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Lack of effects of human calcitonin in osteogenesis imperfecta

The effects of human calcitonin on bone mineral content and certain biochemical markers of bone metabolism were evaluated in a 2–12-month treatment period in seven patients with osteogenesis imperfecta. S-calcium, S-alkaline phosphatase, S-immuno-reactive parathyroid hormone and the urinary excretion of calcium were found to be within the normal range before and during the treatment period. After 4–5 months of therapy, a slight increase in the urinary excretion of hydroxyproline was observed, but the values were still within the normal range. The bone mineral content, measured in the forearm, remained unchanged during the treatment period. Side effects were common, in two cases resulting in discontinuation of the treatment. We concluded that, with the dose of human calcitonin used, it was impossible to detect any beneficial effect in patients with osteogenesis imperfecta.

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Although most published articles on the medical treatment of osteogenesis imperfecta (OI) have claimed beneficial results, no treatment has yet been accepted as effective (Albright 1981).

Though OI is probably caused by a defect in collagen synthesis (for review, see Smith et al. 1983), it has been claimed that the basic lesion in OI is an increased bone turnover with a predominance of bone resorption (Jett et al. 1966, Ramser et al. 1966, Falvo & Bullough 1973). Calctonin acts on bone by an almost complete inhibition of bone resorption (Austin & Heath 1981), accomplished primarily by inhibition of both the number and activity of bone-resorbing osteoclasts (Deftos & First 1981). Increased bone turnover characterizes Paget's disease of bone, and human calcitonin has proved effective in the treatment of this disease (MacIntyre 1976). A favorable treatment response has also been reported in patients with OI using salmon or porcine calcitonin (Caniggia & Gennari 1972, Castells et al. 1972, 1974, 1976, 1979, Goldfield et al. 1972, Castells 1973, Lang et al. 1973, Armstrong et al. 1975, Rosenberg et al. 1977). Therapeutic trials with human calcitonin in OI have not yet been published.

We wanted to evaluate the effects of systemic human calcitonin treatment on bone mineral content (BMC), on certain biochemical parameters and on the hearing loss in patients with OI.

Patients and methods

The study comprised six females and one male, with a median age of 36 (11–52) years. Five patients had OI-tarda and two patients OI-congenita. All patients had a history of multiple fractures (Table 1) and all had blue sclerae. Patients with OI-tarda had a family history compatible with autosomal dominant inheritance. All patients had the typical OI appearance, with a triangular face and an overhanging, so-called "Tam O'Shanter" skull. Conductive or mixed conductive/sensorineural hearing loss was present in all patients. Histological examination of transcortical iliac crest biopsies revealed a bone structure consistent with OI.

Patients with abnormal thyroid function tests, abnormal kidney function, a history of gastrointestinal disease or liver affection and patients receiving chronic medication were excluded from the trial. No fractures occured during the treatment period.

After informed consent, the patients were admitted for a 3-week pretreatment evaluation, including training in subcutaneous self-administration of calcitonin.

Five patients were treated with synthetic human monomer calcitonin (Cibacalcin®) 0.5 mg subcutaneously three times a week and two patients with 0.25 mg daily (Table 1). Three patients were treated for a period of 6 months, two patients gave up treatment

Table 1. Clinical features and treatment schedule for seven patients with osteogenesis imperfecta

Case	Age	Sex	Body weight (kg)	OI-type	No. of fractures	Weekly dose (mg)	Duration of calcitonin therapy (mo)
1	40	F	54	Tarda	19	0.5×3	6
2	33	M	71	Tarda	14	0.5×3	2
3	23	F	46	Cong.	17	0.5×3	6
4	36	F	37	Cong.	21	0.5×3 (6 mo), 0.25×3 (6 mo)	12
5	41	F	38	Tarda	11	0.25×7	9
6	52	F	65	Tarda	8	0.5×3	3
7	11	F	43	Tarda	5	0.25×7	6

