**Clinical Study**

**Effect of short-term treatment with low dosages of the proton-pump inhibitor omeprazole on serum chromogranin A levels in man**

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**Abstract**

**Background:** Measurement of chromogranin A (CgA) levels in blood can be used to monitor neuroendocrine tumors (NETs). CgA levels may also be elevated in several other endocrine and non-endocrine diseases. It is well known that drugs affecting acid gastric secretion can increase gastrin. Proton-pump inhibitors are extensively used but only a few data have been reported on their effects on CgA secretion.

**Design:** The aim of the study was to evaluate the short-term effect of low dosages of omeprazole (OM) on CgA levels and to sensitize endocrinologists to possible false positive values of CgA in order to prevent expensive diagnostic work-up in searching for NETs.

**Subjects and methods:** Thirty-five female and nine male in-patients (18 – 81 years) were studied. Mild or severe hypertension in 20 patients needed therapy. Endocrine and metabolic diseases were diagnosed in the majority of patients. CgA levels were evaluated before and during OM therapy (10 mg/day, orally).

**Results:** Without OM therapy, CgA levels were 64 ± 6 µg/l. Elevated baseline CgA levels were found in nine subjects. CgA levels were significantly related to age (P = 0.001), creatinine levels (P = 0.03) and the severity of hypertension (P = 0.002). On short-term OM therapy (n = 42; 18.8 ± 2.4 days; range 5 – 90 days) a significant (P < 0.001) increase in CgA (145 ± 22 µg/l) from baseline (63 ± 7 µg/l) levels was found. The average net CgA increase on short-term OM therapy was 93 ± 20 µg/l. There was a significant correlation between baseline CgA levels and CgA increase on short-term OM therapy (P = 0.004) but not between the increase in CgA and the duration of the therapy.

**Conclusions:** An increase in CgA levels quickly follows the start of low dosages of OM. This release is more pronounced when the baseline CgA levels are already increased by slight renal insufficiency or severe hypertension. In this common clinical situation an intensive work-up for NETs is not justified before reassessment of CgA after the withdrawal of OM.

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**Introduction**

Chromogranin A (CgA) is a soluble secretory protein which was first isolated from chromaffin cells of the adrenal medulla (1). As a member of the chromogranin–secretogranin family, CgA tends to bind calcium with low affinity but high capacity and to aggregate in vitro at low pH in the presence of calcium (2). The release of CgA with catecholamines indicates that exocytosis is the mechanism of physiologic CgA release, which is related to sympathetic tone (3). The chromogranin–secretogranin family was the subject of a recent review article by Taupenot et al. (4) in which the clinical value of detecting CgA was extensively reported. CgA is now a standard probe for immunohistochemical analysis of neuroendocrine tumors (NETs) (5). Measurement of CgA levels in blood can also be used to monitor the progression or regression of NETs during treatment (6). CgA levels may also be elevated in patients with primary parathyroid hyperplasia (5), thyroid C-cell hyperplasia (5), gastric enterochromaffin-like (ECL) cell hyperplasia (7), prostate cancer (8) and in some other cancers when neuroendocrine cell differentiation is present (4). Increased sympathoadrenal activity may play a causative role in essential hypertension, in which increased CgA levels have been reported (9). CgA levels are elevated in patients with organ failure, as a result of both higher renal retention and lower hepatic metabolism (4, 10).
Drugs commonly used to diagnose or treat pheochromocytoma do not substantially alter serum CgA levels (4), while drugs affecting acid gastric secretion can increase gastrin (11–13) and, as reported by a few authors, also CgA levels (7, 11, 14–17). Considering the widespread administration of proton-pump inhibitors (PPIs), it is strange that so few studies have investigated their effect on CgA secretion. The aim of our study was to sensitize endocrinologists, and physicians in general, to this drug-related CgA increase, even at low dosages and for a short period of time, in order to avoid false positive data and prevent expensive diagnostic work-up in searching for NETs.

