World J. Surg. 26, 1291–1296, 2002
DOI: 10.1007/s00268-002-6528-9

WORLD
Journal of
SURGERY

Intravenous Calcium Injection Test Is a Novel Complementary Procedure in Differential Diagnosis for Gastrinoma

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Published Online: September 4, 2002

Abstract. The current study evaluated efficacy of the intravenous calcium injection test as a new diagnostic approach to clarify the existence of gastrinoma, which often goes undetected with routine testing. Twenty-six patients with hypergastrinemia were studied. For the calcium injection test, blood samples were taken from 12 patients with hypergastrinemia (HG), and three healthy volunteers, and one patient with nonfunctioning endocrine tumor in the pancreas (control). We compared results of the calcium injection test with those of the secretin test and the selective arterial secretagogue injection (SASI) test. The SASI test with secretin was performed in 24 of 26 patients with hypergastrinemia, including 22 of 24 patients with Zollinger-Ellison syndrome (ZES). Accuracy in the diagnosis of tumor localization by the SASI test was 95% (21 of 22) in ZES patients. The secretin test was negative in 3 of 21 patients with ZES (14%). Either the secretin test or the SASI test was positive in 22 of 23 patients (96%). The calcium injection test was administered to 12 patients in the HG group and 4 controls. The HG group showed significantly higher serum gastrin levels than those of the control group in the calcium injection test. Eight of 10 ZES patients (80%) had a positive calcium injection test. We could diagnose gastrinomas in 100% of ZES patients by either the calcium injection test or the secretin test. We have thus confirmed the efficacy of the intravenous calcium injection test in the diagnosis of gastrinoma. The calcium injection test could become an adjunct in the diagnosis of gastrinoma, which often goes undetected with routine testing.

Gastrinoma is a rare tumor that usually arises in the pancreas and the duodenum. In the last 2 decades, total gastrectomy has usually been undertaken in patients with Zollinger-Ellison syndrome (ZES). As the number of patients who have undergone curative operation for duodenal or pancreatic gastrinomas has recently increased, we recognize that even microgastrinomas causing severe peptic ulcers are potentially malignant and may have metastasized to the regional lymph nodes and the liver [1–8]. The appropriate surgical therapy of gastrinoma is still controversial. Eighty percent of ZES patients have a duodenal gastrinoma and 20% to 30% have a pancreatic tumor. Recent studies suggest that gastrinoma enucleation combined with duodenotomy rarely results in cure. Aggressive surgery (Whipple's operation) can result in cure of gastrinoma, but the effect on survival remains unknown. There are important differences in gastrinoma location, extent, and percentage with aggressive disease between patients with and without multiple endocrine neoplasia type I (MEN-1) syndrome. Early resection of gastrinomas is a better therapeutic strategy than nonsurgical treatment in patients without distant metastasis. Therefore, diagnosis of gastrinoma must be firmly established preoperatively.

Angiography is one of the most widely used techniques for visualizing neuroendocrine tumors because they are often detected as hypervascular tumors. The sensitivity and specificity of angiography are not very high, however, in fact they are lower than 80% of trials. Computed tomography (CT) and magnetic resonance imaging (MRI) can sometimes visualize an endocrine tumor as a hypervascular tumor surrounding a pancreatoduodenal lesion, but their specificity and sensitivity also are not high: lower than 70% in pancreatic tumors. Even endoscopic ultrasonography, which is useful for diagnosing insulinoma, is not good for visualizing gastrinomas, especially those that occur in the pancreatic uncus and tail. In diagnosis or localization of endocrine tumors, therefore, we emphasize the usefulness of provocative tests using secretagogues. We have devised the selective arterial secretagogue injection (SASI) test using secretin (Imamura test) [9, 10] to determine localization of endocrine tumors by identifying the feeding artery for those tumors. Just as we have established a method to detect gastrinomas with the SASI test by using secretin as a secretagogue. Doppman and colleagues and we have also developed a SASI test using calcium as a secretagogue, the so-called SACI test, to localize insulinoma [11, 12]. We are able to determine the area and the extent of the resection required, based on the SASI test, regardless of whether any tumor has been previously visualized by preoperative imaging techniques. Since the early 1990s these tests have been used in diagnosis and localization of endocrine tumors because they are the most sensitive and reliable methods available.

