagonists, principally cimetidine, a nonsurgical therapeutic alternative to surgical therapy became available (10,14,15). Treatment with cimetidine has been shown to be effective in reducing gastric acid hypersecretion, improving symptoms, and inducing ulcer healing in most gastrinoma patients (10,14,15). Effective acid suppression with cimetidine also permits consideration of attempts at cure by complete surgical extirpation of a gastrinoma without gastrectomy (16). Surgical removal of these usually slow-growing but biologically malignant tumors is anticipated to be important in reducing mortality due to metastatic disease (9). Nonoperative treatment of gastrinoma patients with metastases with streptozotocin (17,18) or irradiation (7) has met with variable and incomplete success.

Diagnosis of Gastrinoma

The diagnosis of gastrinoma is usually made by demonstration of hypergastrinemia and hypersecretion of gastric acid in a patient with ulcer disease and/or symptoms associated with the Zollinger-Ellison syndrome. However, there is substantial overlap in serum gastrin levels and in rates of gastric acid secretion in patients with gastrinoma, normal individuals, and patients with common peptic ulcer. Marks et al. had proposed that the ratio of gastric acid secretion in the basal to that of the stimulated state was of value in identifying patients with the Zollinger-Ellison syndrome (19); however, this has not proved to discriminate satisfactorily between patients with gastrinoma and duodenal ulcer (20,21).

Demonstration of elevated serum gastrin concentrations by radioimmunoassay has proved to be an invaluable diagnostic tool in the diagnosis of patients with gastrinoma (4–7,22,23). However, hypergastrinemia is not confined to patients with gastrinomas. It may be found in association with achlorhydria and hypochlorhydria, as with pernicious anemia (24), chronic atrophic gastritis (6), gastric carcinoma (25), and with vitiligo (26). It has also been reported in patients with antral G-cell hyperplasia (27), pyloric obstruction (28), chronic renal failure (29), pheochromocytoma (30), postvagotomy (31), small intestinal resection (32), excluded gastric

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antrum (33), and rheumatoid arthritis (34). Finally, a small number of patients with apparently ordinary peptic ulcer disease, without gastrinoma, may have elevated serum gastrin concentrations (5,35). Although the clinical presentation of common duodenal ulcer and gastrinoma are often similar, the routine determination of fasting serum gastrin concentrations in all peptic ulcer patients is probably not necessary. Among others, patients with peptic ulcer in whom fasting serum gastrin should be measured include those with postoperative ulcer recurrence, those with high rates of gastric acid secretion, those who do not respond satisfactorily to usually effective medical treatment, those with associated hypercalcemia (especially if due to hyperparathyroidism), those with urinary tract calculi, or those with a strong family history of peptic ulcer or pituitary or parathyroid tumors.

Approximately 40% of patients with proven gastrinoma may have fasting serum gastrin concentrations from 100 to 500 pg/ml, therefore substantially overlapping those of ulcer patients without tumor (35). In addition, serum gastrin concentrations have been observed to fluctuate between the high-normal and definitely abnormal range in several patients with proven gastrinoma (6). These observations indicate that diagnostic tests, in addition to measurement of fasting serum gastrin and gastric acid secretion, are often required in order to establish or exclude the diagnosis of gastrinoma in patients with ulcer disease. Precise diagnosis is required, since both medical and surgical therapies for the Zollinger-Ellison syndrome differ from those for ordinary duodenal ulcer (35).

Provocative Tests in the Diagnosis of Gastrinoma

Several provocative tests have been developed to identify patients with gastrinomas (36–47). These have included measurements of serum gastrin concentrations in response to a test meal, intravenous calcium infusion, and intravenous injection of secretin. These tests are of greatest value in situations in which the diagnosis of gastrinoma is suggested, but remains in doubt, i.e., in patients with clinical symptoms consistent with the Zollinger-Ellison syndrome, but with fasting serum gastrin concentrations less than 1000 pg/ml.

Berson and Yalow found that after ingestion of a protein-rich meal, patients with gastrinoma showed absent or only minor increases in serum gastrin concentrations (36). However, several studies have reported that some gastrinoma patients, with or without previous gastric surgery, have had significant serum gastrin elevations after ingestion of the test meal, thus limiting the diagnostic usefulness of this test (9,41,43). Lamers and van Tongeren compared the test meal with the calcium infusion and secretin injection tests and found that 11% of gastrinoma patients, 75% of normals, and 100% of duodenal ulcer patients had positive serum gastrin responses to test meals (defined as at least a 50% increase in serum gastrin after the meal) (43). Creutzfeld et al. examined serum gastrin responses to a test meal and found that 4 of 9 patients with the Zollinger-Ellison syndrome had greater than 200% increases in serum gastrin after the meal (41).

