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Comparison of Two Provocative Tests for Calcitonin in Medullary Thyroid Carcinoma: Omeprazole vs Pentagastrin

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Background: **Provocative tests for calcitonin (CT) are fundamental in the diagnosis and follow-up of C-cell disease and in the detection of hereditary medullary thyroid carcinoma (MTC) carriers with unknown *RET* mutations. A recent report has proposed omeprazole, which can increase endogenous gastrin (GT), as a new provocative test for MTC.**

Methods: **We compared the omeprazole test (20 mg twice a day for 4 days) to the pentagastrin test (0.5 μg/kg of body weight) for the diagnosis and management of MTC. Twenty healthy individuals and 20 MTC patients with mildly or moderately increased basal CT serum concentrations underwent the pentagastrin and omeprazole tests.**

Results: **In MTC patients, the pentagastrin test produced a significantly higher increase in serum CT than did omeprazole. After the pentagastrin injection, several patients reported unpleasant side effects, including substantial tightness in 38 of 40 participants. No adverse effects were observed during the omeprazole test. A significant direct correlation was recorded between CT% (ratio of CT peak to basal value × 100) and GT% (ratio of GT peak to basal value × 100) during the omeprazole test in MTC patients ($r = 0.73$; $P < 0.001$).**

Conclusions: **In spite of several adverse effects, pentagastrin remains the best provocative test for the diagnosis of MTC. Omeprazole may be useful when pentagastrin is contraindicated or refused because of the unpleasant side effects, but further validation is needed.**

Medullary thyroid carcinoma (MTC),[5] a malignant neoplasm of parafollicular C cells, represents ~5–10% of thyroid tumors. MTC occurs in the sporadic form in ~70–80% of cases, whereas the remaining 20–30% are represented by three familial forms: multiple endocrine neoplasia type 2A (MEN 2A), multiple endocrine neoplasia type 2B (MEN 2B), and familial MTC not associated with MEN *(1)*.

MTC releases calcitonin (CT) and, occasionally, carcinoembryonic antigen, neuron-specific enolase, serotonin, chromogranin, somatostatin, substance P, pro-opiomelanocortin-derived products, and gastrin (GT)-releasing peptide *(2, 3)*. The main tumor marker used for the diagnosis of MTC is CT, which is usually extremely high in the serum of MTC patients *(4–7)*. However, especially in premalignant C-cell hyperplasia or early tumor stages, basal CT concentrations are mildly increased or not different from reference values *(8)*. This problem has been overcome by the use of provocative tests. In fact, the release of CT is considerable after administration of secretagogues (pentagastrin, calcium, and thyrotropin-releasing hormone) in MTC. This phenomenon has been widely used in the clinical management of patients with MTC to increase detection rates *(9–13)*.

The pentagastrin test for CT is the most widely used provocative test for the diagnosis of MTC and for assessment of cure after surgery for MTC in patients with undetectable basal CT concentrations. However, after pentagastrin administration, several adverse effects have often been recorded, such as substernal discomfort, nau-

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[5] Nonstandard abbreviations: MTC, medullary thyroid carcinoma; MEN, multiple endocrine neoplasia; CT, calcitonin; and GT, gastrin.

sea, vomiting, a metallic taste, abdominal cramping, flushing, warmth, the urge to void, esophageal spasm, tachycardia, and headache *(14, 15)*. In addition, pentagastrin is unavailable in several countries, including Italy. In a recent report, the increase in endogenous GT secretion, achieved by gastric acid inhibition secondary to the administration of omeprazole, has been proposed as a new safe stimulation test for MTC *(16)*.

The aim of this study was to determine whether omeprazole can stimulate CT secretion in the same way as pentagastrin and whether pentagastrin can thus be replaced by omeprazole for CT stimulation to avoid the unpleasant adverse effects related to pentagastrin.

Material and Methods

STUDY POPULATION

Ten healthy Caucasian male (mean age ± SD, 36 ± 14 years; range, 18–60 years) and 10 healthy Caucasian female (mean age ± SD, 36 ± 14 years; range, 19–58 years) volunteers, without any thyroid disease, with no family history of thyroid disease, and who were taking no medications or vitamin, participated in this study. All healthy volunteers were nonsmokers.

Ten Caucasian men (mean age ± SD, 37 ± 14 years; range, 16–61 years) and 10 Caucasian women (mean age ± SD, 36 ± 15 years; range, 14–66 years) with mildly or moderately increased basal CT serum concentrations were included in this analysis. In all 20 patients, MTC was histologically established or subsequently confirmed. In 4 of 20, the diagnosis had not been established histologically before testing; they subsequently underwent total thyroidectomy, and MTC was recognized. These four patients were carriers of *RET* mutations (two cases with familial MTC not associated with MEN, one case with MEN 2A, and one case with MEN 2B). The other 16 patients had been treated previously with thyroidectomy for sporadic MTC.

