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PENTAGASTRIN, CALCIUM AND WHISKY STIMULATED SERUM CALCITONIN IN MEDULLARY CARCINOMA OF THE THYROID

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Medullary thyroid carcinoma (MCT) is a tumour of the calcitonin-secreting parafollicular C-cells of the thyroid gland. The disease may be familial, with an autosomal dominant mode of inheritance and often associated with other endocrine neoplasms.

Determination of serum immunoreactive calcitonin (S-iCT) concentrations is the most sensitive method for the diagnosis (TELENIUS-BERG et coll. 1975), but basal levels may be within normal range in cases of C-cell hyperplasia and small carcinomas. However, calcitonin-secretory capacity is abnormally high in these patients. Determination of S-iCT concentrations after stimulative procedures can therefore disclose the C-cell neoplasm in an early stage (SIZEMORE & GO 1975, MILHAUD et coll. 1975, TELENIUS-BERG et coll. 1977, HILLYARD et coll. 1978, GRAZE et coll. 1978).

Intravenous injection of pentagastrin is now the most commonly used stimulative procedure (TELENIUS-BERG et coll. 1977, GRAZE et coll.), but superiority has been claimed for the use of short-term calcium infusion (RUDE & SINGER 1977) or oral whisky (DYMLING et coll. 1976, HILLYARD et coll.). Therefore, these three stimulative procedures for calcitonin secretion were compared in patients with proven MCT and in healthy controls.

Material and Methods

The material comprised 6 patients (3 males and 3 females, aged 30–65 years), all previously operated upon for MCT, microscopically proven and with persistently elevated basal S-iCT concentration, and 8 healthy volunteers (4 males and 4 females, aged 24–40 years). MCT was familial in one (Fig. 3, E. J.) and sporadic in the other 5 patients.

Serum concentrations of calcium, phosphorus, alkaline phosphatase and creatinine were within normal limits in all subjects. Informed consent was obtained from all individuals.

S-iCT was measured in all subjects before and 2, 5, 15 and 30 min after stimulation with pentagastrin (Peptavlon 0.5 μg per kg body weight diluted in 1 to 2 ml isotonic sodium chloride given i.v. within 5 s), calcium (2 mg per kg body weight as calcium laevulatis 10% given intravenously during 1 min) and whisky (50 ml Johnny Walker, Black Label, by mouth). The order of the tests differed between the subjects. During calcium infusion S-iCT and serum calcium were measured simultaneously. In each individual the calcitonin stimulation tests were initiated at 8.00 a.m. after fasting overnight. The injections were given and the blood samples drawn through an intravenous catheter.

S-iCT was measured by radioimmunoassay as described previously (NIELSEN et coll. 1979, NIELSEN & OLSEN 1979), using a commercial antibody to synthetic human calcitonin (Calbiochem, U.S.A.) and synthetic human monomer calcitonin (Ciba, Switzerland) for standards and iodination. The de-

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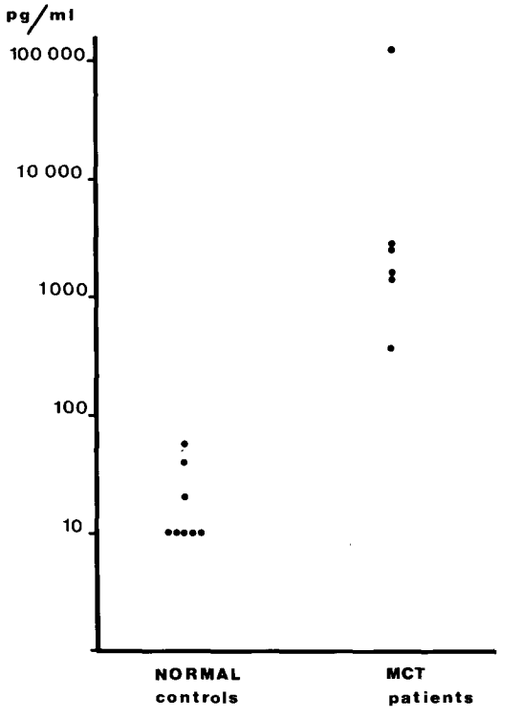