We recently encountered a patient with negative secretin provocative tests including the secretin injection test and the SASI test. Although the secretin injection test is the principal study in the diagnosis of ZES, it is negative in up to 20% of patients with proven gastrinoma. Gibril and associates reported that the combination of the secretin test with the SASI test is useful for the

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diagnosis of gastrinoma, and that accuracy is approximately 99% in their experience [13]. Furthermore, the SASI test was negative in 11% (9 of 80) of patients with ZES and positive in 92% (12 of 13) of those with a negative secretin injection test. It is important to realize that some patients have no response to secretin stimulation; therefore, a different modality has been required to detect precise localization of gastrinoma. In this study, we examine whether a novel calcium injection test could become a useful adjunct in the differential diagnosis of gastrinoma.

Patients and Methods

Differential diagnostic test results were examined in the following patients: 26 patients (16 men and 10 women; age: 21 to 77 years, mean 51.4 years) who were referred to the Department of Surgery, Kyoto University Hospital, with hypergastrinemia or a diagnosis of possible gastrinoma. These patients were found to fit the criteria outlined below for that diagnosis. A patient with nonfunctioning neuroendocrine tumor (NNET) and three healthy volunteers were also examined in this study from November 1991 to July 2001. The criteria for the diagnosis of gastrinoma used in these patients included elevated fasting serum gastrin concentrations ($>$ 300 pg/ml; normal, $<$ 150 pg/ml), patterns typical in gastrinoma of the 24-hour pH monitoring test (pH 4 with a holding time higher than 90% at the antrum), or a histologically confirmed diagnosis of gastrinoma. These patients included 24 with ZES including 6 patients with MEN-I and 2 with pseudo-ZES, that is, antral G-cell hyperfunction.

Selective Arterial Secretagogue Injection (SASI) Test (Imamura test)

We are able to determine the area and the extent of the resection required based on the SASI test by using secretin as a secretagogue. In brief, 30 units of secretin (Secrepan, Eizai, Tokyo) is rapidly injected into an artery feeding the pancreas, for example, the gastroduodenal artery (GDA), the splenic artery (SpA), or the superior mesenteric artery (SMA); the hepatic artery (HA) is used for metastatic liver tumors. Venous blood sampling from the right or left hepatic vein is undertaken before and 20, 40, 60, 90, and 120 seconds after secretin injection. Serum levels of gastrin (IRG) are measured by radioimmunoassay. In each arterial trial the results are considered positive when the maximum increase of serum IRG is higher than 80 pg/ml greater than 20% above the basal serum IRG at 40 seconds after secretin injection [9].

Intravenous Secretin Injection Test

The intravenous secretin injection test (secretin test) has commonly been employed in the differential diagnosis of gastrinoma. In our department, 3 U/kg of secretin (Secrepan) is rapidly injected into a peripheral vein, and blood samples before and at 2-minute intervals up to 10 minutes are taken for measurement of IRG. The test is considered positive when IRG gradients are higher than 80 pg/ml and greater than 20% above the basal IRG at the maximum.

Intravenous Calcium Injection Test

To verify the efficacy of the intravenous calcium test, we have examined in 12 patients with ZES and 4 controls. Calcium gluconate (Ca, Calcicol, Dainippon Co., Tokyo) 255 mg/3 ml was injected intravenously for 30 seconds. Similar to the secretin test, venous blood sampling is performed before and at 2-minute intervals up to 10 minutes after calcium injection.

Statistical Analysis

Results are expressed as mean ± SEM. According to the distribution of the data, normal or non-normal distribution differences between groups and within each group were assessed with the Mann-Whitney U test, the χ^2 test (Fisher exact probability test), or repeated measures of one-way analysis of variance, followed by Fisher's protected least significant difference.

Results

Twenty-four patients with ZES including 6 patients with MEN-I syndrome and 2 patients with pseudo-ZES were studied by differential diagnostic tests for gastrinoma. Clinical and biochemical characteristics for the 26 study patients are summarized in Table 1. There were 16 men and 10 women ranging in age from 21 to 77 years (mean ± SEM, 52.2 ± 2.4 years). Fasting serum gastrin levels, measured in all patients, ranged from 140 to 58,000 pg/ml (mean ± SEM, 4593 ± 2320 pg/ml). Because serum calcium concentrations could affect the results of the provocative tests, we also measured serum calcium levels before each examination. In the 6 patients with MEN-I syndrome, one patient had already undergone parathyroidectomy and 2 patients had hyperparathyroidism and showed high serum calcium levels, with a range of 8.9 to 11.3 mg/ml. Antral G-cell hyperfunction was excluded by the absence of an exaggerated postprandial increase in serum gastrin levels and by a low percentage (lower than 70%) of the pH4 holding time as studied by 24-hours pH monitoring.

