GEP-NET : rare tumour connections. Pathophysiological aspects of gastroenteropancreatic neuroendocrine tumours

Kuiper, P.

Chapter 5

Diagnostic Efficacy of The Secretin Stimulation Test for The Zollinger-Ellison Syndrome: an Intra-Individual Comparison Using Different Dosages in Patients and Controls

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Published in condensed form in Pancreatology 2010;10(1):14-18.

Abstract

The secretin stimulation test is the principal diagnostic tool to identify the Zollinger-Ellison syndrome (ZES).

To investigate by intra-individual comparison which dose of secretin results in the highest diagnostic efficacy to identify the ZES.

We analyzed 57 paired secretin stimulation tests, using both 0.26 µg/kg and 0.78 µg/kg secretin, performed in 13 ZES patients and 12 controls, and confirmed the findings in a validation cohort.

In our study, a gastrin increase of >100 ng/L was found to be the most sensitive and specific criterion for a positive test, also compared to the most frequently used criteria from the literature. Using this criterion, we found that the higher gastrin increases after 0.78 µg/kg compared to 0.26 µg/kg secretin contributed to a slightly more sensitive (82.9% vs. 80.5%) but less specific (68.8% vs. 81.3%) test. Application of this criterion in a confirmative set of 98 tests, using 0.26 µg/kg secretin in 21 ZES patients and 39 controls, provided similar results. In ZES patients with normal fasting serum gastrin levels (<100 ng/L), there was no diagnostic benefit from the use of a higher secretin dose.

We conclude that the 0.26 µg/kg secretin stimulation test has the best diagnostic efficacy for the ZES.

Introduction

Zollinger-Ellison syndrome (ZES) is caused by a gastrin-producing neuroendocrine tumour (gastrinoma), and is characterized by symptoms of gastric acid hypersecretion, i.e., peptic ulcer disease, malabsorption and diarrhea[1]. However, symptoms can be absent for a relatively long time, for example when proton pomp inhibitors (PPI) are used[2]. ZES can be suspected when fasting serum gastrin (FSG) levels are increased, although hypergastrinemia is seen in several, more common, diseases, as well as in PPI users[3]. As a considerable number of ZES patients have FSG levels within the normal range, i.e., <100 ng/L, or FSG levels in a non-diagnostic range, i.e., 100-1,000 ng/L, determinations of FSG levels alone will not be conclusive for the diagnosis of ZES and additional diagnostic methods are needed. For this reason, several gastrin provocation tests have been developed, e.g., calcium infusion test, meal stimulation test and secretin stimulation test. The secretin stimulation test has been shown to be the diagnostic tool of choice in subjects with FSG levels < 1,000 ng/L[4,5]. In the literature, several criteria for a positive test have been reported. We first investigated which criterion for a positive secretin stimulation test results in the highest sensitivity and specificity in our study cohort and used this criterion in further analyses. Furthermore, since the introduction of the secretin stimulation test, the most optimal dose of secretin to use in this test has been disputed. While some studies have shown that a low dose of secretin is sufficient to discriminate between ZES[5,6] and other causes of hypergastrinemia, others believe that only a higher secretin dose can contribute to adequate diagnosing[7-10]. Therefore, we subjected ZES patients and non-ZES controls to sequential secretin stimulation tests with a low and high dose of secretin, and thereby obtained a per-person-comparison between different doses of secretin. To our knowledge, secretin stimulation tests have not been studied with different doses in the same patients before, except for one case report[8]. The aim of our study was to investigate whether; 1) the use of a higher dose of secretin in secretin stimulation tests leads to a higher gastrin increase, and if so, 2) does this contribute to a higher sensitivity and specificity of the secretin stimulation test for ZES, and 3) is the use of a higher secretin dose of benefit in the diagnosis of ZES in

patients with normal FSG levels (<100 ng/L). Lastly, we applied the determined criterion for a positive secretin stimulation test in a confirmative set of 98 secretin stimulation tests using the low dose of secretin in 21 ZES patients and 39 non-ZES controls to validate our initial results.