In the calcium stimulation test, calcium gluconate is infused intravenously (5 mg calcium per kg body weight per hr for 3 hr). Serum gastrin measurements are obtained before and at regular intervals (e.g., 30 min) during calcium infusion. In individuals with common duodenal ulcer, calcium infusion evokes small-to-moderate increases in serum gastrin (usually less than 50%). However, in Zollinger-Ellison patients, increases in serum gastrin concentrations are usually substantial, with maximal levels generally achieved during the final hour of calcium infusion (44–46). Recent studies, however, indicate the occurrences of false-negative responses among gastrinoma patients and false-positive responses in some hypergastrinemic patients without the Zollinger-Ellison syndrome (43,47). In addition, the calcium stimulation test is lengthy and cumbersome and may be associated with adverse reactions (35,43,47).

Secretin Injection Test in the Diagnosis of Gastrinoma

In 1970 Brooks and Grossman demonstrated that secretin administration decreased pentagastrin-stimulated gastric acid secretion (48). Hansky et al. reported small, but significant, decreases in serum gastrin levels in normal human subjects after intravenous secretin injection (49). In 1972 Isenberg et al. reported a patient with the Zollinger-Ellison syndrome, in whom intravenous secretin infusion produced paradoxical increases in both gastric acid secretion and serum gastrin concentrations (50). The mechanism accounting for this phenomenon remains unknown. Nevertheless, this observation led to their conclusion that serum gastrin responses to intravenous secretin infusion may be of diagnostic value in patients with suspected Zollinger-Ellison syndrome. Studies published since their report appear to support this conclusion (37–43,46,47,51–53,55).

The secretion provocation test is preferred over the calcium infusion test in distinguishing patients with the Zollinger-Ellison syndrome from other hyperchlorhydric, hypergastrinemic patients for sev-

eral reasons (35,43,47). The secretin test is shorter in duration, has fewer adverse effects, and yields fewer false-positive and false-negative results (35,43). Some recent studies have questioned the diagnostic reliability of the test (54,56). Review of these and other reports indicates wide variability in testing procedures used in the performance of the secretin provocation test and emphasizes the requirement to examine and compare the manner in which secretin provocation tests have been performed and interpreted.

Table 1 lists the previous reported experience with the secretin provocation test. The data demonstrate a lack of uniformity in both testing procedure and interpretation. Of the 122 patients with gastrinoma, 110 (90.2%) were reported as having a positive test. In those studies using for comparison nonulcer controls and patients with ordinary duodenal ulcer, no false-positive responses were obtained.

Before discussing individual reports, several technical aspects of the secretin provocation test require consideration.

(a) Method of secretin administration. Secretin has been administered by either constant intravenous infusion or intravenous bolus injection. It has been clearly demonstrated that the increase in serum gastrin concentration in gastrinoma patients is significantly greater with bolus injection (49,54). The enhanced gastrin response with bolus injection provides more reliable data in the exclusion or establishment of the diagnosis of gastrinoma. In addition, with intravenous bolus injection the test duration is shortened when compared with constant intravenous infusion.

(b) Type of secretin used. Two different preparations of purified naturally occurring porcine secretin have been utilized extensively in examining serum gastrin concentrations in gastrinoma patients—pure natural GIH secretin (Karolinska Institute, Stockholm, Sweden) and Boots secretin (Warren-Teed Laboratories, Inc., Columbus, Ohio). At the present time there is insufficient information available in the literature to compare secretin provocation results using the several available forms of synthetic porcine secretin with results using the purified naturally occurring porcine secretins. The potency of Boots secretin varies among different preparations; 1 U of GIH secretin is approximately equivalent to from 6 to 8 U of Boots secretin. This requires the use of six to eight times as much Boots as GIH secretin during the provocation test. When Boots secretin was utilized, none of the studies in Table 1 reported use of more than 4 U of Boots secretin/kg, the equivalent of a maximum of 0.5–0.67 U of GIH secretin. Furthermore, Brady et al. recently reported false-positive increases in serum gastrin levels after intravenous Boots secretin injection in patients with chronic gastritis and in normal individuals (57). They found large amounts of material immunoreactive with gastrin antiserum in the Boots secretin preparation and concluded that this material probably accounted for the false-positive serum gastrin responses in these patients. The only previously reported false-positive gastrin response to intravenous secretin was in a patient with hypergastrinemia and achlorhydria (56) in whom testing was also performed with Boots secretin (RL Wollmuch, personal communication). These data support the conclusion that pure GIH secretin, and not Boots secretin, is preferred in performing the intravenous secretin provocation test for gastrinoma.