**Materials and methods**

**Subjects**

The study group consisted of 35 female and nine male in-patients (mean age \(\pm\) S.D. 50±20 years; median 48 years; range 18–81 years). Endocrine and metabolic diseases were diagnosed in the majority of patients (n=34), while other diseases (n=3 chronic psychosis; n=2 breast and endometrial cancer; n=1 sepsis; n=1 essential hypertension; n=1 chronic obstructive pulmonary disease; n=1 alcoholic liver disease; n=1 gastroesophageal reflux disease) were found in the remaining patients. Patient no. 23 with an adrenal incidentaloma showed normal adrenal hormones and catecholamines in both blood and urine. Omeprazole (OM) therapy (10 mg/day orally; Astra Zeneca, Milan, Italy) was in progress before admission to hospital in seven patients for gastroesophageal reflux, while in the remainder it was started as prophylaxis for gastroesophageal damage caused by medications (e.g. anti-coagulants, non-steroidal anti-inflammatory agents, glycoactive corticosteroids, potassium tablets, antibiotics and bisphosphonates) after admission to hospital. Mild or severe hypertension in 19 patients needed chronic medical therapy before admission to hospital, while anti-hypertensive therapy was started in one patient after hospital admission. A group of 57 normal subjects (43 females and 14 males), ranging in age from 18 to 76 years and free from any therapy, was also evaluated as a control group. After an overnight fast, patients were examined for clinical and biochemical parameters and serum levels of CgA. The study was approved by the Ethics Committee of San Martino University Hospital. Written informed consent was obtained by all subjects.

**Analytical methods and statistical analysis**

Serum CgA was measured by means of a solid-phase two-site immunoradiometric assay (CIS Bio International, Gif-Sur-Yvette, France). Recombinant human CgA was used as standard. The detection limit of the assay, defined as the smallest concentration different from zero with a probability of 95%, was 1.5 μg/l. Samples from the same subject were evaluated in duplicate in the same assay. Within-run coefficients of variation were 6% and 4% at CgA levels of 30 μg/l and 144 μg/l respectively. Serum creatinine and serum calcium were evaluated by auto-analyser. Ionized calcium was evaluated by an ion-selective electrode method.

All results are reported as means±S.E.M., unless otherwise indicated. Data were analysed using Prism 3.0 software (GraphPad, San Diego, CA, USA) by means of non-parametric tests. Significance was assumed at \(P\) equal to or less than 0.05. The severity of hypertension was arbitrarily evaluated by assigning a score for each class of anti-hypertensive drug used to control blood pressure (from 1 drug (= score 1) to 4 drugs (= score 4)). In accordance with the data from our control group, CgA values that were 2.5 S.D. above the mean were considered to be elevated.

**Results**

In our control group of subjects who were not on any therapy, CgA levels ranged from 16 to 97 μg/l (means±S.D. 45±18 μg/l; median 42 μg/l), without significant differences between females (44±17 μg/l; median 41 μg/l) and males (48±20 μg/l; median 46 μg/l). In these subjects, a significant positive correlation was seen between CgA levels and age (rS 0.65, \(P\) ¼ 0.003) but not between CgA levels and serum creatinine, calcium (total, ionized) or blood pressure. In accordance with data from our control group, CgA values over 90 μg/l (means±2.5 S.D.) were considered to be elevated.

On hospital admission, elevated CgA levels were found in nine patients from the study group. Table 1 reports the clinical findings from these patients. Four patients had been studied in advance to search for NETs. Five of these nine patients were on OM therapy before hospital admission. In seven patients, OM therapy had been in progress for between a few days and several months before admission. After drug discontinuation, CgA levels decreased in six out of the seven (Table 2), and were significantly (\(P\) ¼ 0.03) lower after OM discontinuation (70±12 μg/l) than when on OM therapy (277±80 μg/l). Only case no. 6, treated for 14 days before admission, did not show any change after OM discontinuation.

In the overall study group, CgA levels were 64±6 μg/l (median 51 μg/l; range 19–225 μg/l) without OM therapy. CgA levels were significantly related to age (rS 0.65, \(P\)  < 0.001) and creatinine levels (rS 0.32, \(P\) ¼ 0.03) but not to calcium (total, ionized) levels. CgA levels were also related to the severity of hypertension (rS 0.46, \(P\) ¼ 0.002) but not to blood pressure levels. In the 42 patients who were on OM therapy only for a short period (18.8±2.4 days, range 5–90 days), a significant (\(P\)  < 0.001) increase in CgA (145±22 μg/l; median 90 μg/l; range 21–692 μg/l)
levels was found in comparison with basal values (63 ± 7 μg/l; median 51 μg/l; range 19–225) (Fig. 1). The average net CgA increase on short-term OM therapy was 93 ± 20 μg/l. There was a significant correlation between baseline CgA levels and CgA increase on short-term OM therapy (rS 0.44, P = 0.004) but not between the increase in CgA and days of therapy.

Discussion

Inhibitors of gastric acid secretion are effective in the treatment and prophylaxis of acid-related diseases. Since their introduction in the late 1980s, PPIs have displayed greater gastric acid suppression than histamine H2-receptor blockers. As they have improved the treatment of various acid-peptic disorders (13, 18), PPIs are frequently prescribed, often for minor complaints.