Materials and Methods

Patients

Sequential 0.26 μg/kg and 0.78 μg/kg secretin stimulation tests in 25 subjects, suspected of ZES based on increased FSG levels (hypergastrinemia) or because of clinical suspicions, were performed in our Gastroenterology Department of the Leiden University Medical Centre. In total, thirteen patients suffering from ZES, of whom four as part of the MEN-1 syndrome, and twelve non-ZES controls suffering from MEN-1 but not ZES (n=3), atrophic gastritis (n=2) or a non-ZES-related (mainly other gastroenteropancreatic) disease (n=7), were included. In the majority of patients (12/13), the diagnosis of ZES was confirmed by identification of a tumour on imaging or at surgery. Thirteen patients were female and twelve patients were male. In a subset of patients, the secretin stimulation test was performed multiple times for follow-up. Therefore, the total number of tests exceeds 25. For a validation study, an additional group of 60 patients, suspected of ZES, was included. In total, 98 secretin stimulation tests with 0.26 μg/kg of 21 ZES patients (20/21 confirmed with imaging or at surgery) and 39 controls were analyzed, using the criterion for gastrin increase of >100 ng/L for a positive test. Seven patients suffered from ZES as part of MEN-1, while ten controls had the MEN-1 syndrome without ZES. It must be noted that in this validation group, fourteen patients (nine ZES patients and five non-ZES controls) were included who also had been tested in the study group, although at different time points.

This study was performed according to the guidelines of the Medical Ethics Committee of the Leiden University Medical Centre in compliance with the Helsinki Declaration.

Secretin stimulation tests

Secretin stimulation tests were done in patients after an overnight fast and acid-suppressing medications were continued, except for the day before and on testing, when possible. The secretin stimulation test was performed by the procedure as described previously[11]. Before, during and after intravenous injection of 0.26 μg secretin (Secretin, ClinAlfa, 255 ng is estimated to be 1 clinical unit) per kg of body weight during 30 seconds, blood samples were collected at -5, 0, +1, +5, +10, +15 and +30 minutes. Serum gastrin levels were measured by a radioimmunoassay, using an antibody raised in rabbits against synthetic human gastrin I (unsulfated gastrin-17) covalently coupled to bovine serum albumin. Labeled gastrin ^{125}I-Tyr^{12}-gastrin-I (human) was purchased by PerkinElmer, USA. The antibody binds to all known circulating gastrin fragments. The upper limit of the normal range for fasting state was taken as 100 ng/L, samples were diluted with repeated measurements as necessary to generate gastrin levels in a measurable range. After a minimum delay of at least 60 minutes, the test was repeated using 0.78 μg of secretin per kg body weight. The basal fasting serum gastrin is calculated as the average of two fasting blood samples before secretin injection. The increase in gastrin levels in ng/L after stimulation was calculated by:

[maximal value after secretin injection] – [basal fasting value prior to secretin stimulation].

In daily practice, according to our hospital protocol, a gastrin increase of more than 50% of basal value with a minimum rise of 100 ng/L was defined as a positive test.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 16 (SPSS). The Wilcoxon signed ranks test was performed for comparison of differences between serum gastrin levels before administration of distinct secretin doses. Linear regression analysis was used to evaluate the linear relationship between the different doses of secretin. In particular, an orthogonal regression was used, to minimize the orthogonal or perpendicular distances from the data points to the fitted regression line. A receiver operating characteristic

(ROC) curve was used to determine the discrimination threshold of gastrin increase for a positive secretin stimulation test. A p-value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

An overview of included patients in the initial study group (n=25) and confirmation group (n=60) is presented in Table 1.

Table 1. Patient characteristics				
	Initial study group		**Confirmation group**	
	25 patients	**57 tests**	**60 patients**	**98 tests**
Sex	n	n	n	n
Male	12	25	31	46
Female	13	32	29	52
Age at test	yrs	yrs	yrs	yrs
Mean	51.9	-	46.4	-
St. dev.	11.7	-	13.7	-
Diagnosis	n	n	n	n
ZES	13	41	21	56
Preoperatively	7	10	13	18
Postoperatively	10	31	12	38
Non-ZES controls	12	16	39	42
MEN-1 present	n	n	n	n
ZES patients	3	4	7	19
Non-ZES controls	3	4	10	13

Table 1. Patient characteristics of study group and validation group.

