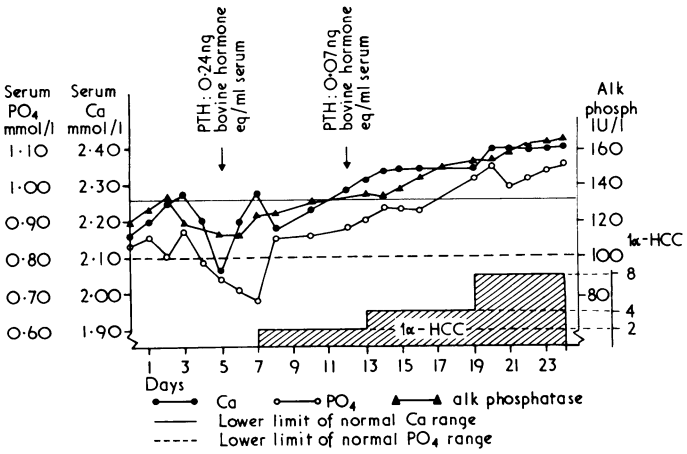
Treatment of anticonvulsant osteomalacia with 1α-hydroxycholecalciferol

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.

We are grateful to Dr Ernst N H Jansen (department of neurology) for referring the patient to us and Dr J H Schade for the determination of 25-hydroxycholecalciferol. We thank Leo Pharmaceutical Products, Copenhagen, Denmark, for the supply of 1α-hydroxycholecalciferol.

[1] Dent, C E, Richens, A, and Rowe, D J F, *British Medical Journal*, 1970, **4**, 69.
[2] Hahn, T J, *et al*, *Journal of Clinical Investigation*, 1972, **51**, 741.
[3] Castells, S, *et al*, *Current Therapeutic Research*, 1976, **19**, 410.
[4] Maclaren, N, and Lifshitz, F, *Pediatric Research*, 1973, **7**, 914.
[5] Chan, J C M, *et al*, *Journal of the American Medical Association*, 1975, **234**, 47.

(*Accepted 28 October 1976*)

Department of Internal Medicine (III) and of Clinical Endocrinology, University Hospital "Dijkzigt," Erasmus University, Rotterdam, The Netherlands
J R JUTTMANN, MD, physician
J D BARTH, MD, physician
J C BIRKENHÄGER, MD, professor of internal medicine and clinical endocrinology

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.

Deep-tissue factors—Provided the turgor of the deep tissues is sufficiently low, swelling of the epidermis will lead to wrinkling. Turgor is high when the sympathetic tone is low and the vessels are dilated. Thus in sympathectomised hands, which are typically warm, dry, and swollen, the tissue turgor is too great to allow the swelling of the epidermis to lead to wrinkling. Wrinkling will also fail to occur when sufficient oedema is present.

We suggest that the phenomenon of finger wrinkling may be of value in the diagnosis and assessment of patients in whom autonomic neuropathy is suspected. The test is easy to apply and, unlike the Valsalva manoeuvre or loss of sinus arrhythmia, reflects peripheral rather than cardiac sympathetic denervation.

We thank Mr D A Bailey for allowing us to study his patients. Requests for reprint should be addressed to JAH.

[1] Lewis, T, and Pickering, G W, *Clinical Science*, 1935, **2**, 149.
[2] O'Riain, S, *British Medical Journal*, 1973, **3**, 615.
[3] Moynahan, E J, *Lancet*, 1974, **2**, 907.
[4] Lewis, T, *Clinical Science*, 1942, **4**, 349.
[5] Elliott, R B, *Lancet*, 1974, **2**, 108.

(*Accepted 28 October 1976*)

University College Hospital, London WC1E 6AU
C BULL, MB, BCHIR, house physician
J A HENRY, MB, MRCP, medical registrar

Fatal oxprenolol poisoning

We describe what we believe to be the first recorded case of fatal oxprenolol overdosage.

Case report

A 57-year-old woman was brought to the casualty department on 27 February 1976. For some time she had been complaining of discomfort in her throat that she thought might be due to cancer, but had refused to see a doctor. Her husband noticed at breakfast on the day of admission that she was rather pale and staggering, and she said that she had taken his oxprenolol tablets. He knew that he had exactly 112 40-mg tablets left and he found the bottle empty. He gave her a drink with salt and she vomited several tablets, but soon afterwards became unconscious. She was then brought to the casualty department. Her husband estimated that the time between her taking the tablets and her appearance at breakfast could not have been more than 15 or 20 minutes.

She was deeply unconscious; her peripheries were cold and clammy and she had central cyanosis. Her pulse was impalpable and her blood pressure unrecordable. Heart sounds were soft with a ventricular rate of 36/min and she had bilateral basal crepitations. She was flaccid and reflexes were absent. Her electrocardiograph showed a regular ventricular rate of 36/min with a right bundle-branch block pattern. P waves could not definitely be identified.

