Is thyrotropin-releasing hormone as reliable a calcitonin stimulant as pentagastrin in medullary thyroid carcinoma?

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Abstract. Calcitonin determination is of central importance in the diagnosis and follow-up of medullary thyroid carcinoma. Stimulation tests must be applied, particularly for early recognition of familial medullary thyroid carcinomas and for early diagnosis of relapses/metastases, since the basal calcitonin levels are still within the normal range initially. The pentagastrin stimulation test has proven to be the most effective one, though it is associated with considerable adverse effects. TRH is also able to stimulate calcitonin secretion in medullary thyroid carcinoma. The present study examines the value of TRH stimulation compared with pentagastrin stimulation in patients with occult or manifest metastases of medullary thyroid carcinoma. Both patients with occult metastases displayed a marked calcitonin increase after pentagastrin stimulation, but not after TRH stimulation. While calcitonin increased after pentagastrin in the two patients with manifest metastases, TRH produced a clear rise in only one of them and even caused the serum calcitonin concentration to drop continuously in the other one. Thus, TRH cannot be regarded as a reliable calcitonin stimulant in medullary thyroid carcinoma.

Medullary thyroid carcinoma is usually associated with an extremely high elevation of serum calcitonin levels. However, especially in premalignant C-cell hyperplasia or early tumour stages, basal calcitonin levels are not different from those found in normals (1). Calcitonin secretion can be stimulated through various substances such as pentagastrin (2), calcium (3,4) ethanol (whisky) (5), cholecystokinin (6), and glucagon (7). Pentagastrin and calcium have proven to be the most effective substances, and the pentagastrin stimulation test is most commonly applied. This test is, however, associated with considerable adverse effects (8,9). Nakamura et al. (10) observed a rapid significant serum calcitonin increase in two patients with medullary thyroid carcinoma after iv application of 500 mg of TRH. Calcitonin secretion was even higher after TRH than after pentagastrin in the monolayer culture of medullary thyroid carcinoma cells of one of these patients.

The aim of our study was to determine whether TRH can stimulate calcitonin secretion in the same way as pentagastrin and whether pentagastrin can thus be replaced by TRH for calcitonin stimulation in order to reduce adverse effects.

Patients and Methods

Examinations were performed in 4 patients whose primary treatment of medullary thyroid carcinoma dated back four to ten years: 2 women and 2 men between 26 and 54 years of age, one with the familial and three with the sporadic type of medullary thyroid carcinoma. Metastases, detected by the pentagastrin stimulation test, were occult in two patients and manifest in the other two. All four patients were submitted to a TRH stimulation test (400 mg of TRH iv) followed by a pentagastrin stimulation test (0.5 mg of pentagastrin/kg) 30 min later. For both tests, blood samples for calcitonin determination were taken prior to application of the stimulant and 2, 5, 8 and 10 min thereafter. The calcitonin concentration in the serum samples was determined with a commercial
radioimmunoassay (INC, USA, marketed by Biermann, Frankfurt a.M., lower detection limit 7.5 pmol/l, normal range of serum calcitonin concentration: <30 pmol/l).

Results

All four patients showed a markedly lower calcitonin secretion after TRH than after pentagastrin: of the two patients with occult metastatic spread, one displayed an only minimal increase in the serum calcitonin levels after TRH, and the other none at all, whereas pentagastrin produced calcitonin levels ranging up to 12 times the initial value (Table 1). In one of the two patients with manifest metastases, the serum calcitonin concentration rose nearly 3-fold after TRH stimulation. The second patient with manifest metastases surprisingly showed a continuous decrease of the calcitonin level after TRH stimulation and a slight, continuous increase after pentagastrin stimulation (Table 1).

Discussion

Calcitonin determination after stimulation is decisive in family screening for early recognition of a medullary thyroid carcinoma or precancerous C-cell hyperplasia and is important in tumour aftercare for early detection of tumour recurrence or metastases. This method permits establishment of the diagnosis much earlier than any other procedure (1,11-17). The pentagastrin stimulation test has proved to be very reliable for this purpose (13). The unpleasant adverse effects, however, have made it seem advisable to search for substances with fewer adverse effects that likewise reliably stimulate calcitonin secretion. The study results of Nakamura et al. (10) made it seem possible that TRH could replace pentagastrin. In our 4 patients, however, TRH was less effective than pentagastrin in stimulating calcitonin secretion. The calcitonin decrease observed after TRH application in one patients suggests that TRH may even suppress calcitonin secretion from medullary thyroid carcinoma cells in some patients.

Conclusions

TRH is less effective than pentagastrin as a calcitonin stimulant in medullary thyroid carcinoma.

TRH is particularly unsuitable for screening examinations in patients with normal basal serum calcitonin levels.

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