Determination of the optimal criterion for a positive secretin stimulation test

In our hospital daily practice, a secretin stimulation test is defined as positive in case of a gastrin increase of more than 50% of basal value with a minimum rise of 100 ng/L. In the literature, several criteria for a positive secretin test have been described. Therefore, the most sensitive and specific secretin stimulation test was

assessed in our study population (Table 2). To determine the most optimal criterion for differentiation between Zollinger-Ellison syndrome and non-Zollinger-Ellison disease within our study group, a ROC curve analysis was performed. The optimal cut-off point for absolute gastrin increase with 0.26 µg/kg secretin was found to be 100 ng/L, with a sensitivity and specificity of 80.5% and 81.3% respectively. For 0.78 µg/kg secretin the cut-off point was found to be 95 ng/L, with a sensitivity and specificity of 82.9% and 68.8% respectively, but for the cut-off point of 100 ng/L identical results were found. Therefore, in this study, an absolute gastrin increase >100 ng/L as the uniform criterion with the highest sensitivity and specificity was chosen and used in our further analysis. In combination, we found that the criterion of a gastrin increase >100 ng/L is optimal for the diagnostic effectiveness for ZES, as this criterion led to equal or higher sensitivity and specificity compared to other criteria. Only when 0.78 µg/kg of secretin is used in the secretin stimulation test, the criterion of a gastrin increase of >100 ng/L + >50% leads to a slightly higher sensitivity and specificity.

Fasting serum gastrin analysis

We were also interested whether a higher dose of secretin contributes to a more diagnostic efficiency of the secretin stimulation test, and therefore 57 secretin stimulation tests were sequentially performed with two doses of secretin. For optimal comparison of gastrin increases after stimulation with 0.26 µg/kg or 0.78 µg/kg secretin, it is favorable that FSG levels before administration of secretin are comparable. We found that the FSG concentrations (mean 339 ng/L, range 7.5-43200 ng/L and 289 ng/L, range 5-47850 ng/L for 0.26 µg/kg and 0.78 µg/kg, respectively) did not significantly differ in the paired analysis and that there was a significant correlation (Spearmans rho = 0.9854 with $P<0.01$) between FSG levels before the use of 0.26 µg/kg and 0.78 µg/kg of secretin.

Table 2. Determination of optimal criterion			
Gastrin increase		**Sensitivity**	**Specificity**
0.26 µg/kg secretin	>100 ng/L[#]	80.5%	81.3%
	>110 ng/L[$]	80.5%	81.3%
	>120 ng/L[&]	78.0%	81.3%
	>200 ng/L*	58.5%	81.3%
	>50%[+]	80.5%	75.0%
	>100%[¶]	65.9%	81.3%
	>100 ng/L+>50%[§]	68.3%	87.5%
0.78 µg/kg secretin	>100 ng/L	82.9%	68.8%
	>110 ng/L	82.9%	68.8%
	>120 ng/L	80.5%	68.8%
	>200 ng/L	73.2%	68.8%
	>50%	95.1%	68.8%
	>100%	78.0%	81.3%
	>100 ng/L+>50%	80.5%	87.5%
Criteria of Lamers *et al.* (#,§)[11], Deveney *et al.* ($)[12], Berna *et al.* (&)[5], McGuigan and Wolfe (*)[10], Lamers and van Tongeren (+)[13], and Modlin *et al.* (¶)[14].			

Table 2. Specificity and sensitivity, using different criteria as reported in the literature, calculated for secretin tests using 1 and 3 clinical units per kg of secretin for diagnosing ZES. Remarkably, sensitivity was higher for 0.78 µg/kg compared to 0.26 µg/kg of secretin for each criterion, while specificity showed an opposite pattern, resulting in higher specificity when the secretin stimulation test is performed using 0.26 µg/kg of secretin.

Gastrin increase analysis

In Figure 1, gastrin increase levels after the use of 0.26 µg/kg of secretin are plotted on a logarithmic scale against gastrin increase levels after the use of 0.78 µg/kg of secretin. To determine if the use of 0.78 µg/kg of secretin leads to a higher gastrin increase, an orthogonal regression analysis was performed. For the total group of 57 tests, this resulted in a slope of 1.400 ± 0.0770 with a 95% confidence interval between 1.245 and 1.554, indicating that the use of 0.78 µg/kg leads to a higher gastrin increase compared to the use of 0.26 µg/kg of secretin. This effect was also found when ZES patients were analyzed separately; 1.403 ±

0.0929 with a 95% confidence interval between 1.215 and 1.591. Furthermore, in these ZES patients a previous low dose secretin provocation did not affect the response to the high secretin dose as illustrated by the significantly higher maximum gastrin level (mean 10,920 ng/L, range 29-110,000 ng/L versus 13,740 ng/L, range 38-188,000 ng/L, respectively; $P<0.03$). The resulting mean maximum gastrin level ratio of 1.17 was similar to that observed in two patients where the two secretin stimulation tests were performed with an approximately two-week interval having a ratio of 1.16.