In considering the significance of provocative tests, it is important to note that both the calcium injection test and the secretin injection test represent diagnostic tests, whereas the SASI test represents a localization test. At first, we compared the results of the SASI test with secretin to those of the secretin injection test in 24 patients with ZES. The SASI test with secretin was performed in 24 of the 26 patients with hypergastrinemia and in 22 of the 24 patients with ZES. Accuracy in tumor localization by the SASI test was 95% (21 of 22 patients with ZES). Among the 24 ZES patients, two patients who were not given the SASI test in our hospital had had a positive SASI test in another hospital. The result of the SASI test was negative in only one patient who had multiple liver metastases and a vertebral bone metastasis in Th7. The SASI test was found to be positive in the GDA in 9 patients, the proper hepatic artery (PHA) in 3 patients, the right hepatic artery (RHA) in 1 patient, the inferior pancreatoduodenal artery (IPDA) in one patient, both the GDA and SMA in 5 patients, the PHA and SMA in 1 patient, and the GDA and SpA in 1 patient. Interestingly, 2 patients with G-cell hyperfunction responded positively to the SASI test by arterial secretin injection into the right gastroepiploic artery (RGEA).

The intravenous secretin injection test was performed in 23 of 26 patients with hypergastrinemia. The results were negative in 3

Table 1. Clinical and biochemical characteristics of study patients with hypergastrinemia.

Patient no.	Age and sex	MEN-I	Gastrin (pg/ml)	Secretin test	SASI test	Calcium test	Serum calcium (mg/ml)	24h pH monitor (%)	Diagnosis
1	39F	+	2900	+	GDA	np	nm	np	G
2	49M	+	580	+	GDA, SMA	np	nm	np	G
3	61F	+	394	+	GDA	np	7.3–8.6	99	G
4	51F	+	566	+	SMA, GDA	+	9.4	99	G
5	48M	+	2920	+	SMA, PHA	+	10.7–11.3	np	G
6	43F	+	811	+	GDA	+	8.9–10.0	np	G
7	21M	−	593	+	GDA	np	8.9–9.7	93.7	G
8	61F	−	1070	np	PHA	np	8.4–9.3	90.2	G
9	65M	−	9780	np	np	np	9.0–9.1	np	G
10	58F	−	420	+	GDA	np	8.6–9.4	np	G
11	62M	−	455	+	SpA, GDA	np	9.1–10.1	np	G
12	77M	−	2220	+	np	np	8.6–8.9	np	G
13	46M	−	140	+	GDA	np	8.6–9.1	np	G
14	45M	−	6370	+	GDA, SMA	+	8.6–9.1	99	G
15	57M	−	353	+	PHA	+	8.5–9.2	np	G
16	30M	−	58,000	−	PHA	+	8.2–8.4	93	G
17	56M	−	1680	−	?	+	8.8–9.0	99	G
18	56M	−	1480	+	RHA	−	8.6	np	G
19	47F	−	19,000	+	GDA, SMA	−	8.0–8.5	99	G
20	65M	−	1410	+	IPDA	np	8.5–9.2	99	G
21	59F	−	702	−	GDA	np	8.6–9.1	np	G
22	54F	−	560	+	GDA	+	8.7–9.1	100	G
23	44M	−	1200	+	GDA, SMA	np	8.8–9.7	np	G
24	44M	−	443	np	GDA	np	8.6–9.3	np	G
25	51M	−	1070	−	RGEA	+	8.6–9.0	53	G-C H
26	68F	−	4100	−	RGEA	−	9.3–10.6	67	G-C H

MEN-I: multiple endocrine neoplasia-I syndrome; SASI test: selective arterial secretagogue injection test; GDA: gastroduodenal artery; SMA: supramesenteric artery; PHA: proper hepatic artery; IPDA: inferior pancreatoduodenal artery; RGEA: right gastroepiploic artery; np: not performed; nm: not measured; G: gastrinoma; G-C H: G-cell hyperfunction; RHA: right hepatic artery; SpA: splenic artery.

Table 2. Results of the secretin test.

	Secretin test			
	Positive	Negative	Total	
ZES	18	3 (14%)	21	$p=0.006$
P-ZES	0	2	2	
Total	18	5	23	

ZES: Zollinger-Ellison syndrome; P-ZES: pseudo Zollinger-Ellison syndrome.

Table 3. Diagnostic criteria of gastrinoma in the intravenous calcium injection test.