after 2 and 3 months, respectively, because of substantial side effects, one patient had a 9-month treatment period and one patient continued the treatment for 12 months, the last 6 months at a reduced dose of 0.25 mg three times a week (Table 1). Serum levels of calcium, alkaline phosphatase and renal 24-h excretions of calcium, hydroxyproline and creatinine were determined on a gelatine-free diet before and after 1, 2, 3, 4, 5 and 6 months of therapy. In the adult patients, urinary excretion of calcium and hydroxyproline was evaluated in relation to urinary creatine in the 24-h urine. Serum calcium was corrected for individual variations in serum protein concentration and calculated as the calcium concentration corresponding to a protein level of 70 g/l serum (Pedersen 1973).

S-immuno-reactive parathyroid hormone (S-iPTH) was measured by a radio-immunoassay using an antibody directed against the C-terminal part (65–84) of the parathyroid hormone.

All patients were examined at the ENT-department before and after 1, 2, 3, 4, 5 and 6 months of therapy. Otoscopy, tone- and speech audiometry, test of stapedial reflex and tympanometry were performed.

The BMC in the forearm was measured with the aid of a GAMMATEC osteodensitometer model GT 30 with a 50 mCi ^{25}I source (Christiansen et al. 1975). The scan site was situated in the most distal position of the forearm where the separation of radius and ulna exceeds 8 mm. The values of 6 scans with a separation of 4 mm between each were recorded in both arms, and the mean values calculated. The results were expressed in per cent of the mean value for normal individuals of the same sex and age (BMC per cent). The reproducibility of the BMC measurements expressed as the coefficient of variation is about 1 per cent in normal individuals (Christiansen & Rødbro 1977).

Results

The BMC per cent was found to be reduced in two patients ($p < 0.05$) and slightly but insignificantly reduced in five patients. The BMC per cent remained unchanged for each patient during the treatment period. In all patients serum calcium was found to be within the normal range before and during therapy.

The urinary excretion of calcium and hydroxyproline was within the normal range during therapy. In four patients who accomplished 6 months of therapy, a slight increase was ob-

Table 2. BMC% and biochemical parameters in Case 7 before and during treatment with human calcitonin

Normal range	Months of therapy						
	0	1	2	3	4	5	6
BMC%	80	–	79	78	–	86	88
S-Ca (mmol/l) (2.25–2.60)	2.59	2.80	2.62	2.45	–	2.65	2.60
S-iPTH (ng/l) (15–50)	8	30	44	55	45	40	40
S-alk. phosph (u/l) (200–800)	398	433	454	424	401	–	411

Table 3. BMC% and biochemical parameters in Case 2 before and during treatment with human calcitonin

	Months of therapy 0	1	2
BMC%	75	77	75
S-Ca (mmol/l) (normal range: 2.25–2.60)	2.47	2.34	2.49
U-Ca (mg/mg creatinine) (normal range: 0.025–0.25)	0.22	0.19	–
U-hydroxyproline (mg/mg creatinine) (normal range: 0.004–0.050	0.012	0.020	0.013
S-iPTH (ng/l) (normal range: 15–50)	20	25	20
S-alk. phosphatase (U/l) (normal range: 80–220)	247	413	309

served in the urinary excretion of hydroxyproline after 4–5 months of therapy.

All patients had normal levels of S-iPTH during the treatment period. In patient no. 7 a marked increase in S-iPTH was observed during therapy, but the values were still below the upper normal limit (Table 2).

Five patients had normal serum alkaline phosphatase before and during the treatment period. In patient no. 2, serum alkaline phosphatase was elevated, and a corresponding increase in urinary excretion of hydroxyproline was noted indicating an increased bone turnover (Table 3). Serum level of phosphorus, complete blood counts and the erythrocyte sedimentation rate were normal before and during treatment. The hearing level in the five patients who accomplished at least 6 months of calcitonin treatment was measured monthly. One patient had a normal hearing level, one had a minor bilateral sensorineural hearing loss, two had unilateral conductive hearing loss and one showed bilateral mixed perceptive and conductive hearing loss. No significant change in pure tone hearing level, speech reception threshold and stapedial reflex was observed during calcitonin administration.