In contrast, orthogonal regression analysis of non-ZES controls (n=16) revealed a slope of 0.6743 ± 0.0616, with a 95% confidence interval between 0.5421 and 0.8064, lower than 1. No points in Figure 1 are located in the right lower quadrant representing a gastrin increase with 0.26 μg/kg >100 ng/L and with 0.78 μg/kg <100 ng/L, which means that in none of the tests in this quadrant the use of 0.78 μg/kg of secretin was superior to the use of 0.26 μg/kg. In contrast, there are three points (two controls and one ZES patient) located in the left upper quadrant representing a gastrin increase with 0.26 μg/kg <100 ng/L and with 0.78 μg/kg >100 ng/L, indicating that in one ZES patient the 0.78 μg/kg secretin stimulation resulted in a positive test, while the 0.26 μg/kg secretin stimulation test was falsely negative, but this was also the case in two non-ZES patients indicating false-positive results with 0.78 μg/kg in these patients.

To asses whether this increase was clinically relevant, sensitivity and specificity were compared between 0.26 μg/kg and 0.78 μg/kg secretin stimulation tests. Hereby the secretin stimulation test was defined as positive when gastrin increase was >100 ng/L. This led to a higher number of truly positives for 0.78 μg/kg secretin stimulation tests, but to a higher number of false positives as well. Therefore, sensitivity was slightly higher in tests using 0.78 μg/kg compared to 0.26 μg/kg secretin stimulation tests (82.9% vs. 80.5%), but specificity was lower (68.8% vs. 81.3%).

Figure 1.