Criteria for a positive test
Serum gastrin gradients are increased more than 20% at any time point 2, 4, or 6 minutes after intravenous calcium injection
Serum gastrin levels are more than 300 pg/ml

of 21 (14%) patients with ZES; 18 of the 21 (86%) patients had a positive test. These results were similar to those of previous reports [13]. Of the 3 patients with a negative secretin test, 2 had a positive SASI test. Two patients with pseudo-ZES (G-cell hyperfunction) had a negative secretin test. Thus there was a significant difference in the results of the secretin test between ZES patients and pseudo-ZES patients by the Mann-Whitney U test ($p = 0.006$) (Table 2). Either the secretin test or the SASI test was positive in 22 of 23 (96%) patients, and only one patient had negative results in both tests.

The intravenous calcium injection test was administered to 12 patients with hypergastrinemia (10 ZES patients and 2 pseudo-ZES patients) and to 3 healthy volunteers and one patient with NNET, who were referred to our department from April 2000 to July 2001. The side effects of rapid calcium injection were not serious. Two patients reported slight burning in the chest and another experienced systemic hotness and heart palpitations. Serious symptom like arrhythmia or tachycardia were not observed. The mean ± SEM of increased serum gastrin gradients in the hypergastrinemia (HG) group was 24.5 ± 4.6% 2 minutes after calcium injection, whereas the mean ± SEM of increased serum gastrin gradients in the control group was −4.7 ± 3.7% 2 minutes after calcium injection. Serum gastrin gradients increased over 11% of basal gastrin levels after calcium injection in all patients with ZES. We therefore proposed the criteria for a positive calcium test result as summarized in Table 3. In short, like the secretin test, serum gastrin gradients showed a greater than 20% increase above baseline at any time point 2, 4, or 6 minutes after intravenous calcium injection, and the serum gastrin levels were higher than 300 pg/ml. We compared the results of patients in the HG group with those of three healthy volunteers and one patient with NNET (the control group) (Fig. 1). There was a significant difference between the HG group and the control group in the results of the calcium test by repeated measures one-way analysis of variance (ANOVA) ($p = 0.0185$, Fisher's protected least significant difference). Values in the HG group at each time point after calcium injection increased significantly more than those in the control group. Percentage of serum gastrin levels as compared with the baseline (%IRG) in the HG group was 120 ± 4.3% 2 minutes after calcium stimulation, 124.5 ± 4.6% at 4 minutes, 120.9 ± 8.7% at 6 minutes; at the same time points %IRG in the

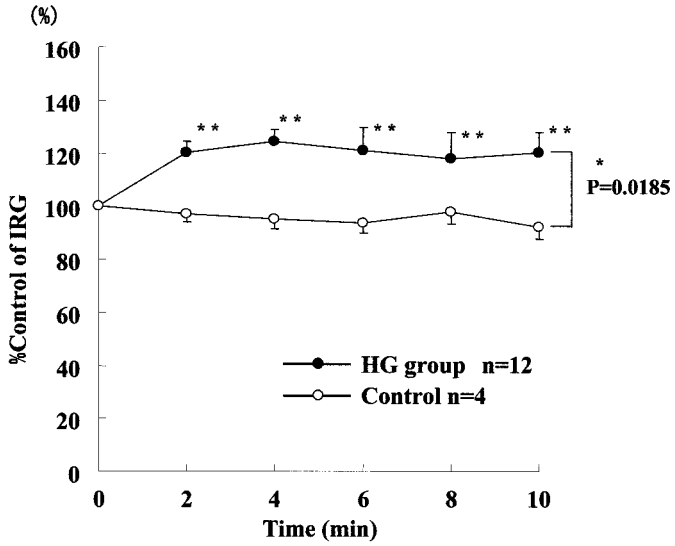

Fig. 1. Results of the intravenous calcium injection test in patients with hypergastrinemia (HG group, $n = 12$) and in the control group (1 patient with nonfunctioning endocrine tumor and 3 healthy volunteers). Gastrin release responds significantly to calcium application in patients with hypergastrinemia as compared with controls. In the HG group, calcium stimulation effects a greater than 20% increase over baseline (control group) at each time point up to 10 minutes. Values are expressed as mean ± SEM. $^{*}p < 0.05$ vs. control at all time points by repeated measure one-way analysis of variance (ANOVA), $^{**}p < 0.05$ vs. control at corresponding time point by Fisher's protected least significant difference. IRG: immunoradio-level of gastrin.

Table 4. Results of the intravenous calcium injection test in patients with hypergastrinemia and in the control group.