All participants gave informed consent, and the study was approved by the local ethics committee.

STIMULATION TESTS

All participants underwent the pentagastrin and omeprazole tests. Both stimulation tests were performed in a random sequence and were spaced at least 10 days apart.

Pentagastrin test. Pentagastrin (Pentagastrin Injection BP; Cambridge Laboratories) was administered as a slow intravenous injection over 3 min at a dose of 0.5 μg/kg of body weight. Blood samples for CT evaluation were taken at 0, 1, 2, 3, 5, and 10 min after the pentagastrin injection. All participants were studied in the supine position. After an overnight fast, including abstinence from caffeine and tobacco, blood was obtained from an antecubital vein through a lightly heparinized indwelling needle. The test was considered positive if the peak serum CT concentration after stimulation was ≥100 ng/L, uncertain if the peak serum CT concentration was 30–100 ng/L, and negative if the peak serum CT concentrations was <30 ng/L *(17, 18)*.

Omeprazole test. After the overnight fast, including abstinence from caffeine and tobacco, blood was taken for basal CT and GT determinations, omeprazole (20 mg twice a day) was given by the oral route for 4 days, and fasting blood samples for CT and GT were collected every morning at 0900 (the fifth and the last morning of the test inclusive).

CT AND GT ASSAYS

Serum CT concentrations were determined by a commercially available IRMA (Byk Gulden Italia S.p.A.). The detection limit of the assay was <0.7 ng/L. The intra- and interassay CVs were 2.3% and 4.2%, respectively, at 200 ng/L.

GT was measured by a double-antibody RIA (Diagnostic Products Corporation). The assay system uses a broad-spectrum antibody capable of recognizing several forms of GT (G-14, G-17, and G-34). The detection limit of the assay was 4.5 ng/L. The intra- and interassay CVs were 5.2% and 6%, respectively, at 100 ng/L.

STATISTICAL ANALYSIS

Statistical analyses were performed with the statistical package SPSS/PC for Windows, Release 6.0. Data are presented as the mean (SD). *t*-Tests for paired and unpaired data were performed to estimate intra- and intergroup differences, respectively, after logarithmic transformation. Because most distributions were skewed, logarithmic transformation was performed to achieve a gaussian distribution. Linear regression analyses and a partial correlation test using the Pearson method were used to assess univariate relationships between CT% (CT peak to basal value × 100) and GT% (ratio of GT peak to basal value × 100) during the omeprazole test. The null hypothesis was rejected at $P < 0.05$.

Results

PENTAGASTRIN TEST

Basal and peak CT concentrations and CT% values were significantly higher in healthy men than in healthy women ($P < 0.05$, <0.01, and <0.05, respectively; Table 1). In all 20 healthy controls, basal CT was ≤10 ng/L and the CT peak concentration and CT% after pentagastrin administration were <30 ng/L and 300%, respectively. In MTC patients there was no significant difference between men and women regarding CT baseline, CT peak, and CT% values after the pentagastrin test (Table 1). In 18 of 20 MTC patients, basal CT concentrations were >10 ng/L. In all MTC patients, the peak concentrations and CT% were >100 ng/L and 300%, respectively. Basal CT, peak CT, and CT% values after pentagastrin administration were significantly higher in MTC patients than in healthy controls for both males (basal CT, $P = 0.0001$; peak CT, $P < 0.0001$; CT%, $P < 0.0001$) and females (basal CT, P

Table 1. Mean (SD) values for basal CT, peak CT, and CT% after pentagastrin test and statistical analyses in healthy controls and MTC patients.[a]

	Basal CT, ng/L	Peak CT, ng/L	CT%, %
Healthy men	6.1 (3.1)[b,d]	14.9 (9.2)[c,e]	229 (55)[b,d]
Healthy women	3.0 (1.0)[f]	4.9 (2.3)[f]	165 (55)[f]
MTC men	23.4 (10.3)[g]	319 (116)[g]	1427 (350)[g]
MTC women	18.6 (6.2)	252 (133)	1327 (431)

[a] Statistical tests were performed with means and SDs of data modified with logarithmic transformation.

[b,c] Compared with healthy women: [b] $P < 0.05$; [c] $P < 0.01$.

[d,e] Compared with MTC men: [d] $P < 0.0001$; [e] $P < 0.0001$.