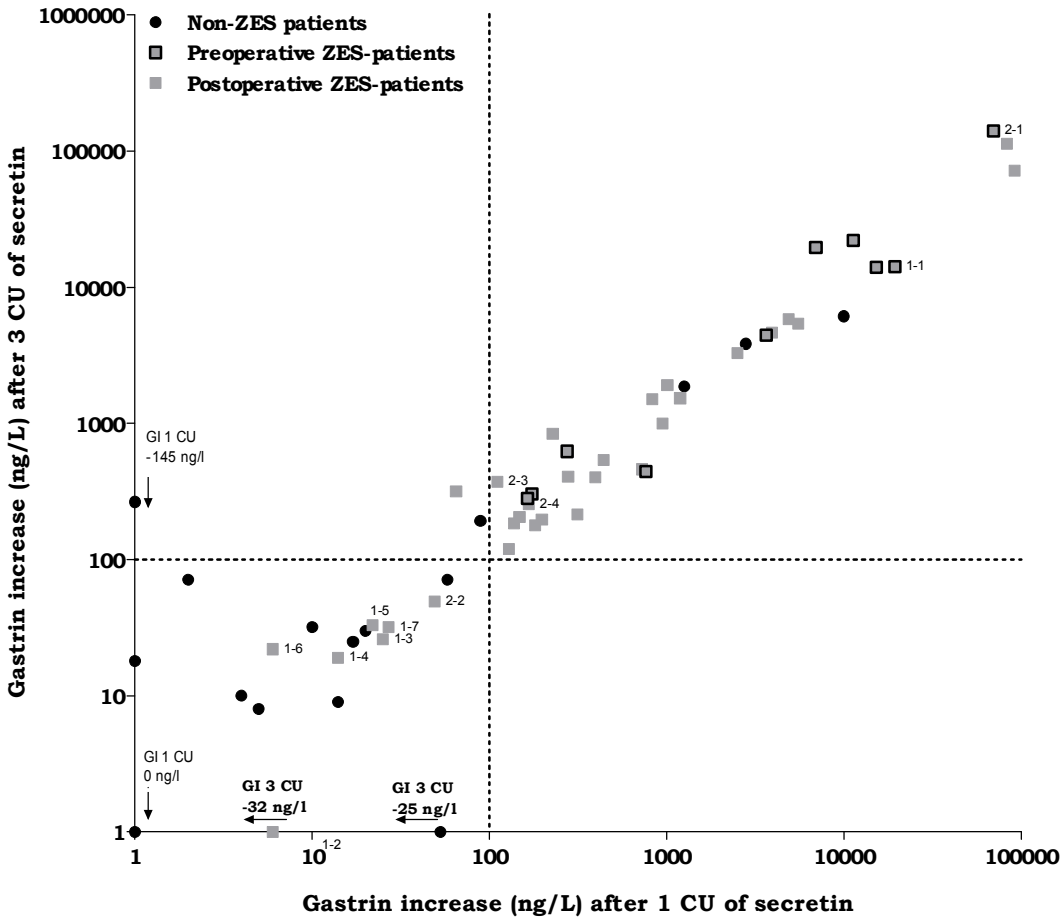

Figure 1. Gastrin increase levels after the use of 0.26 µg/kg of secretin are plotted against gastrin increase levels after the use of 0.78 µg/kg of secretin. A logarithmic scale is used. Arrows indicate gastrin increase levels of values which would originally fall outside the graph, therefore exact values are mentioned above the arrows. Numbers next to individual points represent 2 patients with an exceptional disease course; 1-1 till 1-7 represent a patient with normal postoperative serum gastrin levels without any symptoms or signs of recurrence; 2-1 till 2-5 represent a patient with initially normal but thereafter increased postoperative serum gastrin levels, while tumour recurrence could not be confirmed on imaging studies.

Effect of the use of 0.78 µg/kg on ZES patients with normal fasting serum gastrin levels

To assess whether the use of 0.78 µg/kg of secretin is more contributory to diagnose ZES in patients with normal FSG concentrations (<100 ng/L), this group of ZES patients was analyzed separately (Figure 2a and b). In total, 12 tests of four patients after resection were examined. A Chi-square analysis revealed no significant difference between groups, as the use of 0.78 µg/kg led to an almost equal number of true positive tests (6/12 vs. 5/11, Figures 2b and 2a, respectively) as the use of 0.26 µg/kg in the secretin stimulation test when a cut-off for gastrin increase of 100 ng/L was used. Thus, when gastrin increase are <100 ng/L or

when FSG levels are >100 ng/L, the diagnosis remains uncertain but in the case of normal FSG levels <100 ng/L) in combination with a gastrin increase >100 ng/L, the diagnosis of ZES is highly likely.

Figure 2a.