Fig. 1

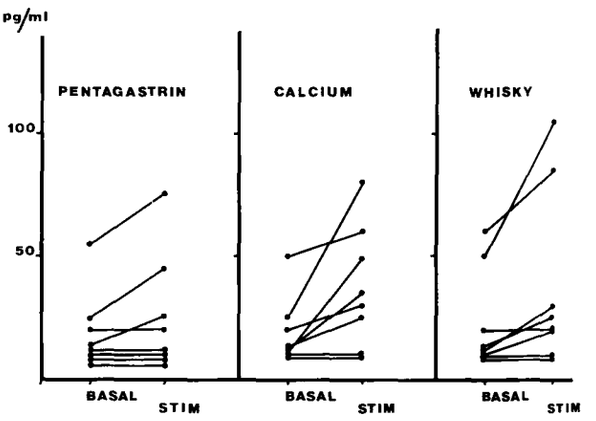

Fig. 2

Fig. 1. S-iCT (pg/ml) in 6 patients with medullary carcinoma of the thyroid (MCT) and in normal controls.

Fig. 2. S-iCT (pg/ml) in 8 healthy individuals before and after (maximum value) stimulation with pentagastrin 0.5 μg/kg body weight, calcium 2 mg/kg body weight and whisky 50 ml.

tection limit was 20 pg/ml. Normal range was 0 to 120 pg/ml, and detectable serum values could be found in 65 per cent of normal subjects. The intraassay coefficient of variation was below 3 per cent at a serum concentration of 350 pg/ml and 14 per cent at a serum concentration of 30 pg/ml. The interassay variation coefficient was 14 per cent at a S-iCT concentration of 140 pg/ml.

Statistical evaluation. A significant increase in S-iCT was defined as an increase exceeding twice the analytical error. The relative increases in S-iCT were compared using Student's t-test for paired comparisons.

Results

The basal S-iCT values in MCT patients and normal controls are given in Fig. 1. S-iCT was increased in all patients with MCT, ranging from 380 to 120 000 pg/ml. S-iCT was undetectable in 5 of the 8 volunteers and within normal limits (less than 120 pg/ml) in the rest.

The maximum increases in S-iCT during stimulation with pentagastrin, calcium and whisky in the normal controls appear in Fig. 2. A significant increase in S-iCT ($p<0.05$) was found in 2 controls following pentagastrin, in 3 following calcium and in 3 following whisky. The maximum increase in S-iCT was found 2 to 15 min following stimulation, with no differences between the stimulation procedures. None of the stimulated values exceeded the upper normal basal range of 120 pg/ml. The mean rise in serum calcium during calcium infusion was 1.4 mg/100 ml (range 1.0–1.7).

The effects of stimulation with pentagastrin, calcium and whisky on S-iCT in the 6 patients with MCT appear in Fig. 3. A significant increase in S-iCT ($p<0.05$) was found in all 6 patients following pentagastrin, in 5 patients following calcium and in 3 patients following whisky. The maximum increases in S-iCT were found 2 to 5 min following stimulation without differences between the stimulation procedures.

The average absolute increase in S-iCT was 81 500 pg/ml (range 2 150–400 000) following pentagastrin, 23 400 pg/ml (range 0–115 000) following calcium, and 13 800 pg/ml (range 0–80 000) following whisky. The relative mean increase in S-iCT was 827 per cent (range 130–1 475) after pentagastrin, 244 per cent (range 0–686) after calcium, and 38 per cent (range 0–89) after whisky. The mean rise in serum calcium during calcium infusion was 1.3 mg/100 ml (range 0.4–1.9).

