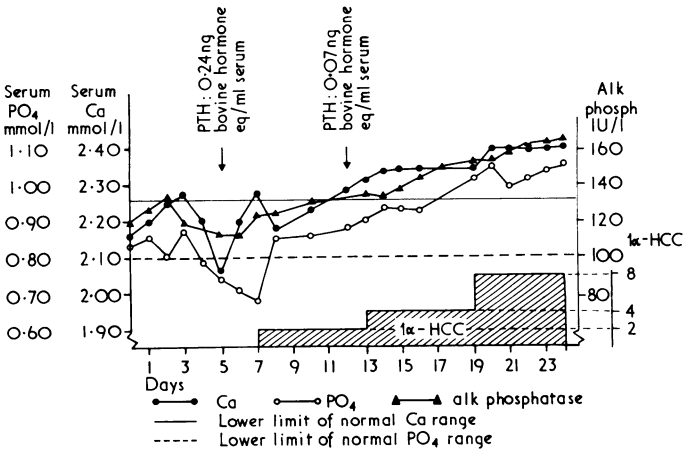
Treatment of anticonvulsant osteomalacia with 1α-hydroxycholecalciferol

Anticonvulsants cause osteomalacia,[1] possibly by the induction of an altered vitamin-D metabolism in the liver leading to a lack of 25-hydroxycholecalciferol (25-HCC).[2] We describe the short-term treatment of a patient with anticonvulsant osteomalacia with small amounts of 1-HCC, a vitamin-D analogue that has been used in renal osteodystrophy[3] and other metabolic bone diseases.

Case history

A 51-year-old woman with an infantile spastic paresis on the right, and epilepsy treated for 30 years with phenobarbital 50 mg and phenytoin 75 mg three times a day was seen because of fatigue and increasing pains in the trunk and legs. She had had little exposure to sunshine for six years and her diet was deficient in vitamin D. The whole thorax and vertebral column were extremely painful on palpation and percussion. Pelvic side-pressure evoked pain in the pubic region. She had spastic paresis of the right arm and leg. Relevant laboratory data were: serum Ca 2·01 mmol/l (8·04 mg/100 ml) and P 0·52 mmol/l (1·6 mg/100ml), total protein 73 g/l (7·3 g/100 ml), albumin 55 g/l (5·5 g/100 ml), alkaline phosphatase 112 IU/l (normal < 45), 25-HCC 1·9 nmol/l (normal >12), parathyroid hormone (PTH) 0·24 ng bovine hormone eq/ml (normal < 0·20), urinary calcium 50 mg/24 h, calcium retention after infusion of 10 mg/kg 82 % (normal < 60), and ^{47}Ca absorption 15 % dose (normal >25). An iliac crest biopsy showed complete coverage of the trabeculae by osteoid with a thickness of more than 25 μm. Radiological examination showed a low contrast, especially of the vertebral column and pseudofractures in the right scapula and bilaterally in the pubic region.

We concluded that the patient was suffering from osteomalacia caused mainly by taking anticonvulsants for 30 years. She continued the antiepileptic treatment and received a diet containing 1200 mg calcium. The figure shows the dosage scheme of 1-HCC. The serum calcium concentration rose steadily after five days of treatment to level off in the normal range



Dosage scheme of 1-HCC.

after eight days. After the second dose increment the calcium concentration rose further. The serum phosphorus concentrations showed nearly the same reaction pattern, while the alkaline phosphatase further increased to the end of the observation period. In other therapeutic schemes of osteomalacia this phenomenon has usually been observed initially. The serum PTH concentration decreased to 0·07 ng bovine hormone eq/ml after six days of treatment. The urinary excretion of calcium scarcely increased. Bone pain and muscular weakness disappeared rapidly, so that after five days of treatment she could stand up and walk without pain.

Comment

The excellent clinical and biochemical response to a low dose of 1-HCC, despite the continuation of anticonvulsant treatment, suggests that either 1-HCC need not be hydroxylated at C-25 for biological activity or that anticonvulsant osteomalacia is not caused by interference with liver vitamin-D metabolism. Good long-term results of vitamin-D treatment of anticonvulsant osteomalacia have been described with daily dosages of about 15 000 IU corresponding to 375 μg of cholecalciferol.[4] Our findings seem to contrast with the apparent lack of response that Chan *et al*[5] found in two patients with renal osteodystrophy who were treated with 1-HCC as well as anticonvulsants. We cannot explain the apparent lack of short-term effect of 1-HCC on our patient's calciuria.

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Finger wrinkling as a test of autonomic function

Finger wrinkling in water has a neurological basis. Lewis and Pickering[1] found that the skin of the median nerve distribution failed to wrinkle in median nerve palsy. We investigated the role of the autonomic nervous system in this phenomenon and suggest that it may be used as a test of autonomic function.

Methods and results

Two patients with Raynaud's disease and hyperhidrosis respectively were tested for finger wrinkling before and two days after unilateral upper thoracic sympathectomy. In each case both hands were immersed in tapwater at 40 C for 30 minutes.[2] In both cases wrinkling occurred bilaterally before operation and on only the non-sympathectomised side after operation. Three diabetic patients with other evidence of autonomic failure—for example, orthostatic hypotension and diarrhoea—but without clinical evidence of peripheral neuropathy were similarly tested and failed to wrinkle, while other diabetics wrinkled normally. A patient with Guillain-Barré polyneuropathy failed to wrinkle in the acute phase. An anaesthetised finger (ring block) failed to wrinkle in water, and the fingers of a sympathectomised hand deprived of its blood supply (cuffed to systolic pressure) wrinkled normally.

Comment

These results indicate that failure of the skin to wrinkle may be due to loss of the sympathetic nerve supply to the hand. We suggest that wrinkling depends on two sets of factors, epidermal and deep-tissue.

Epidermal factors—After immersion the stratum corneum of the epidermis absorbs water and swells, the degree of swelling itself depending on several factors: (*a*) the greater the difference between the pH of the fluid and the pK of the epidermal keratin (3·5-5·0) the more the swelling,[3] (*b*) the higher the water temperature the more the swelling,[4] (*c*) the higher the ambient sodium chloride concentration the more the swelling,[3] and (*d*) sebum tends to prevent hydration of the epidermis. Hence the fingers wrinkle particularly rapidly when immersed in 20 m sodium hydroxide solution,[1] soapy water, or hot water, as do the fingers of patients with cystic fibrosis.[5] Only the palms and soles wrinkle, since they are devoid of sebaceous glands, sebum exerting a waterproofing effect.