	Calcium test			
	Positive	Negative	Total	
ZES	8	2(20%)	10	$p=0.015$
P-ZES	1	1	2	
NNET	0	1	1	
Healthy volunteers	0	3	3	

NNET: nonfunctioning neuroendocrine tumor.

control group was 97.1 ± 3.1%, 95.3 ± 3.3% and 93.8 ± 3.8%, respectively. Eight of 10 (80%) patients with ZES had a positive calcium test, and 2 of 10 (20%) patients had a negative calcium test. One of the two patients that we judged to have a negative calcium test, was undergoing chemotherapy by transarterial infusion of anticancer drugs; the other did not have a pattern typical of the calcium injection test. In fact, the serum gastrin gradients increased biphasically and reached the maximum 10 minutes after calcium injection. This patient had multiple lymph node metastases. One of 2 patients with G-cell hyperfunction had a positive calcium test and another patient had a negative test. All patients in the control group had negative calcium tests. As compared with results in the control group, the ZES group had a significantly high rate of calcium test positivity by χ^2 test (Fisher exact probability test; $p = 0.015$; Table 4). Thus, when compared with the result of the secretin test in the ZES patients, the calcium test showed the same sensitivity (80%). Moreover, by using the secretin test in combination with the calcium test, we were able to

Table 5. Comparison of results of the secretin test with those of the calcium injection test in ZES.

	Calcium injection test	
	Positive	Negative
Secretin provocation test		
Positive	6	2
Negative	2	0

diagnose gastrinomas in 100% of the ZES patients (Table 5). Only one patient with negative secretin and SASI tests had a positive calcium test (Fig. 2). This was the same patient who had multiple liver metastases and a bone metastasis confirmed by needle biopsy and pentetreotide scintigraphy. Serum gastrin was suppressed by secretin administration in the secretin test. We repeated the SASI test in this patient, but we could not determine the localization of tumors. Therefore, the calcium test and the SASI test with calcium as the secretagogue (SACI test) were tried. The serum gastrin level quickly responded to both the intravenous injection of calcium and the arterial injection of calcium. We performed the SACI test in another 2 patients with ZES, and both had a positive result.

Discussion

Calcium is well known to be a potent stimulant of several hormones secreted by gastroenteropancreatic endocrine tumors. The diagnostic usefulness of the calcium infusion test has been evaluated extensively in ZES [14–16]. Deveney et al. preferred a secretin provocative test in screening for gastrinoma because they found it to be quicker and more reliable than a calcium infusion test [16]. In contrast, Vezzadini et al. recommended the calcium infusion test, because they had positive calcium infusion tests in 3 of 4 patients with ZES in whom the response to secretin injection was false negative [14]. Likewise, we have found the calcium injection test to be more useful than any of the other diagnostic procedures. In this study, two ZES patients showed false-negative calcium injection tests because they had already received some treatments in other hospitals. We therefore speculated that all patients with primary gastrinoma would respond to the calcium injection test.

Because the serum calcium level could affect the results of the provocative test, we measured the serum calcium concentration before each examination. We found no correlation between serum calcium and the provocative tests. We recently examined the distribution of calcium-sensing receptor (CaR) in three kinds of duodenal-pancreatic endocrine tumors including insulinoma, glucagonoma, and gastrinoma [17–19], and another investigator has reported the presence of CaR mRNA and protein in gastrinoma [20]. In most tissues studied to date, the primary role of the CaR is to control extracellular Ca^{2+} homeostasis. However, the function of the CaR in gastrinoma cells remains unclear. The presence of the CaR in antral gastrin-producing cells has provided yet another function for this receptor [21]. This report included the observation that increased Ca^{2+} concentrations led to increased gastrin release from antral gastrin-producing cells, and it provides evidence for mediation of the secretory function of Ca^{2+} on endocrine tumor cells. It is well known that increased extracellular Ca^{2+} elicits insulin secretion from insulinoma cells, and this effect