The greatest increase in S-iCT occurred in 5 pa-

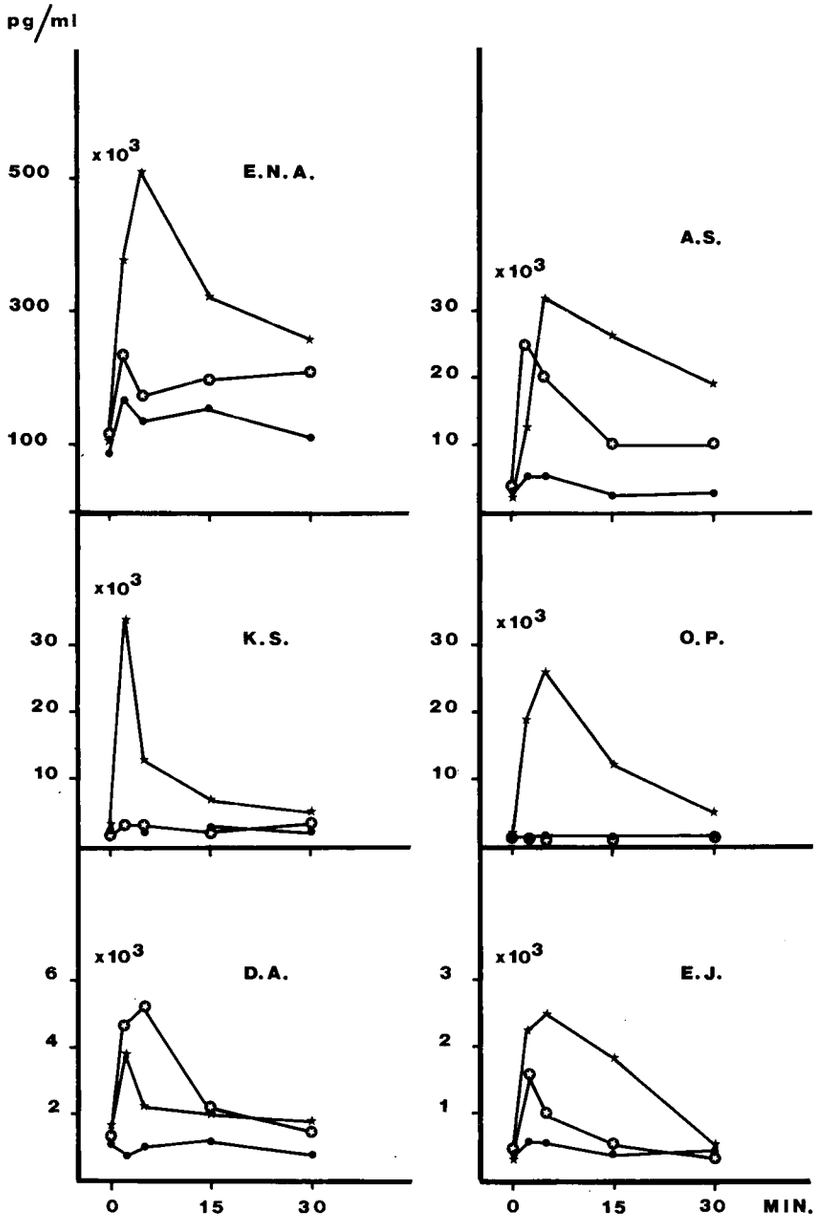

Fig. 3. S-iCT (pg/ml) in 6 patients with medullary carcinoma of the thyroid before and after stimulation with pentagastrin (*) 0.5 μg/kg body weight, calcium (o) 2 mg/kg body weight and whisky (●) 50 ml.

tients after stimulation with pentagastrin and in one patient after stimulation with calcium. No significant difference was found between the relative increase in S-iCT following stimulation with pentagastrin or calcium. However, the relative increase in S-iCT following whisky was significantly ($p<0.02$) lower than following pentagastrin, whereas no significant difference was found between the increases in S-iCT following whisky and calcium.

