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Alfonso Libroia

Uberta Verga

Gianleone Di Sacco

Marco Piolini

Fabrizio Muratori

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Alfonso Libroia,* Uberta Verga,* Gianleone Di Sacco,* Marco Piolini,† and Fabrizio Muratori*

We have studied seven subjects with medullary thyroid carcinoma. Each had elevated basal serum calcitonin (CT) levels following total thyroidectomy. After subcutaneous administration of 100 μg of SMS 201-995, blood samples were collected at 60-minute intervals for six hours. Two patients showed a marked decrease of CT levels (patient A: baseline 565 pg/mL, nadir 150 pg/mL; patient B: baseline 1,632 pg/mL, nadir 416 pg/mL). The other five patients showed no significant change in comparison with saline infusion. Two patients were treated with SMS 201-995 (300 μg/day) for 90 days. One of these patients responded to the acute SMS 201-995 test and had CT levels persistently 50% lower than pretreatment values during this 90-day period. The other patient, whose CT levels did not decrease during the acute test, had persistently high values during this 90-day period but had relief of watery diarrhea even after the therapeutic trial was discontinued. (Henry Ford Hosp Med J 1989;37:151-3)

Medullary thyroid carcinoma (MTC), first described by Hazard et al (1), develops from thyroid parafollicular cells or C-cells and secretes calcitonin (CT) (2). MTC occurs in sporadic and occasionally in hereditary forms as multiple endocrine neoplasia type 2 (3). Measurement of plasma CT is important for the diagnosis of MTC. Secretion of CT is influenced by a variety of substances. Somatostatin, found in some C-cells (4), has been reported to inhibit basal and stimulated CT secretion from MTC cells (5), suggesting a possible paracrine relationship between the two. Because of its ultrashort half-life, the native somatostatin-14 peptide is not useful clinically. However, somatostatin analogs developed recently can be used clinically. Bauer et al (6) developed a somatostatin analog, code-named SMS 201-995 (octreotide, Sandostatin), and several reports have shown that acromegalic patients respond favorably to chronic treatment with SMS 201-995 (7). We have recently reported that acute administration of SMS 201-995 (Sandostatin, Sandoz Pharmaceuticals, Milan, Italy) decreased CT levels in some patients with MTC (8). The aim of the present study was to evaluate the acute effect of SMS 201-995 on CT plasma levels in patients with MTC and its possible role in the chronic treatment of patients with recurrent disease after total thyroidectomy.

Methods

Seven patients, two females and five males, were included in the study. One had hereditary MTC and six had a sporadic form. Each had undergone total thyroidectomy and had elevated serum CT concentrations postoperatively.

SMS 201-995 acute test

On the first day, the fasting patients received a saline infusion over a six-hour period. Blood samples were obtained at −30, 0, 60, 120, 180, 240, 300, and 360 minutes. On the second day, the subjects received 100 μg of SMS 201-995 subcutaneously at time 0.

SMS 201-995 chronic treatment

Two patients who had had total thyroidectomy for MTC and persistently high basal CT levels were treated with SMS 201-995 (300 μg/day) for 90 days. One patient, a 68-year-old man with persistently elevated basal CT levels (650 pg/mL), was asymptomatic and had responded to the acute test with SMS 201-995 for CT. The other patient, a 58-year-old man, did not respond to the acute SMS 201-995 test. He had watery diarrhea (eight to ten episodes daily) and showed normal values of fasting plasma pancreatic polypeptide (PP), vasoactive intestinal polypeptide (VIP), and gastrin and 5-hydroxyindolacetic acid (5HIAA) urinary excretion. His PP response to secretin was physiological.

The quantitative determination of CT in serum was performed using a radioimmunoassay method (RIA-MAT-Calcitonin II, Byk-Santec Diagnostica, Dietzenbach, RFA).

Results

SMS 201-995 acute test

Two of the seven patients, both affected by sporadic MTC, had a marked decrease of serum CT levels (patient A: baseline

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*Department of Endocrinology, Niguarda Hospital, Milan, Italy.
†Sandoz spa, Milan, Italy.
Address correspondence to Dr. Libroia, Department of Endocrinology, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy.