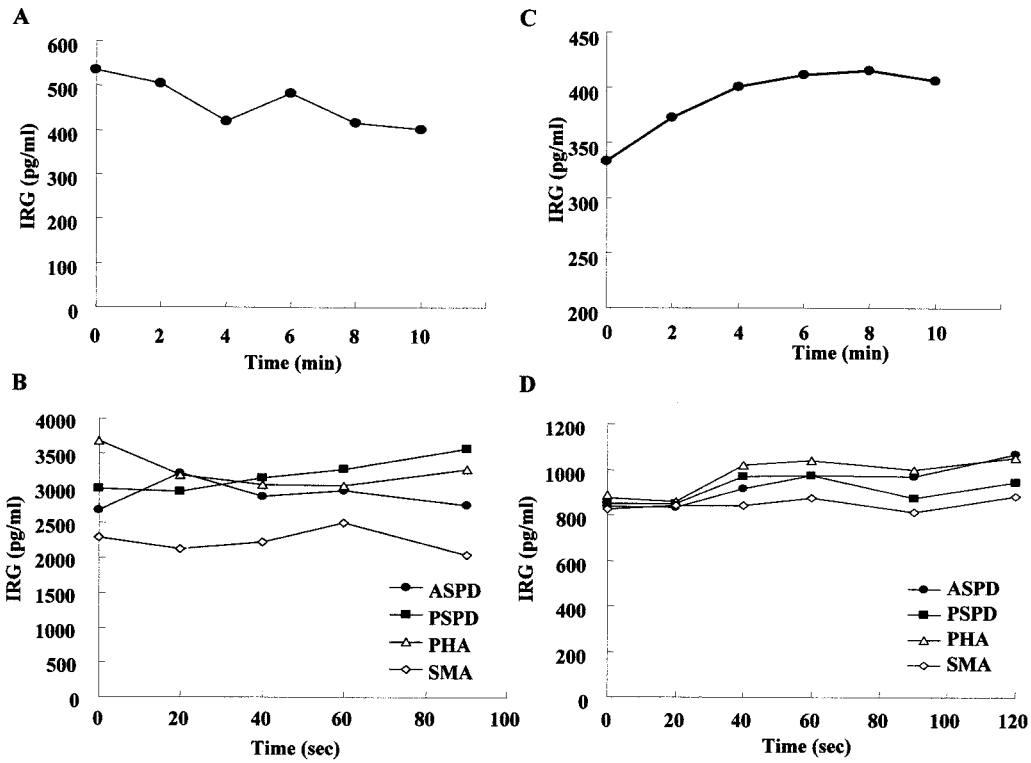

Fig. 2. A typical patient with both a negative secretin test and a negative selective arterial secretagogue injection (SASI) test. **A.** A negative secretin test. Gastrin release is inhibited 4 minutes after intravenous secretin stimulation. This test is diagnosed as negative. **B.** A negative SASI test. Secretin is injected into the pancreatic feeding arteries: anterior suprapancreatoduodenal artery (ASPD), posterior suprapancreatoduodenal artery (PSPD), proper hepatic artery (PHA), superior mesenteric artery (SMA). Blood samples are then obtained from the right hepatic vein. Gastrin increase does not reach 20% of basal levels of gastrin for each artery, and this test is diagnosed as negative. **C.** A positive intravenous calcium injection test. Gastrin increase reaches more than 80 pg/ml and about 22% of basal level at the maximum. **D.** SASI test stimulated by calcium injection. With the proper hepatic artery as the feeding artery, secretin stimulation of gastrin release satisfies the diagnostic criteria. This test suggests that gastrinomas exist in liver.

has been used in clinical localization procedures [11]. As extracellular Ca^{2+} application can similarly provoke a huge gastrin release in gastrinoma patients, it might be proposed that this gastrin secretion is at least partially dependent on the function of the CaR.

Recently, we have encountered one ZES patient who had a negative secretin test and a negative SASI test. Two years earlier this patient had distal pancreatectomy for removal of a giant gastrinoma on the pancreatic tail and now had recurrence of gastrinoma as multiple liver metastases and a vertebral bone metastasis. It should be noted that diagnosis and localization of suspected gastrinoma in ZES patients with suggestive clinical features must be clarified with a fair degree of certainty. To this end, we have preliminary investigated efficacy of the intravenous calcium injection test in ZES patients. In this study we sought to determine if the intravenous calcium injection test is a useful adjunct in the diagnosis of gastrinoma in patients with hypergastrinemia. Using the calcium test in combination with the secretin test, we were able to diagnose gastrinoma in 100% of patients with ZES. In a patient with negative secretin test and/or negative SASI test, localization of gastrinomas could be clarified with the SASI test with calcium stimulation (the SACI test). In recent years, we recommended the secretin stimulation test as primary in the diagnosis of gastrinoma. In patients with a negative secretin test, we then employed the calcium injection test. Where secretin is not easily obtained, we recommend use of the calcium injection test. Moreover, to localize gastrinomas, especially in local recurrent cases after operation or in patients with multiple metastases, the SACI test should be used before the SASI test.

In 1972, Isenberg et al. first reported that infusion of secretin solution elicits an increase of both serum calcium levels and serum gastrin levels (IRG) [22]. At first, they speculated that secretin stimulation of IRG was indirectly regulated by the increase in serum calcium levels; that is, secretin administration might bring about the upregulation of parathyroid function. A number of studies have demonstrated that serum calcium levels could affect the biological behavior of neuroendocrine tumors, including insulinoma, gastrinoma, and somatostatinoma [14, 23, 24].