(c) Dosage of GIH secretin. Isenberg et al. showed that in gastrinoma patients gastrin release in response to secretin is dose-dependent (50). Table 1 contains four studies which utilized GIH secretin 1 U/kg via i.v. bolus injection (41,43,46,54) and three studies which used GIH secretin 2 U/kg via i.v. bolus injection (47,50,53). Of the 40 patients with gastrinoma who received 1 U/kg, 34 (85%) were considered to have test results which supported the diagnosis of the Zollinger-Ellison syndrome. However, 100% of the 30 patients who received 2 U/kg were considered to have positive tests (See Table 2).

(d) Timing of serum samples. The increase in serum gastrin which is produced by intravenous secretin in gastrinoma patients is prompt. The peak serum gastrin concentration after intravenous bolus injection of secretin is almost always noted at 5 min, less commonly at 10 min, with a gradual return to basal values by 30 min. Therefore, in order to maximize the efficacy of the secretin provocation test in discriminating between patients with gastrinoma and common duodenal ulcer, serum gastrin measurements should be made early after intravenous secretin injection.

(e) Evaluation of results. Because of the wide variability in testing procedures, absolute criteria for interpretation of positive secretin provocation test responses are difficult to obtain from the literature. Whereas it is important to limit false-negative results, because of the therapeutic implications it is of utmost importance to prevent false-positive interpretations. A review of the studies listed in Table 1 indicates that these objectives are probably best achieved by using the criterion of an absolute increase in serum gastrin concentration after secretin injection, rather than percent increase. If an absolute increase in serum gastrin concentration of 200 pg/ml after secretin injection is required for a positive response, no false-positive responses and few, if any, false-negative responses have been reported.

It is recognized that histologic verification of gas-

trinoma is optimal in developing a critical analysis of results obtained with the secretin provocation test in the diagnosis of gastrinoma. It is also recognized that histologic verification of gastrinoma was not provided for each patient with the diagnosis of Zollinger-Ellison syndrome (Table 1). In some instances surgery was not performed and in other instances, even when sought, the tumor could not be located. In order to evaluate the impact of patients considered to have the Zollinger-Ellison syndrome, but in whom histologic verification of gastrinoma was lacking, we examined and compared the frequency of positive secretin provocation tests in the total group of patients with the diagnosis of Zollinger-Ellison with results obtained when patients lacking histologic verification of gastrinoma were excluded. Histologic verification of gastrinoma was established in 62 of the total group of 122 patients with the diagnosis of Zollinger-Ellison syndrome in Table 1, and 56 (90.3%) of these patients had positive secretin provocation tests, a figure essentially the same as for the group as a whole (90.2%). These data provide no evidence that the absence of histologic verification impairs or modifies conclusions concerning the frequency of positive secretin provocation tests in patients with the diagnosis of Zollinger-Ellison syndrome.

Of all the reports listed in Table 1, only one concludes that the secretin provocation test is not reliable in the diagnosis or exclusion of gastrinoma (54). Stage et al. studied 15 gastrinoma patients and 8 patients with common duodenal ulcer. They found significantly higher serum gastrin responses to secretin injection in gastrinoma patients, but they also indicated that "values were overlapping and some Zollinger-Ellison patients did not respond." However, careful examination of their data suggests that the authors' conclusions may reflect variation in testing methodology and interpretation. They performed the secretin provocation test by intravenous administration of only 1 U/kg of GIH secretin; review of available data suggests that this is a less than optimal dosage (see Tables 1 and 2). Also, although overlap in serum gastrin responses in gastrinoma and duodenal ulcer patients was detected at approximately 30 min after intravenous bolus injection of secretin, there were significant differences between the two groups of patients after 5 min. Finally, basal serum gastrin concentrations were not reported in this study. Provocative testing, including the secretin provocation test, is of greatest value in patients with clinical manifestations consistent with gastrinoma and basal serum gastrin levels which are less than 1000 pg/ml.

