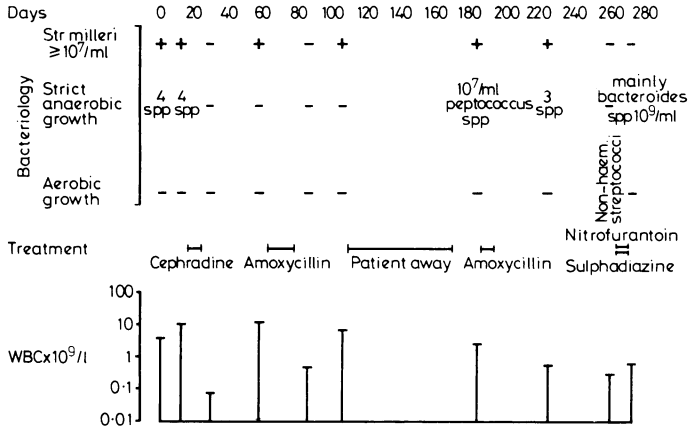
(95·6 mg/100 ml)) and creatinine (170 μmol/l (1·9 mg/100 ml)) concentrations, but electrolyte, liver function, and haematological values were normal. An excretory pyelogram performed in May 1980 showed no abnormalities.

Two mid-stream specimens of urine (MSU) showed gross pyuria (up to 30×10^9/l white blood cells) but no significant bacterial growth aerobically. The result of culture for *Mycobacterium tuberculosis* was negative. Subsequent MSUs were cultured both anaerobically and aerobically using a dilution technique,[3] and the findings are shown in the table. A microaerophilic species, *Streptococcus milleri* (10^7/ml), and four species of strict anaerobes were present in two successive specimens, with gross pyuria, but few aerobic organisms were isolated ($<10^3$/ml).



Serial results of MSU culture and white cell counts and treatment given.

Three separate courses of antibiotic treatment, first with cephradine (1 g 12-hourly) then twice with amoxycillin (500 mg 8-hourly), all produced a similar clinical response: the bacteriuria was initially eradicated and pyuria greatly reduced, but relapse occurred each time, *Str milleri* returning in large numbers ($>10^7$/ml). *Peptococcus* sp was also present (10^7/ml) on one occasion. Bacteriological relapse was associated with an increase in white cell excretion. Eventually *Str milleri* disappeared spontaneously, but an aerobic streptococcus (10^6/ml) was then found. Combined treatment with nitrofurantoin (50 mg 12-hourly) and sulphadiazine (150 mg 12-hourly) cleared the streptococci, but the urine then contained large numbers of anaerobic species (predominantly *Bacteroides* spp, 10^9/ml). The patient remained symptom-free at all times. In view of the recurrent nature of relapses and reinfections, and the fact that the patient was well, no further antibiotic treatment was given, and the infection cleared spontaneously. Four months later *Str milleri* (10^6/ml) was again found; phenoxymethylpenicillin (250 mg 8-hourly) cleared this infection, and since March 1980 the urine has remained free of anaerobes and microaerophilic bacteria.

Comment

Anaerobes and microaerophilic bacteria may be isolated in large numbers ($>10^5$/ml) in mid-stream urine specimens from patients without signs of infection[3] and from normal subjects (unpublished work). Nevertheless, we are convinced, after repeated cultures and temporary eradication of bacteriuria together with concomitant reductions of pyuria after treatment, that genuine infective processes were occurring in this patient. Our findings lend weight to the theory that growth conditions for strict anaerobes and microaerophilic organisms are favourable in the urinary tract[4] and that such species can cause true infections.[5]

In this case *Str milleri* was usually the predominant species, often accompanied by several species of strict anaerobes in large numbers ($>10^5$/ml) always including *B melaninogenicus*. Metronidazole was not given because it is inactive against *Str milleri*.

Our findings highlight the difficulty of treating infections of this nature, which can be associated with urological abnormalities. Thus when persistent "sterile pyuria" is reported the clinician should look for microaerophilic and anaerobic bacteria as well as excluding infection by *M tuberculosis*. In this patient the use of appropriate culture techniques enabled us to diagnose the microaerophilic and anaerobic infection and eventually to eradicate it.

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Osteomalacia developing during treatment of osteoporosis with sodium fluoride and vitamin D

Combined treatment with sodium fluoride, calcium, and vitamin D is claimed to be beneficial in some patients with osteoporosis.[1 2] Fluoride alone leads to accumulation of unmineralised bone, producing the histological picture of osteomalacia.[3] The addition of calcium or vitamin D, or both, is believed to prevent this complication.[1 2] We report a case where osteomalacia developed during sodium fluoride treatment despite large doses of vitamin D and associated high plasma 25-hydroxyvitamin D (25-OHD) concentrations.