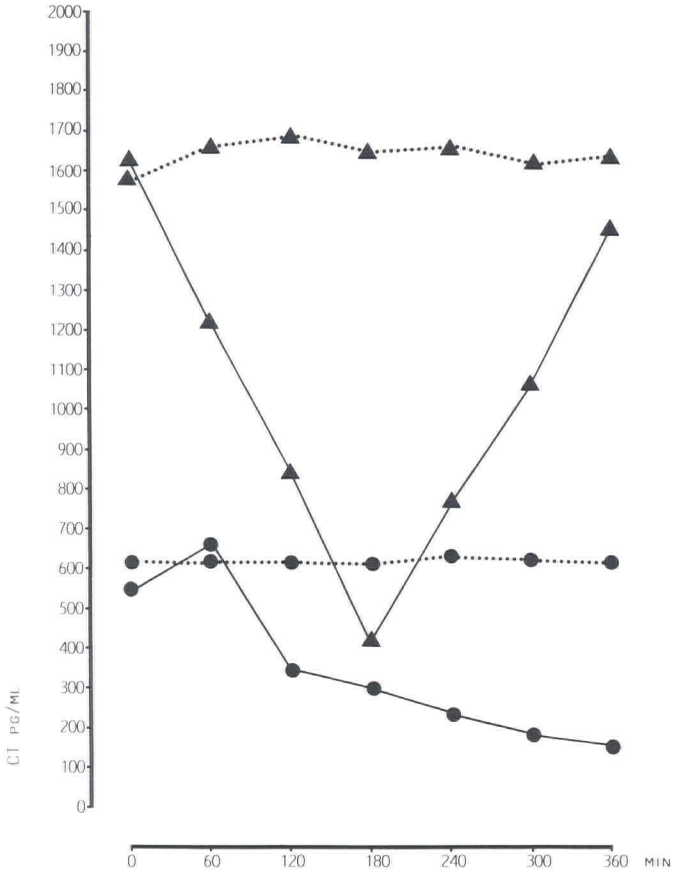

Fig 1—Comparison of calcitonin levels in an acute test with SMS 201-995, 100 μg subcutaneously, and saline infusion in two responders (solid circle indicates patient A, triangle indicates patient B, dotted line indicates saline infusion, solid line indicates SMS 201-995 administration).

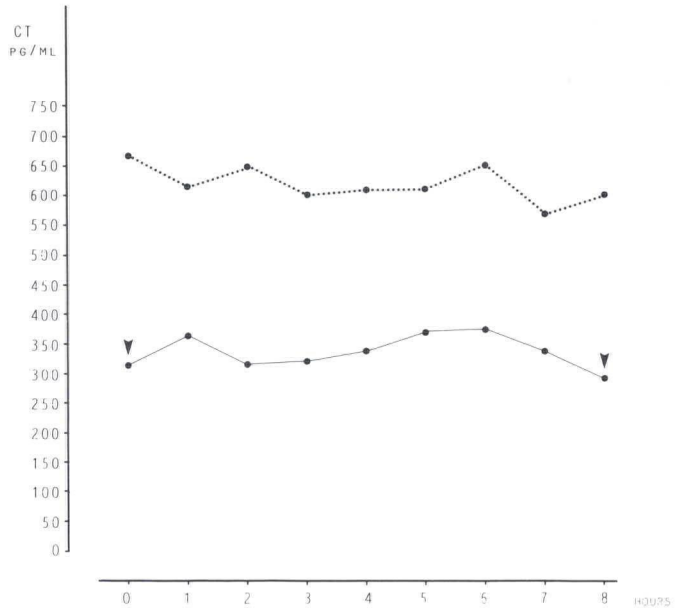

Fig 2—Calcitonin responses to chronic SMS 201-995 administration (arrowhead indicates SMS 201-995 administration, 100 μg subcutaneously; dotted line indicates pretreatment calcitonin levels; solid line indicates calcitonin levels after 90-day treatment period with SMS 201-995, 300 μg/day).

565 pg/mL, nadir at 6 hrs 150 pg/mL; patient B: baseline 1,632 pg/mL, nadir at 3 hrs 416 pg/mL) (Fig 1). The other five patients showed no significant change in CT in comparison with saline infusion.

SMS 201-995 chronic treatment

One patient had a sustained progressive fall in plasma CT levels during the SMS 201-995 acute test. Before the start of chronic treatment with SMS 201-995 (300 μg/day), his CT serum levels were persistently about 50% lower than pretreatment values. However, this patient's CT levels did not return to normal during long-term SMS 201-995 therapy (Fig 2). The other patient's CT levels remained similar to the pretreatment values, but the watery diarrhea was absent even after discontinuing chronic therapy.

Discussion

Total thyroidectomy with excision of central lymph nodes is indicated in MTC (9). Once residual tumor becomes palpable, no present treatment is likely to be curative (10). In some patients elevated CT levels may persist following total thyroidectomy even in the absence of evident residual tumor (11). In patients with metastatic MTC, radioactive iodine has been found to be of no therapeutic value, and the effectiveness of external radiotherapy in these patients is controversial (12,13). Somatostatin is found in CT-containing parafollicular cells or C-cells of the thyroid (14). Somatostatin does inhibit pentagastrin-stimulated CT release in some patients with MTC (5) and also directly inhibits pancreatic exocrine and endocrine secretion (15). In our study, the acute administration of SMS 201-995 had no effect on plasma CT in five of seven patients; in these patients we suggest that the somatostatin receptor in MTC cells may be lost or nonfunctional or the affinity of the analog for the receptor may differ from that of native somatostatin. However, one patient with MTC and unexplained watery diarrhea, whose plasma PP, VIP, and gastrin and urinary 5HIAA excretion were normal, had resolution of symptoms with chronic SMS 201-995 administration. No changes in plasma PP or CT concentrations were observed. The role of CT in production of watery diarrhea has not been established (16,17), and the release of other peptides by MTC may be a causative factor. The analog may have improved the diarrhea by inhibiting gut responses directly. Experimental studies have demonstrated that SMS 201-995 is a potent inhibitor of the intestinal secretion evoked by bradykinin, prostaglandins, and serotonin. The most likely explanation of the effects of SMS 201-995 is that it interferes with the adenylate cyclase-cyclic AMP system (18). In two of our seven patients the acute administration of SMS 201-995 provided a decrease in plasma CT levels. One of these patients was treated with 300 μg/day of SMS 201-995 for three months. In this patient a clear correlation existed between the acute responsiveness of CT levels to a single

administration of SMS 201-995 and the decrease of 8-hour CT levels achieved during chronic treatment (Fig 2). The therapeutic effect of SMS 201-995 may be mediated by a specific somatostatin receptor (19). These data suggest a possible trial of radioiodinated octreotide (tyr-3-octreotide) for the localization of MTC tumors (20).

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