External cardiac massage and assisted respiration were carried out. There was no response in pulse rate to intravenous atropine and to isoprenoline. A transvenous pacing catheter was passed through the right median cubital vein and positioned in several areas inside the right venticle, but the ryhthm could not be captured. The patient died in asystole about one hour after her arrival in hospital.

Post-mortem examination showed no gross structural abnormality in any of the systems, particularly the heart, which was normal with no evidence of ischaemic heart disease. Several samples of tissue were sent for forensic examination and the concentrations of oxprenolol in the stomach, blood, brain, and liver were estimated at 1·05 g, 37·7 μmol/l (1 mg/100 ml), 267 μmol/l (7·09 mg/100 ml), and 866 μmol/l (23 mg/100 ml), respectively. The cause of death was established as poisoning from overdosage of oxprenolol hydrochloride.

Comment

Determined and prompt attempts both with drugs and electrical pacing were made to stimulate the myocardium and reverse the effects of oxprenolol, but, as in other cases of severe poisoning with cardiosuppressants, they were unsuccessful in either increasing the ventricular rate or the cardiac output. In normal therapeutic doses the antiarrhythmic effect of beta-blocking agents is accepted as being due to antisympathetic Class II effect (Vaughan Williams Classification).[1] Higher concentrations of these agents, however, which are powerful anaesthetics, also have a Class I action.[2]

The effects of beta-adrenergic drugs on cardiac contractibility are complex and include withdrawal of sympathetic support, which may be at least partially reversed by sympathomimetic agents. Naylor and Chang[3] have shown that propranolol and to a lesser extent oxprenolol and practolol reduce the capacity of the sarcoplasmic reticulum to accumulate Ca^{2+} for subsequent release, and also that a drug interaction with the cell membrane depletes the membrane-based store of Ca^{2+}. These stores are normally released and made available for the reactions associated with the excitation-contraction coupling,[4] thus affecting the rising phase of the action potential, part of which is maintained by an inward current of Ca^{2+}.[5]

This mechanism probably contributes to the dose-dependant negative inotropic effects of many of these drugs, and may explain the failure of pharmacological and electrical stimulation in this particular case. The rapid loss of consciousness in this patient was notable and was probably due to the high concentrations of the drug in the central nervous system. The degree of penetration of beta-adrenergic blocking agents through the blood-brain barrier varies with different compounds and depends on the different lipid solubilities of the drugs—for example, practolol appears in the brain in very low concentrations.

The rapidity of onset of severe symptoms in our patient was alarming. The estimated time between ingestion and the onset of symptoms was only 15 to 20 minutes, and the intrinsic stimulating effect of oxprenolol did not appear to offer any protective mechanism.

[1] Vaughan Williams, E M, in *Symposium of Cardiac Arrhythmias*, ed E Sandøe, *et al*, p 449. Soderstalje, Sweden, A B Astra, 1970.
[2] Coltart, D J, and Shand, D G, *British Medical Journal*, 1970, **3**, 731.
[3] Naylor, W G, and Chang, A, in *International Symposium: New Perspectives in Beta Blockage*, ed D M Burley, *et al*, p 56. Horsham, Ciba Laboratories, 1973.
[4] Naylor, W G, and Merrilees, N C R, in *Calcium and the Heart*, ed P Harris and L Opie. New York, Academic Press, 1971.
[5] Beeler, G W, and Reuter, H, *Journal of Physiology*, 1970, **207**, 211.

(*Accepted 4 November 1976*)

Royal Halifax Infirmary, Free School Lane, Halifax
A KHAN, MB, BS, medical registrar
J M MUSCAT-BARON, MD, MRCP, consultant physician

Successful treatment of ischaemic ulceration of the skin in azotaemic hyperparathyroidism with parathyroidectomy

Ischaemic ulceration of the skin in azotaemic hyperparathyroidism has rarely been described.[1-4] We report two cases of this unusual condition.

Case reports

Case 1—A 63-year-old man on haemodialysis for hypertensive nephrosclerosis noticed reddening and itching of the skin of his lower legs in February 1973. Within a few days small, painful ulcers developed that enlarged progressively, reaching a size of approximately 8 × 10 cm in November 1973. Due to the pain the patient became incapacitated, and generalised itching appeared. Serum calcium ranged from 2·7-2·9 mmol/l (10·8-11·8 mg/100 ml) and phosphorus from 1·6-2·6 mmol/l (5·0-8·2 mg/100 ml); serum alkaline phosphatase was 14-19 KA units (normal ⩽ KA units). The calcium content of the skin was 640 mg/kg dry weight (normal <400 mg/kg). Several local therapeutic trials and intravenous antibiotics failed to improve the ulceration. Subtotal parathyroidectomy was performed in November 1973. Histological examination showed generalised nodular adenomatous hyperplasia. Three weeks after surgery pain and itching had disappeared and the ulcers were healing within four months.

Case 2—A 52-year-old man with polycystic kidney disease noticed tender, hardened, dark red patches on the lower parts of both legs in November