[f,g] Compared with MTC women: [f] $P < 0.0001$; [g] $P > 0.05$.

<0.0001; peak CT, P <0.0001; CT%, P <0.0001). The cutoff values were calculated as the means between the higher and lower values of the healthy controls and MTC patients, respectively. The cutoffs for CT peak after pentagastrin stimulation were 90.5 and 65.5 ng/L for male and female patients, respectively (Fig. 1).

In the healthy controls and MTC patients, several transitory side effects were observed during the pentagastrin test: a feeling of substernal tightness in 38 of 40 cases, nausea in 34 of 40 cases, abdominal pain in 29 of 40 cases, tachycardia in 26 of 40 cases, generalized feeling of warmth in 23 of 40 cases, tachypnea in 20 of 40 cases, flushing in 16 of 40 cases, and headache in 5 of 40 cases.

omeprazole test (table 2)

Basal and peak CT concentrations and CT% values were significantly higher in healthy men than in healthy women (P <0.01, <0.005, and <0.05, respectively). In 19 of 20 healthy volunteers, basal CT concentrations were <10 ng/L, in 1 volunteer, the basal CT value was 10.6 ng/L. In all healthy controls, the CT peak and CT% values after omeprazole were <30 ng/L and 300%, respectively.

In MTC patients, there was no significant difference between men and women regarding CT baseline, CT peak and CT% values after omeprazole (Table 2). Basal CT values were >10 ng/L in 18 of 20 MTC patients. CT peak and CT% values after omeprazole were >100 ng/L and 300% in 8 of 20 and 12 of 20 patients, respectively. In 7 of 20 patients, the CT peak ranged from 30 to 100 ng/L. The CT peak occurred in 13 of 20 (65%) and 7 of 20 (35%) MTC patients, respectively, on days 4 and 5 of the test. There was no significant difference for mean CT on days 4 and 5 of the test in MTC patients. During the omeprazole test, basal and peak CT concentrations and CT% values were significantly higher in MTC patients than in healthy controls. The cutoffs for peak CT concentrations after omeprazole stimulation were 18.5 and 10.7 ng/L for male and female patients, respectively (Fig. 2).

In both healthy controls and MTC patients, there was no statistically significant difference between men and women for GT baseline, GT peak, and GT% values. GT baseline, GT peak, and GT% values also showed no significant difference between healthy controls and MTC patients. Linear regression analyses showed a significant direct correlation between GT% and CT% (r = 0.73; P <0.001) after omeprazole administration in all MTC patients (Fig. 3). Seven of 20 healthy controls (35%) and 5 of 20 MTC patients (25%) showed no marked increase in GT (GT% <200%) after omeprazole administration. There was no significant difference for mean GT on days 4 and 5 of the test in MTC patients.

During the omeprazole test, no adverse effects were observed in the control or MTC groups.

omeprazole vs pentagastrin test

In healthy controls, peak CT and CT% values after pentagastrin were significantly higher than after omeprazole in both men (peak CT, P <0.005; CT%, P <0.005) and women (peak CT, P <0.05; CT%, P <0.05).

In all MTC patients, peak CT and CT% values after pentagastrin were significantly higher than after omeprazole (peak CT, P <0.0001; CT%, P <0.0001). In addition,

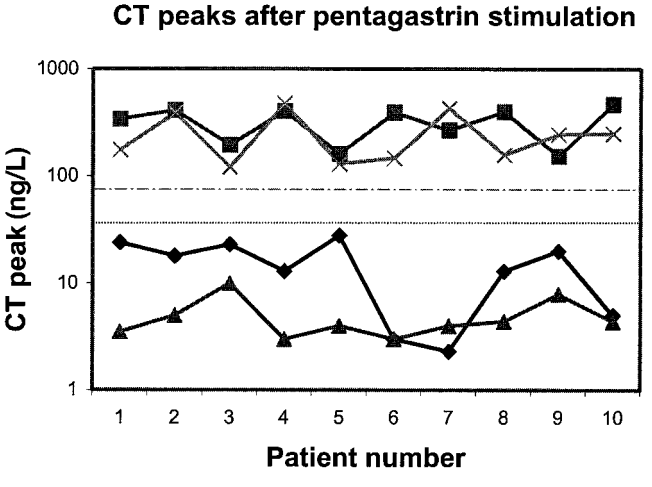

Fig. 1. CT peak values after pentagastrin stimulation in healthy individuals and MTC patients.

Cutoff values are the means between the higher and lower values of the healthy controls and MTC patients. ◆, healthy males; ■, male patients; ▲, healthy females; ×, female patients; *dashed line*, male cutoff; *dotted line*, female cutoff.