Like the secretin test, intravenous administration of calcium has been advocated as a provocative test for the diagnosis of gastrinoma. It has also been recognized that calcium infusion can evoke greater increases in serum gastrin levels in patients with ZES [25, 26]. Jansen and Lamers also demonstrated that an increase in serum gastrin after calcium infusion is not specific for ZES [15]. Our current results are in agreement, showing that infusion of calcium into a patient with hypergastrinemia caused by idiopathic antral G-cell hyperfunction led to large increases in IRG [15]. Indeed, one of two patients with pseudo-ZES showed a positive

response to the calcium injection test. As Goebel et al. [20] and we have reported, more than 80% of gastrinomas express the calcium-sensing receptor (CaR) on the cell surface. We can speculate that CaR might be much involved in the calcium-triggered gastrin release in gastrinoma cells and in G-cell hyperplasia.

Résumé. Cette étude évalue l'efficacité du test d'injection du calcium (Ca) en intraveineux pour savoir si ce nouveau test diagnostique peut détecter des cas de gastrinomes non décelés par les investigations de routine. On a étudié 26 patients atteints d'hypergastrinémie (HG). Après le test d'injection du calcium, on a prélevé du sang chez 12 patients atteints d'HG, chez trois volontaires sains, et chez un patient porteur d'une tumeur endocrine non-fonctionnelle du pancréas (contrôle). Nous avons comparé les résultats après injection du Ca avec ceux après injection de la sécrétine ou après injection d'un sécrétagogue artériel sélectif (ISAS). Le test ISAS par la sécrétine a été réalisé chez 24/26 patients atteints d'HG y compris 22/24 patients atteints du syndrome de Zollinger-Ellison (SZE). La précision de la localisation tumorale par le test d'ISAS a été de 95% (21/22) dans le SZE. Le test à la sécrétine a été négatif chez 3/21 patients ayant un SZE (14%). Le test à la sécrétine ou le test d'ISAS ont été positifs chez 22/23 (96%). Le test à l'injection de Ca a été réalisé chez 12 patients dans le groupe HG et chez quatre contrôles. Après l'injection du Ca, les taux de gastrine sérique étaient significativement plus élevés dans le groupe HG que ceux dans le groupe contrôle. Huit des 10 SZE (80%) avaient un test d'injection de Ca positif. Nous avons pu diagnostiquer un gastrinome chez 100% des patients porteurs de SZE par soit le test d'injection du Ca ou le test à la sécrétine. Nous avons confirmé l'efficacité du test d'injection intraveineuse du Ca pour diagnostiquer le gastrinome. Le test d'injection pourrait être un adjuvant pour le diagnostic de gastrinome échappant souvent au diagnostic par les tests de routine.

Resumen. El presente trabajo tiene por objeto valorar la eficacia de una nueva prueba diagnóstica consistente en la inyección intravenosa de calcio, para aclarar el diagnóstico de pacientes con gastrinomas que no han podido ser detectados mediante pruebas rutinarias. Se estudiaron 26 pacientes con hipergastrinemia. Tras el test de inyección de calcio (Ca) se obtuvieron muestras sanguíneas en 12 pacientes con hipergastrinemia (HG), en 3 voluntarios sanos y en 1 paciente con un tumor no funcionante del páncreas endocrino. Comparamos los resultados del test (Ca) con el de la secretina y con el de la inyección secretagoga arterial selectiva (SASI). El test de SASI y de secretina se realizó en 24/26 pacientes con hipergastrinemia incluyendo 22/24 pacientes con síndrome de Zollinger-Ellison (ZES). La eficicia en el diagnóstico de localización tumoral del test de SASI fue del 95% para los pacientes con ZES. El test de secretina fue negativo en 3/21 pacientes con ZES (14%). Tanto el test de secretina como el de SASI fue positivo en 22/23 pacientes (96%). El test de la inyección de calcio (Ca) se realizó en 12 pacientes con HG y en 4 casos control. El grupo (HG) mostró unos niveles séricos de gastrina significativamente más altos que los observados en el grupo control. 8 de los 10 ZES (80%) mostraron una evidente positividad en el test (Ca). Pudimos diagnosticar el gastrinoma en el 100% de los pacientes con ZES, bien mediante la inyección de calcio o por el test de la secretina. Confirmamos por tanto, la eficacia del test de la inyección i.v. de calcio en el diagnóstico del gastrinoma. Este test puede ser de gran utilidad para el diagnóstico de gastrinoma cuando éste no se detecte mediante las pruebas rutinarias.