A decrease in acidity always causes an increase in gastrin (11–13). The trophic effect of gastrin leads to hyperplasia of the ECL cells (7, 13), and the role of ECL cell hyperplasia secondary to hypergastrinemia in inducing carcinoids, and perhaps in developing malignant tumors, is currently under debate (13).

OM and other PPIs appear to have similar efficacy (18). Sharma et al. (19) reported that OM has a very steep concentration–response curve with regard to the inhibition of acid secretion, and that sensitivity differs among subjects. The usual dosages of OM, alone or combined with other agents, range from 10 to 40 mg/day for adults. Approximately 80% of doses of OM seem to be cleared by cytochrome P450 2C19 (CYP2C19), but altered CYP2C19 activity does not seem to increase the risk of adverse effects (16, 20). The rates of common adverse events during treatment with OM in general practice have been reported in several publications. Occurring relatively infrequently, these effects include diarrhoea, nausea, vomiting, abdominal pain and headache, and display a clear age-response relationship (21).

Waldum et al. (17) first reported elevated CgA levels after short-term high-dosage (40 mg/daily) treatment with OM in a small group of patients with reflux esophagitis, which suggested the possible use of this parameter in evaluating ECL cell hyperplasia in patients with hypergastrinemia secondary to acid inhibition. A year later, Houben et al. (15) reported that, after short-term OM (20–40 mg/daily) administration in healthy volunteers, serum gastrin and CgA levels rose as the degree of acid inhibition increased, and that these three values were strongly correlated. Further studies by this group demonstrated that OM in dosages ranging from 20 to 80 mg daily doubled CgA levels in dyspeptic patients (14). Serum CgA levels correlate positively with the degree and duration of acid inhibition (7, 14). Patients with helicobacter pylori-positive serology have been reported to have higher serum gastrin and CgA levels than those with negative serology (14). Increased CgA
values during long-term profound gastric acid inhibition could reflect either gastric ECL cell hyperfunction or proliferative changes (7,14).

Our study documents that even low dosages of OM (10 mg/daily) are able to induce a significant increase in CgA levels in a short period of time. Moreover, in our study period, we were unable to find a relationship between increase in CgA and duration of therapy. On the other hand, patients on long-term (1 – 8 years) OM therapy have been reported to have significantly higher CgA levels than those on medium-term (6 weeks to 1 year) OM therapy (14).

Data regarding the effect of aging on CgA levels are few and inconclusive (9). Our data show an age-related trend in CgA levels. While this phenomenon may be secondary to the worsening of the patient’s general conditions (e.g. hypertension and renal insufficiency) it should also be borne in mind that an age-related increase is seen in motility and secretory disorders of the gastrointestinal tract and associated glands (21). Age-related changes in amine/peptide-producing cells, including CgA-producing cells, of the duodenum have been documented, with no difference between sexes (22). CgA has been found to be significantly higher in essential hypertensive subjects than in normotensive subjects (9), and some authors (23, 24) have recorded elevated CgA levels in untreated hypertensive patients. Thus, its elevation is unlikely to be simply a response to hypertension, a conclusion also supported by unchanged CgA values after anti-hypertensive treatment (9). We did not find any relationship between blood pressure and CgA levels in our study population, although many of our subjects had a history of hypertension. However, when CgA levels were correlated with the number of drugs necessary to achieve acceptable pressure control, a significant influence of the hypertensive state emerged.

CgA levels are elevated in patients with organ failure, as a result of both higher renal retention and lower hepatic metabolism (4,10). The present study shows that there is a significant relationship between minimal increase in creatinine levels and CgA release, as a further link between production and metabolism. However, in spite of the reported link between calcium and protein secretion in vitro (2), we were unable to document any relationship between serum calcium and CgA levels either on or off OM therapy.

A practical consideration to emerge from our study is that even low-dosage OM therapy should be discontinued at least 7–10 days before evaluating CgA secretion. Moreover, the failure of CgA levels to decrease could be caused either by an inadequate wash-out period (present study case no. 6) or by a reduced ability to metabolize the drug on account of defective CYP2C19 activity (20).

Finally, it is interesting that alternate-day long-term (3 – 36 months) treatment with OM (20 mg/daily) has been reported to achieve adequate remission in patients with reflux esophagitis while maintaining serum gastrin levels in the normal range (11). It is not known whether the same OM regimen is able to maintain CgA levels within the normal range; if so it might well reduce the potential risk for ECL cell hyperplasia and avoid false positive data suggestive of NETs.

In conclusion, the present data clearly indicate that an increase in CgA levels quickly follows the start of OM therapy, even at low dosages, and that this release is more pronounced when the baseline CgA levels are already increased by slight renal insufficiency or severe hypertension. In this common clinical situation an intensive work-up for NETs is not justified before reassessment of CgA after withdrawal of OM.

References

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