Table 2. Mean (SD) values for basal CT, peak CT, and CT% after omeprazole test and statistical analyses in healthy controls and MTC patients.[a]

	Basal CT, ng/L	Peak CT, ng/L	CT%, %
Healthy men	6.0 (3.1)[b,e]	9.2 (4.7)[c,e]	153 (31)[d,f]
Healthy women	2.9 (0.8)	3.6 (1.0)	124 (21)[h]
MTC men	23.7 (11.2)[i]	8.1 (44.9)[i]	364 (162)[i]
MTC women	19.1 (6.2)	67.0 (55.6)	318 (193)

[a] Statistical tests were performed with means and SDs of data modified with logarithmic transformation.

[b–d] Compared with healthy women: [b] $P < 0.01$; [c] $P < 0.005$; [d] $P < 0.05$.

[e,f] Compared with MTC men: [e] $P < 0.0001$; [f] $P < 0.005$.

[g–i] Compared with MTC women: [g] $P < 0.0001$; [h] $P < 0.001$; [i] $P > 0.05$.

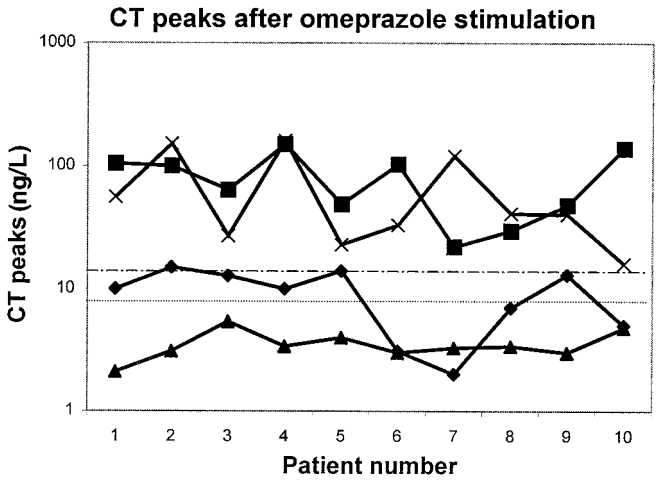

Fig. 2. CT peak values after omeprazole stimulation in healthy individuals and MTC patients.

Cutoff values are the means between the higher and lower values of the healthy controls and MTC patients. ◆, healthy males; ■, male patients; ▲, healthy females; ×, female patients; *dashed line*, male cutoff; *dotted line*, female cutoff.

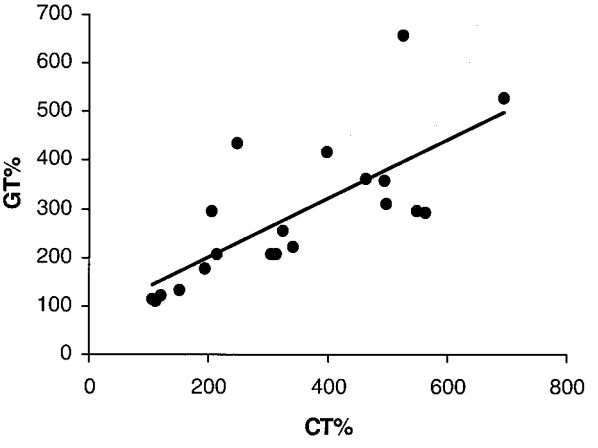

Fig. 3. Relationship between CT% and GT% during omeprazole test in the overall population of MTC patients.

$r = 0.73$; $P < 0.001$.

the CT peaks after pentagastrin stimulation were always well above the cutoff values in both males and females (cutoff values, 90.5 and 65.5 ng/L, respectively; Fig. 1).

The CT peak values for the overall population after omeprazole stimulation never overlapped. However, the CT peak value was near the cutoff point in one male patient (patient 7) and in six healthy males (volunteers 1, 2, 3, 4, 5, and 9). On the other hand, in the female population, the CT peak value after omeprazole stimulation was near the cutoff point only in one patient (patient 10; Fig. 2).

Discussion

At present, the diagnostic approach to MTC includes the molecular analysis of DNA to detect *RET* protooncogene mutations in the familial form. DNA testing is a highly reliable method for the identification of individuals with or at risk of familial MTC. This procedure has a very high specificity and can be helpful in making therapeutic decisions, even in asymptomatic family members with negative biochemical tests *(19–21)*. However, measurement of CT still represents a valid tool for the diagnosis of MTC. In fact, the pentagastrin provocative test for CT is the most important method for the diagnosis of sporadic MTC, which represents ~70–80% of cases, and for the detection of postsurgical recurrences in patients with familial and sporadic MTC *(14, 15)*. In addition, the pentagastrin test is useful for detecting hereditary MTC carriers in families where no *RET* mutations are identifiable *(19)*. Pentagastrin is a synthetic pentapeptide containing the carboxyl-terminal tetrapeptide, the active portion found in all natural gastrins. Therefore, it acts as a gastric acid and CT secretagogue *(10, 11, 22)*.