Acknowledgments

This study was supported in part by a grant (#B-13470254) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

References

1. Fraker DL, Norton JA, Alexander HR, et al. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. Ann. Surg. 1994;220:320–328 discussion 328–330
2. Imamura M, Takahashi K, Isobe Y, et al. Curative resection of multiple gastrinomas aided by selective arterial secretin injection test and intraoperative secretin test. Ann. Surg. 1989;210:710–718
3. Thompson NW, Vinik AI, Eckhauser FE. Microgastrinomas of the duodenum. A cause of failed operations for the Zollinger-Ellison syndrome. Ann. Surg. 1989;209:396–404
4. Thompson NW, Bondeson AG, Bondeson L, et al. The surgical treatment of gastrinoma in MEN I syndrome patients. Surgery 1989; 106:1081–1085 discussion 1085–1086
5. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome. Results of a 10-year prospective study. Ann. Surg. 1992;215:8–18
6. Imamura M, Kanda M, Takahashi K, et al. Clinicopathological characteristics of duodenal microgastrinomas. World J. Surg. 1992;16:703–709 discussion 709–710
7. Thompson NW, Pasieka J, Fukuuchi A. Duodenal gastrinomas, duodenotomy, and duodenal exploration in the surgical management of Zollinger-Ellison syndrome. World J. Surg. 1993;17:455–462
8. Delcore R Jr, Cheung LY, Friesen SR. Characteristics of duodenal wall gastrinomas. Am. J. Surg. 1990;160:621–623 discussion 623–624
9. Imamura M, Takahashi K, Adachi H, et al. Usefulness of selective arterial secretin injection test for localization of gastrinoma in the Zollinger-Ellison syndrome. Ann. Surg. 1987;205:230–239
10. Imamura M, Takahashi K. Use of selective arterial secretin injection test to guide surgery in patients with Zollinger-Ellison syndrome. World J. Surg. 1993;17:433–438
11. Doppman JL. Pancreatic endocrine tumors—the search goes on. N. Engl. J. Med. 1992;326:1770–1772
12. Imamura M, Hattori Y, Nishida O, et al. Unresponsiveness of insulinoma cells to secretin: significance of the secretin test in patients with insulinoma. Pancreas 1990;5:467–473
13. Gibril F, Doppman JL, Chang R, et al. Is selective intra-arterial secretin (IAS) during angiography useful in patients suspected of Zollinger-Ellison syndrome (ZES) with a negative intravenous secretin? A prospective study. Gastroenterology 2000;118:A674
14. Vezzadini C, Poggioli R, Casoni I, et al. Use of calcium provocative test in the diagnosis of gastroenteropancreatic endocrine tumors. Panminerva Med. 1996;38:255–258
15. Jansen JB, Lamers CB. Effect of changes in serum calcium on secretin-stimulated serum gastrin in patients with Zollinger-Ellison syndrome. Gastroenterology 1982;83:173–178
16. Deveney C, Deveney K, Jaffe B, et al. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison syndrome). Ann. Intern. Med. 1977;87:680–686
17. Kato M, Doi R, Imamura M, et al. Calcium-evoked insulin release from insulinoma cells is mediated via calcium-sensing receptor. Surgery 1997;122:1203–1211
18. Komoto I, Kato M, Imamura M, et al. Distribution of calcium-sensing receptor in duodenopancreatico endocrine tumors. Gastroenterology 1999;117:A773
19. Itami A, Kato M, Komoto I, et al. Human gastrinoma cells express calcium-sensing receptor. Life Sci. 2001;70:119–129
20. Goebel SU, Peghini PL, Goldsmith PK, et al. Expression of the calcium-sensing receptor in gastrinomas. J. Clin. Endocrinol. Metab. 2000;85:4131–4137
21. Ray J, Squires P, Curtis S, et al. Expression of calcium-sensing receptor on human antral gastrin cells in culture. J. Clin. Invest. 1997;99: 2328–2333
22. Isenberg J, Walsh J, Passaro E. Unusual effect of secretin on serum gastrin, serum calcium and gastric acid secretion in a patient with suspected Zollinger-Ellison syndrome. Gastroenterology 1972;62:626–631
23. Norton J, Cornelius M, Doppman J, et al. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome and multiple endocrine neoplasia type-I: a prospective study. Surgery 1987;102:958–966
24. Frucht H, Howard JM, Slaff JI, et al. Secretin and calcium provocative tests in the Zollinger-Ellison syndrome. A prospective study. Ann. Intern. Med. 1989;111:713–722
25. Passaro J, Basso N, Walsh J. Calcium challenge in the Zollinger-Ellison syndrome. Surgery 1972;72:60–67
26. Lamers C, Van Tongeren J. 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;18:128–134