Additional studies recorded in Table 1 also require further comment. Korman et al. found that secretin injection induced substantial increases in serum gastrin concentration in 6 of 9 gastrinoma patients (38). Of the 3 patients with false-negative responses, 2 had basal serum gastrins of 1000 pg/ml or greater. Also, the study was performed utilizing a very small dose of secretin (Boots secretin, 2 U/kg). Eight of 9 patients with gastrinoma reported by Creutzfeld et al. (41) exhibited paradoxical augmentation of serum gastrin concentrations which were greater than 200 pg/ml after secretin injection; the 9th patient had an increase of 131 pg/ml. However, these investigators used approximately 1 U/kg of GIH secretin during testing. In a study by Bradley et al. (51) in 1976, intravenous bolus injection of Boots secretin (3 U/kg) in 13 patients with histologically proven gastrinoma produced significant increases in serum gastrin levels; 3 patients with presumed gastrinoma, but without tissue diagnosis, failed to exhibit paradoxical increases in serum gastrin in response to secretin.

Administering 1 U/kg of GIH secretin by intravenous bolus injection to 15 patients with histologically proven Zollinger-Ellison syndrome, Lamers et al. (43), reported that 2 of the 15 patients had negative responses. These 2 patients had fasting serum concentrations of 1300 and 960,000 pg/ml. Thus they would hardly have required a provocation test to establish the diagnosis of gastrinoma. Two patients with presumed gastrinoma cited by Deveney et al. (47) had increases in serum gastrin in response to secretin of only 110 and 190 pg/ml, respectively. However, their diagnoses were not established histologically; the clinical diagnosis of gastrinoma in those patients was concluded in retrospect.

Conclusions and Recommendations

Based on the above analysis of reported experience with the secretin provocation test in the diagnosis of gastrinoma the following recommendations are proposed in an attempt to achieve standardization of performance and interpretation of the testing procedure. These recommendations are summarized in Table 3. The diagnosis of the Zollinger-Ellison syndrome can be established in a hyperchlorhydric patient with compatible clinical features and a fasting serum gastrin concentration which is greater than 1000 pg/ml. If the diagnosis is suspected, because of potential fluctuation in serum gastrin levels, several serum gastrin measurements should be performed. If the diagnosis of gastrinoma is still not established or excluded, the secretin provocation test should be performed. For this test it is recommended that GIH secretin,* 2 U/kg body wt, be injected intravenously over 30 sec. Gastrin measurements should be performed on sera obtained be-

Table 1. Previous Experience with the Secretin Provocation Test

No. of subjects	Form of secretin and method of immunization	Test criteria	Results	References
5 ZE	A. 1 ZE studied with GIH secretin 3 U/kg, 6 U/kg, 9 U/kg all via 1 hr i.v. infusion B. 4 with ZE studied with GIH 2 U/kg i.v. bolus injection	Paradoxical increase in serum gastrin after secretin indicative of gastrinoma	A. Patient showed dose-dependent increase in serum gastrin. B. 4/4 demonstrated a significant early serum gastrin increase.	Isenberg et al.[50]
6 ZE	Boots 3 U/kg i.v. bolus injection	Significant increase after secretin indicative of ZE (no quantitation)	6/6 showed a significant increase; mean increment in 5 postgastrectomy patients was 2406 pg/ml.	Bradley et al.[37]
9 ZE	Boots 2 U/kg i.v. bolus injection	Paradoxical augmentation of serum gastrin after secretin consistent with ZE (no quantitation)	6/9 demonstrated a significant increase; 3/9 had no change.	Korman et al.[38]
3 ZE	GIH 0.1 U/kg, 0.33 U/kg, 1 U/kg, 3 U/kg, all via i.v. infusion over 45 min	Considerable increase in serum gastrin after secretin infusion diagnostic of gastrinoma (no quantitation)	3/3 showed large increases after secretin.	Schrumpf et al.[39]
3 ZE 3 Control	GIH 9 U/kg/hr i.v. infusion (2) and GIH 1 U/kg i.v. bolus injection (1)	Paradoxical augmentation of serum gastrin after secretin consistent with ZE (no quantitation)	3/3 ZE showed paradoxical augmentation with infusion or injection; 3/3 controls demonstrated suppression.	Kolts et al.[46]
2 ZE 6 Control 1 PA	Boots 4 U/kg i.v. bolus injection	>300% increase indicative of ZE	2/2 ZE had >300% increase; 6/6 controls and 1/1 PA showed 0% increase.	Straus and Yalow[40]
9 ZE 6 Control	GIH 75 U i.v. bolus injection (approximately 1 U/kg)	Increase in serum gastrin after secretin injection consistent with gastrinoma (no quantitation)	8/9 ZE had an increase of >200 pg/ml; 1/9 ZE increased 131 pg/ml after secretin; 6/6 controls showed suppression.	Creutzfeld et al.[41]
12 ZE	GIH 1 U/kg/hr i.v. infusion	Increased serum gastrin after secretin infusion indicative of ZE (no quantitation)	12/12 demonstrated an increase ranging from 283 to 8466 pg/ml.	Thompson et al.[42]
16 ZE	Boots 3 U/kg i.v. bolus injection	Increased serum gastrin after secretin injection indicative of ZE (no quantitation)	13/16 increased from 122 to 8850 pg/ml; 3/16 decreased after secretin.	Bradley and Galambos[51]
15 ZE 34 Control 14 DU 11 Achlorhydria 4 Billroth I 6 Billroth II	GIH 1 U/kg i.v. bolus injection	50% Increase in serum gastrin concentrations after secretin injection consistent with gastrinoma	13/15 ZE had >50% increase, while 2/15 did not; 0/69 of remaining patients had a significant increase.	Lamers and Van Tongeren[43]
18 ZE 29 DU	GIH 2 U/kg i.v.. bolus injection	>110 pg/ml Increment after secretin injection used as discriminatory level	18/18 ZE had a positive test; 0/29 with ordinary DU had a positive result.	Deveney et al.[47]
15 ZE 8 DU	A. GIH 1 U/kg hr i.v. infusion B. GIH 1 U/kg i.v. bolus injection	Study designed to discern whether secretin provocation can discriminate between ZE and ordinary DU patients	A. 12/15 ZE increased >135 pg/ml; 8/8 DU increase <100 pg/ml. B. 11/15 ZE increased >150 pg/ml; the other 4/15 increased at least 400%. 8/8 DU increased <100 pg/ml and 8/8 increased <50%.	Stage et al.[54]
8 ZE 18 DU	GIH 2 U/kg i.v. bolus injection	Study performed to discern whether or not secretin provocation adequately discriminates between ZE and ordinary DU patients	8/8 ZE increased, ranging from 450 to 9275 pg/ml; 18/18 DU increase <150 pg/ml, 17/18 <100 pg/ml.	Mihas et al.[53]