In a recent report, Erdogan et al. *(16)* proposed a new CT stimulation test with omeprazole for the diagnosis, follow-up, and family screening in MTC. Omeprazole, a substituted benzimidazole, suppresses gastric acid secretion by selective interference with the proton pump (H^+K^+-ATPase) in the secretory membrane of the parietal cells. It is well known that antral acidification inhibits the release of GT from the antrum. Therefore, the marked inhibition of gastric acidity secondary to omeprazole administration induces an increase in serum GT concentrations *(23)*. Erdogan et al. *(16)* showed a GT response to omeprazole from a mean basal value of 30 ± 18 ng/L, reaching 98 ± 76 ng/L in MTC patients. These patients had a similar CT response, from a mean basal value of 647 ± 919 ng/L to 1351 ± 1257 ng/L. The means (SD) of GT% and CT% during the omeprazole test were 354% ± 279% and 356% ± 230%, respectively.

In the present report, we compared the pentagastrin and omeprazole tests for the first time. In MTC patients, pentagastrin seemed to be more effective than omeprazole at stimulating the secretion of CT. In our series, all patients with MTC were identified by an abnormal CT response (CT peak ≥100 ng/L) to pentagastrin. On the other hand, the CT response to omeprazole was severe (CT peak ≥100 ng/L) in 8 of 20 patients (40%) and moderate (CT peak values, 30–100 ng/L) in 7 of 20 patients (35%) with MTC. Erroneously, in 5 of 20 patients with MTC (25%), the CT response to omeprazole did not reveal the C-cell disease (CT peak <30 ng/L). In these five cases, we observed a slight increase in endogenous GT (GT% <200%) during the omeprazole test. Therefore, according to our experience, the omeprazole test presented two disadvantages:

- GT responsiveness to omeprazole had great variability. In 12 of 40 participants (30%), GT% was <200%. This value appears to be inadequate to assure a valid stimulation of CT for C cells.

- Endogenous GT after omeprazole administration, excluding 12 nonresponding patients, increased 3.4-fold from the basal value. This stimulation for CT is significantly lower than that for pentagastrin. In fact, according to Owyang et al. *(24)*, the serum dosage of endogenous GT plus pentagastrin achieved during the pentagastrin test in their study was ~20-fold higher than the GT basal concentration.

The value of the GT increase is very important to obtain a good stimulus for CT. In fact, a significant direct correlation between CT% and GT% was observed during the omeprazole test (Fig. 3). Therefore, a further increase in GT could improve the sensitivity of this test. It is well known that serum GT concentrations increase during omeprazole therapy and reach a peak at 2–4 months, after which they generally remain stable at 2–4 times the baseline values *(25–27)*. However, we did not observe a significant difference in CT and GT between days 4 and 5. Therefore, day 5 could be omitted in the omeprazole test. On the basis of our results, future experimental approaches should include the use of more potent inhibitors of the proton pump and other drugs able to induce a severe hypergastrinemia in a short time. In a recent report, Hammer et al. *(28)* described the dramatic hypergastrinemic effect of the peroxisome proliferator ciprofibrate administered together with omeprazole in female rats. The concomitant administration of omeprazole and ciprofibrate induced a 27-fold increase in serum GT from the basal concentration. This increase was approximately sevenfold higher than the increase achieved with omeprazole alone. Therefore, in the future it would be interesting to evaluate the effects of simultaneous administration of peroxisome proliferator and inhibitors of proton pump drugs on CT values in healthy individuals and MTC patients.

In conclusion, in spite of several adverse effects, pentagastrin remains the first-choice test for the diagnosis of MTC. Omeprazole is a safe and inexpensive drug, widely available in several countries, but it appears to be a less potent CT secretagogue than pentagastrin and it is not as sensitive as the pentagastrin test. Despite these limitations, the omeprazole test can be used when the pentagastrin test is contraindicated or refused on the basis of the unpleasant side effects and in countries where pentagastrin is not available. However, future trials including MTC patients and gene carriers with normal CT concentrations are needed to evaluate the role of the omeprazole test in the diagnosis and management of C-cell disease.

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