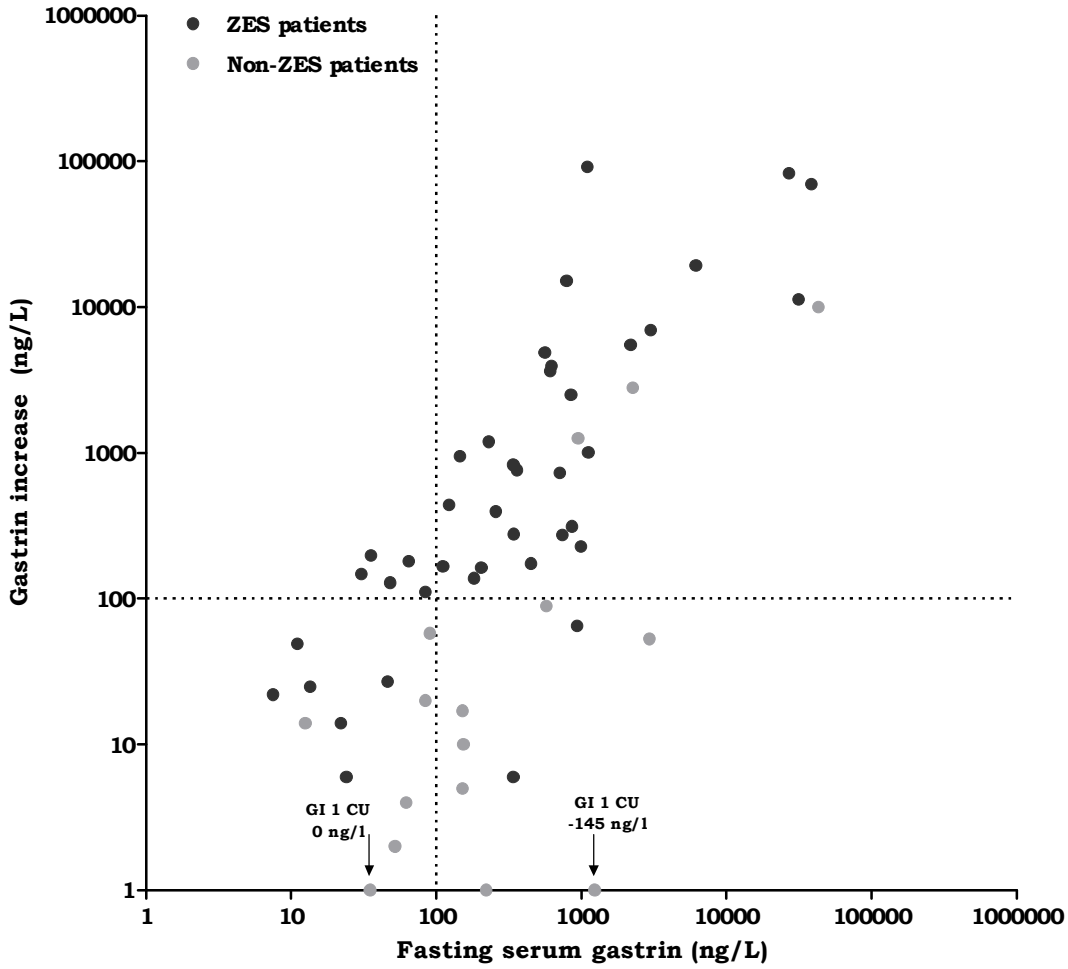

Figure 2b.

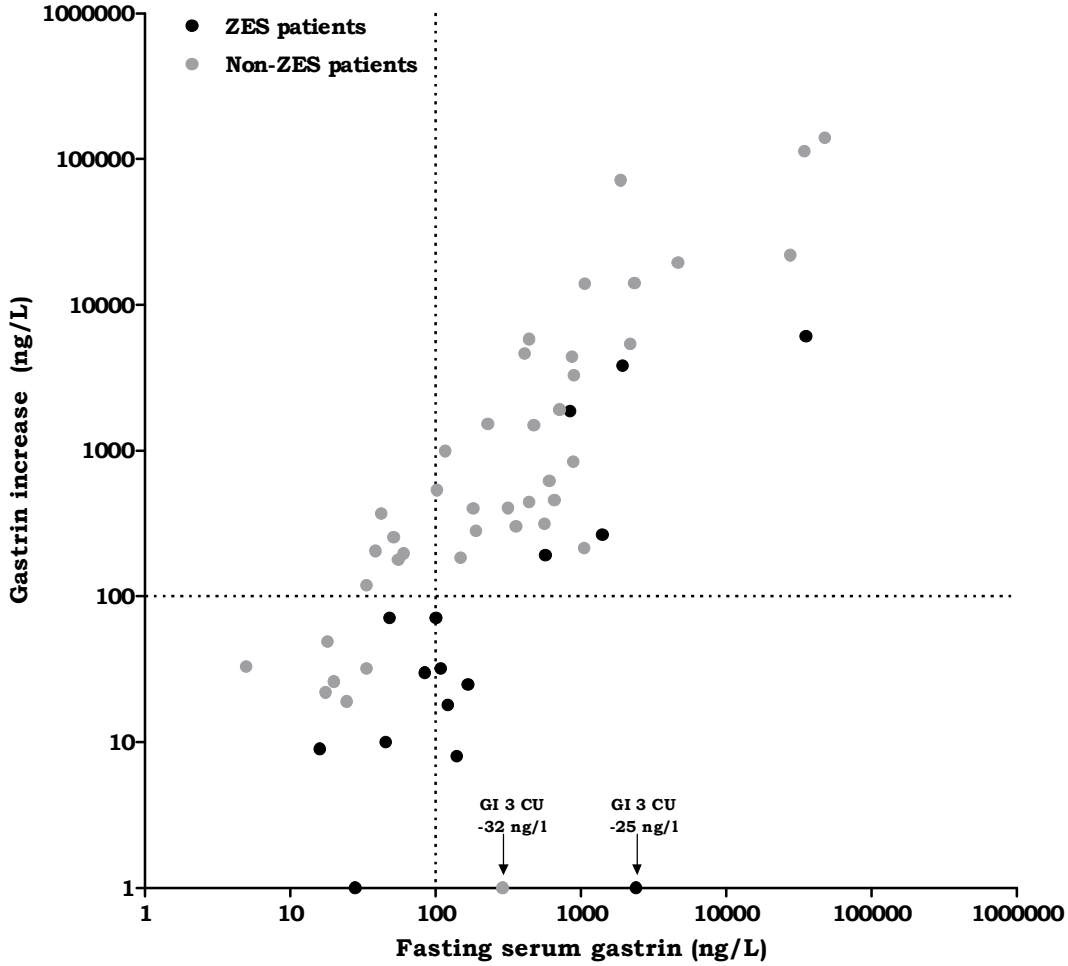

Figure 2a,b. Fasting serum gastrin levels are plotted against gastrin increase after stimulation with a low (0.26 µg/kg, 2a.) or high (0.78 µg/kg, 2b.) secretin dose are presented. A logarithmic scale is used. Arrows indicate gastrin increase levels of values which will originally fall outside the graph, therefore exact values are mentioned above the arrows.