1 ZE	A. ZE patient-Boots 1 U/kg i.v. injection	Study performed to discern whether secretin provocation can discriminate between ZE and "nontumorous hypergastrinemic hyperchlorhydria"	A. ZE patient increased 300 pg/ml.	Straus et al.[55]
1 DU	B. DU patient- GIH 75 U (Approximately 1 U/kg) i.v. bolus injection		B. DU patient showed no change.	

ZE = Zollinger-Ellison syndrome. DU = duodenal ulcer. PA = pernicious anemia.

Table 2. Positive Secretin Provocation Tests Related to GIH Secretin Dose

Secretin dosage	No. of Z-E Patients	Positive Tests	False-negative Tests
1 U/kg i.v. bolus injection	40	34 (85%)	6 (15%)
2 U/kg i.v. bolus injection	30	30 (100%)	0
Total	70	64 (91.4%)	6 (8.6%)

Table 3. Proposed Protocol for the Secretin Provocation Test for Gastrinoma

1. Secretin—GIH preferable.
2. Route of administration—intravenous bolus injection (30 sec).
3. Dosage of GIH secretin—2 U/kg body wt (in 10 ml 0.9% NaCl).
4. Timing of serum gastrin measurements—basal (fasting) and at 5-min intervals for 30 min.
5. Interpretation of results—an increase in serum gastrin at least >200 pg/ml supports the diagnosis of gastrinoma.

fore and at 5-min intervals for 30 min after intravenous secretin injection. A positive test, consistent with the diagnosis of gastrinoma, is indicated by an increase in serum gastrin concentration which is at least 200 pg/ml greater than the basal level.

Consideration of the available data summarized in Table 1 demonstrates the need for a more detailed evaluation of the secretin provocation test, performed as we have proposed, in larger numbers of patients with gastrinoma, common duodenal ulcer, pernicious anemia, and other states associated with hypergastrinemia. In conclusion, although the secretin provocation test may be imperfect, as are all clinical diagnostic tests, when properly performed and interpreted, it does appear to offer a safe, expeditious, and reliable means for establishing or excluding the diagnosis of gastrinoma.

* In the United States, use of GIH secretin in human subjects is limited to clinical investigation. Individuals wishing to use GIH secretin should apply to: Armand Littman, M.D., VA Hospital, Hines, Illinois 60141, for coverage under his Master IND. Alternatively, one may apply to the U.S. Food and Drug Administration for an individual IND. Once an IND is secured, the secretin can then be obtained directly from AB Kabi Diagnostica, S-112 87, Stockholm, Sweden.

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