Three patients experienced only slight or negligible side effects. In four patients the side effects occurred within 60 min of the injection and were tolerated by two patients (Table 4). For the remaining two, discontinuation of treatment was necessary because of intolerable side effects. During calcitonin therapy, two patients perceived an improvement in symptoms from the joints, muscles and back.

Discussion

In a previous study of 22 patients with OI we found a reduced BMC in the forearm bones compared to a sex- and age-matched control group (Pedersen et al. 1979). In the present study, where the BMC values were used to determine any change in bone mass during the treatment period, only two patients revealed a significant reduction in BMC. In disagreement with Rosenberg et al. (1977), we found no changes in BMC during calcitonin therapy. Rosenberg's patients were children treated with salmon calcitonin for periods ranging from 14 to 35 months. The discrepancy between the results might arise because children are in the bone modelling while adults are in the bone remodelling period (Frost 1969), and because of the relatively short treatment period in our investigation. The reason might also be that salmon calcitonin is more efficient. In 48 children and two adults with OI, Castells et al. (1979) found a significant improvement

Table 4. Side effects of human calcitonin treatment for 7 patients with osteogenesis imperfecta

Case	Diarrhoea	Nausea	Flushing	Urinary frequency	Hot sensation and sweating	General malaise	Chills	Abdominal cramps
1	×	×	×	×	×	×	×	
2		×	×			×		×
3		×	×			×		×
4				×				
5			×				(×)	
6		×	×		×	×	×	
7		(×)						(x)

in radiographic bone density in patients under 5 years of age.

A possible beneficial effect of calcitonin administration could be explained by a lack of calcitonin in patients with OI. In a previous study, however, we found normal serum calcitonin levels in all but one of 21 patients (Nielsen et al. 1979).

In conformity with previous findings (Smith et al. 1975, Rosenberg et al. 1977), all patients but one showed normal serum alkaline phosphatase levels. Like others (Castells et al. 1972, 1976), we found no changes in serum calcium or phosphorus concentrations during treatment. Rosenberg et al. (1977) found that long-term therapy with salmon calcitonin resulted in serum values for calcium and phosphorus which in most cases were lower than the pre-treatment values. In our study the 24-h excretion of hydroxyproline was normal, but at the end of the treatment period a slight increase in the hydroxyproline excretion was noted. Elevated, normal and subnormal hydroxyproline excretions in patients with OI have previously been reported, but in none of these studies has it been proved that OI is predominantly a disorder with increased bone turnover (Caniggia & Gennari 1972, Castells et al. 1972, 1979, Goldfield et al. 1972, Riley et al. 1973, Smith et al. 1975, Rosenberg et al. 1977).

As stated by Smith et al. (1983), the effect of calcitonin on measurements used to assess bone turnover varies from one patient to another. However, a few patients with OI may have increased bone turnover, as some of the studies described earlier have shown beneficial effects in some patients treated with calcitonin.

The development of secondary hyperparathyroidism with continuous calcitonin administration may explain certain aspects of calcitonin resistance (Deftos & First 1981). In agreement with Castells et al. (1979), we found normal serum levels of PTH. The marked increase in S-iPTH in the 11-year-old girl could be explained by the age of puberty or, less likely, by a calcitonin-induced secondary hyperparathyroidism.

The present study showed no improvement in hearing level in four patients with hearing loss. Unaltered audiometry during porcine and salmon calcitonin therapy has been described previously (Castells et al. 1972, 1974). However, all seven patients included in these investigations were children with normal hearing. The dosage of calcitonin is possibly important both for the therapeutic effect and for the occurrence of side effects. However, with the dose of human calcitonin used in the present study of seven patients with OI, no effect of calcitonin therapy on the BMC, biochemical determinants of bone metabolism and the hearing loss could be proved, and most of the patients experienced substantial side effects.

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