Validation study

Based on the results described above, we concluded that an absolute gastrin increase >100 ng/L leads to the highest sensitivity and specificity in the study group. Therefore, this criterion was validated in 60 patients suspected of ZES, by performing 98 secretin stimulation tests using 0.26 µg/kg of secretin. Using the criterion of a gastrin increase of >100 ng/L for a positive test, 35/42 tests of 39 non-ZES controls were indeed negative, while 45/56 tests of 21 ZES patients were truly positive. This led to a sensitivity of 80.3% and specificity of 83.3%, comparable to the sensitivity and specificity of the initial study cohort (80.5% and 81.3%, respectively).

Discussion

Hypergastrinemia is a common characteristic of the Zollinger-Ellison syndrome, although the extent of hypergastrinemia can differ considerably between patients. Furthermore, the use of acid suppressing medications may delay the diagnosis of ZES, by masking the symptoms in ZES patients or mimic ZES by causing hypergastrinemia in patients without ZES. Therefore, FSG levels alone are not conclusive in a considerable number of ZES patients. Particularly, in case of mild to moderate hypergastrinemia (100 – 1,000 ng/L), additional diagnostics are required to confirm or exclude the diagnosis of ZES[3]. The secretin stimulation test is preferred above the calcium or meal stimulation tests, as the secretin stimulation test is more sensitive, easy to perform and less inconvenient for patients[14]. However, several aspects of the secretin stimulation test have been disputed, e.g., the criterion for a positive test and the dose of secretin to be used. In most previous publications, serum gastrin responses to secretin of > 200 ng/L, introduced by McGuigan and Wolfe, are used as the criterion for a positive secretin stimulation test[10]. Recently, Berna *et al.* studied the secretin stimulation test in 293 patients and 537 patients from the literature, and recommended to use a gastrin increase of 120 ng/L[4,5]. We investigated the most optimal criterion (sensitivity) for a positive test to diagnose ZES in our study group and not the best criterion to exclude the disease in other patients and controls (specificity). By both sensitivity/specificity determinations and ROC analysis we found a post-secretin gastrin elevation of >100 ng/L to be the most optimal discriminating value between ZES and non-ZES patients. Applying this criterion in a validation cohort of 21 ZES patients and 39 non-ZES controls led to a similar sensitivity and specificity for this criterion and confirmed the initial findings.

As also the most optimal dose of secretin has been disputed, we investigated whether a higher dose of secretin would lead to more sensitive and specific tests, by subjecting ZES patients and non-ZES controls to sequential secretin stimulation tests using both a low and a high dose of secretin. Comparison-studies for secretin doses have been reported before, but, except for a case report in which two doses of secretin were compared in one patient, these have all been based on the

comparison with patients from literature and were not performed in the same subjects[8]. Although the number of included patients in this study is relatively low, this is the first study in which Zollinger-Ellison patients and non-ZES patients are subjected to multiple secretin stimulation tests with different doses, making this an intra-individual comparison. We found that the use of 0.78 µg/kg of secretin provokes a higher post-secretin serum gastrin increase, resulting in a higher number of true-positive ZES patients but also in a higher number of false-positives, leading to a higher sensitivity but a decrease in specificity, compared to the use of 0.26 µg/kg of secretin. Therefore, we concluded that a higher dose of secretin did not contribute to a better discrimination between ZES patients and non-ZES controls in secretin stimulation tests. In general, a relatively small group of Zollinger-Ellison patients have FSG levels in the normal range (<100 ng/L), often after gastrinoma excision, and are therefore hardly recognized as (recurrent) ZES. In the present study, patients suffering from ZES having normal FSG levels (<100 ng/L), had no diagnostic benefit from the use of a higher secretin dose in the secretin stimulation test. Hence, the use of 0.26 µg/kg of secretin seems to be appropriate. From a financial point of view, the use of a low dose of secretin is preferential, as a three times higher dose leads to higher costs, but does not contribute to a more valuable secretin stimulation test.