Discussion

The results showed that all 6 patients with MCT responded to pentagastrin with a marked increase in S-iCT, while 5 patients responded to short-term calcium infusion and 3 to oral whisky. The maximum stimulated S-iCT values were found after pentagastrin in 5 patients and after calcium in one patient. Among the 8 normal controls only a modest increase in S-iCT after pentagastrin, calcium and whisky was

found, with no difference between the three procedures.

In several reports on screening for familial MCT (SIZEMORE & GO, TELENIUS-BERG et coll. 1977, GRAZE et coll.) it was stated that pentagastrin 0.5 μg/kg body weight given intravenously as a bolus is a potent stimulator for iCT secretion in patients with C-cell neoplasms, an excessive response being almost diagnostic. On the other hand RUDE & SINGER showed that short-term infusion of calcium 2 mg/kg body weight during one minute was a more potent stimulator for iCT secretion than pentagastrin in 4 patients with MCT. In this series one patient did not respond at all to pentagastrin.

A 4-hour infusion of calcium 15 mg/kg body weight was previously the standard stimulative procedure for disclosing the abnormally high S-iCT response in patients with C-cell neoplasms. However, this method is time consuming, frequently causes nausea and vomiting, and gives no advantage compared with pentagastrin (TELENIUS-BERG et coll. 1975, SIZEMORE & GO, GRAZE et coll.).

Injection of pentagastrin is followed by a sudden onset of generalized unpleasantness with oppression and abdominal discomfort lasting for about 2 min. Short-term calcium infusion produces less severe side effects, but may give nausea and a general feeling of warmth.

As a convenient and well tolerated stimulative procedure oral whisky has been introduced. Ingestion of 50 ml whisky increased S-iCT by a mean of 185 per cent in 14 patients with MCT (DYMLING et coll.). This method was subsequently used for detection of familial MCT (DYMLING et coll., HILLYARD et coll.). In these series patients with basal S-iCT concentrations within normal range and abnormally high S-iCT responses to whisky did not undergo thyroidectomy with microscopic examination for C-cell neoplasms. Thus the frequency of true and false positive reactions could not be determined. Likewise, when evaluating stimulative procedures in family members at risk with borderline elevation of S-iCT, the frequency of false negative reactions cannot be evaluated unless all family members undergo thyroidectomy. Therefore, the three stimulative procedures were tested in patients with known C-cell neoplasms, assuming that results obtained in these patients are valid also in patients with small C-cell neoplasms and borderline elevated S-iCT concentration. Using the iCT assay, whisky was a weak and unreliable stimulator for S-iCT compared with pentagastrin in 6 patients previously operated upon for MCT and with elevated basal S-iCT concentrations, indicating persistent C-cell neoplasia. Similar results have been obtained by TELENIUS-BERG et coll. (1977).

In screening for familial MCT intravenous pentagastrin is recommended as the stimulative agent with measurement of S-iCT concentrations before and 2 and 5 min after injection. Considering the single patient with MCT of RUDE & SINGER who did not respond to pentagastrin, short-term calcium infusion should be carried out if results obtained after pentagastrin are equivocal or if clinical suggestion persists despite a negative S-iCT response to pentagastrin.

SUMMARY

The efficiency of pentagastrin, calcium and whisky in raising serum immunoreactive calcitonin (S-iCT) concentrations was analysed in 6 patients with medullary carcinoma of the thyroid and in 8 healthy controls. All 6 patients responded to pentagastrin with a significant increase in S-iCT, 5 responded to calcium and only 3 to whisky. In the 8 controls no or only a modest increase in S-iCT occurred following pentagastrin, calcium and whisky with no difference between the three. It is concluded that pentagastrin is the most useful stimulative agent for ICT secretion in patients with C-cell neoplasms. In selected cases the additional use of calcium could be advantageous.

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