It is generally known that the use of PPIs or other acid suppressing medications can lead to elevated fasting serum gastrin levels, and therefore might falsely suggest ZES. Indeed, Hirschowitz *et al.* have shown that longterm use of PPIs in non-ZES-patients increases FSG-levels but does not lead to a further gastrin increase in the ZES patients[15]. In addition, a recent case report by Goldman *et al.*, suggests that the use of a PPI can also lead to a false positive secretin stimulation test resulting in diagnosing ZES in non-ZES controls[16]. In our study, however, 39% (7/18) of the PPI-using non-ZES controls, with a FSG level of >100 ng/L, had a false positive secretin stimulation test, as opposed to 30% (3/10) of those free of acid-suppressing medication. These findings illustrate that there is no direct relation between PPI use and a false positive secretin stimulation test. Therefore,

we believe that it is not necessary to discontinue acid-reducing medications for the secretin stimulation test, also to reduce the risk of developing ulcer complications.

In conclusion, we found that a gastrin increase after stimulation with secretin of >100 ng/L leads to the highest sensitivity and specificity to diagnose ZES. Applying this criterion in our study revealed that the use of a higher dose of secretin did not contribute to a more valuable secretin stimulation test in diagnosing ZES. Therefore, we recommend the use of 0.26 µg/kg of secretin in secretin stimulation tests to diagnose or exclude ZES, with a gastrin increase >100 ng/L as the optimal criterion for a positive secretin stimulation test.

References

1. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann Surg* 1955;142:709-728.
2. Jensen RT. Consequences of long-term proton pump blockade: insights from studies of patients with gastrinomas. *Basic Clin Pharmacol Toxicol* 2006;98:4-19.
3. Murugesan SV, Varro A, Pritchard DM. Review article: Strategies to determine whether hypergastrinaemia is due to Zollinger-Ellison syndrome rather than a more common benign cause. *Aliment Pharmacol Ther* 2009;29:1055-1068.
4. Berna MJ, Hoffmann KM, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. *Medicine (Baltimore)* 2006;85:295-330.
5. Berna MJ, Hoffmann KM, Long SH, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. Evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine (Baltimore)* 2006;85:331-364.
6. Malagelada JR, Glanzman SL, Go VL. Laboratory diagnosis of gastrinoma. II: A prospective study of gastrin challenge tests. *Mayo Clin Proc* 1982;57:219-226.
7. Matsui T, Iida M, Nanbu T, Kohrogi N. A study of secretin dosage of secretin provocation test in the Zollinger-Ellison syndrome. *Nippon Shokakibyo Gakkai Zasshi* 1985;82:288-295.
8. Yamamoto C, Aoyagi K, Iwata K, Morita I, Hotekezaka M, Funakoshi S, Sakamoto K, Iida M, Sakisaka S.. Double doses of secretin contribute to diagnosis of Zollinger-Ellison syndrome in secretin and selective arterial secretion injection tests – a case report. *Dig Dis Sci* 2005;50:2034-2036.

9. Mignon M, Rigaud D, Cambray S, Chayvialle JA, Accary JP, René E, Vatier J, Bonfils S. A comparative evaluation of secretin bolus and secretin infusion as secretin provocation tests in the Zollinger-Ellison syndrome. *Scand J Gastroenterol* 1985;20:791-797.
10. McGuigan JE, Wolfe MM. Secretin injection test in the diagnosis of gastrinoma. *Gastroenterology* 1980;79:1324-1331.
11. Lamers CB. Clinical usefulness of the secretin provocation test. *J Clin Gastroenterol* 1981;3:255-259.
12. Deveney CW, Deveney KS, Jaffe BM, Jones RS, Way LW. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison syndrome). *Ann Intern Med* 1977;87:680-686.
13. Lamers CB, van Tongeren JH. Comparative study of the value of calcium, secretin, and meal stimulated increase in serum gastrin in the diagnosis of the Zollinger-Ellison syndrome. *Gut* 1977;18:128-135.
14. Modlin IM, Jaffe BM, Sank A, Albert D. The early diagnosis of gastrinoma. *Ann Surg* 1982;196:512-517.
15. Hirschowitz BI, Simmons J, Mohnen J. Long-term lansoprazole control of gastric acid and pepsin secretion in ZE and non-ZE hypersecretors: a prospective 10-year study. *Aliment Pharmacol Ther* 2001;15:1795-1806.
16. Goldman JA, Blanton WP, Hay DW, Wolfe MM. False-positive secretin stimulation test for gastrinoma associated with the use of proton pump inhibitor therapy. *Clin Gastroenterol Hepatol* 2009;7:600-602.