Case report

A 61-year-old woman presented in 1978 with a 15-year history of lower back pain which had rapidly increased over the previous nine months. Plasma concentrations were: calcium 2·50 mmol/l (10 mg/100 ml), phosphate 1·1 mmol/l (3·4 mg/100 ml), and plasma alkaline phosphatase 9 KA U/100 ml. Radiographs showed severe osteoporosis with vertebral compression fractures of T 7, 8, and 11 and L 1, 3, and 5. Iliac bone tissue was normal on biopsy (table). Sodium fluoride 50 mg daily, vitamin D_2 50 000 U weekly,

Quantitative bone histology before and after sodium fluoride and vitamin D treatment. The mineralisation rate was not measured in the first biopsy

	Before treatment (May 1978)	After treatment (March 1980)	Normal (mean ± SD)
Cancellous bone volume (% total cancellous area)	21·5	25·6	23·7 ± 4·9
Osteoid volume (% total cancellous volume)	3·9	18·5	3·9 ± 1·9
Total resorption surface (% total cancellous surface)	7·3	77·7	3·0 ± 1·2
Calcification fronts (% total osteoid surface)	60·0	33·3	76·4 ± 7·8
Mineralisation rate (μ/day)		<0·1	0·64 ± 0·06

and calcium gluconate 600 mg twice daily were given by mouth. Calcium supplements were discontinued after two months because the patient was unable to tolerate them. Dietary calcium intake was assessed at 851 mg/day. Renal function was normal. The plasma 25-OHD concentration was measured by competitive protein-binding assay[4] and plasma 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) by radioimmunoassay.[5] Undecalcified sections (8 μm) of transiliac bone tissue were quantitatively assessed. Control values were obtained from six healthy women aged 51-69 years (mean 58). The mineralisation rate was measured by double labelling with demethylchlortetracycline.

During treatment bone pain increased and three further vertebral compression fractures occurred. Plasma calcium, phosphate, and alkaline phosphatase concentrations remained normal throughout treatment and in March 1980 were 2·49 mmol/l (10 mg/100 ml), 0·9 mmol/l (2·86 mg/100 ml), and 11 KA U/100 ml respectively. At this time the plasma 25-OHD concentration was 125 nmol/l (50 ng/ml) and the plasma 1,25-$(OH)_2D_3$ was 19 pg/ml. Bone biopsy in March 1980 showed moderately severe osteomalacia and secondary hyperparathyroidism. Most of the bone and osteoid showed a normal lamellar pattern under polarised light.

Comment

Increases in osteoid volume with sodium fluoride, calcium, and vitamin D treatment are well documented. Small decreases in mineralisation rate have also been reported.[2] But osteomalacia in the presence of high plasma 25-OHD concentrations has not been described in patients treated with this regimen. The plasma $1,25\text{-}(OH)_2D_3$ concentration in our patient was just below the lower limit of normal, but the total plasma $1,25\text{-}(OH)_2D$ ($1,25\text{-}(OH)_2D_2 + 1,25\text{-}(OH)_2D_3$) concentration was probably normal since she was taking vitamin D_2 and the radioimmunoassay did not measure plasma $1,25\text{-}(OH)_2D_2$.

The mechanisms by which fluoride may produce osteomalacia despite high plasma 25-OHD concentrations require further investigation. Possibilities include fluoride-induced end-organ resistance in bone to active vitamin D metabolites or an effect of fluoride on processes of bone mineralisation that are unaffected by vitamin D metabolites. Alternatively, fluoride might affect the metabolism of 25-OHD to other metabolites. Although lack of calcium supplements was probably unimportant in our patient, since the plasma calcium concentration remained above 2·40 mmol/l throughout treatment and dietary calcium intake was adequate, we cannot exclude it as a factor in the development of osteomalacia. Our results indicate that vitamin D in doses that produce high plasma 25-OHD concentrations does not protect against fluoride-induced mineralisation defects and that patients treated with this regimen require careful supervision. Transiliac biopsy provides a sensitive method for diagnosing generalised bone disease such as osteomalacia and may be necessary to detect its development when, as in our patient, plasma biochemical changes are not diagnostic.

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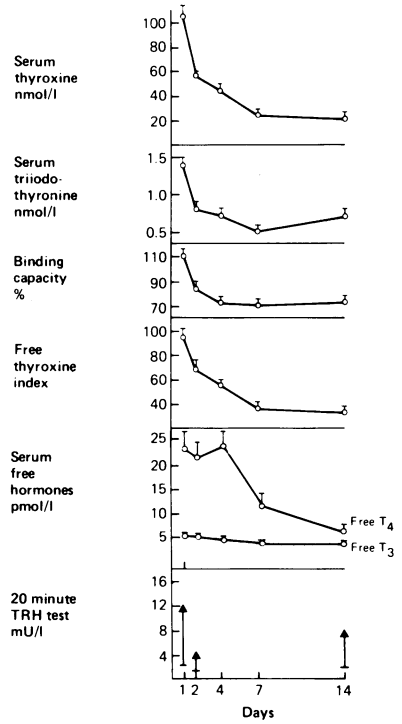
Prospective study of effect of fenclofenac on thyroid function tests

The observation of a very low serum thyroxine concentration in a clinically euthyroid patient receiving fenclofenac suggested that this phenylacetic acid group anti-inflammatory agent may displace thyroxine from its binding sites. To test this hypothesis a group of patients about to be given fenclofenac for rheumatoid arthritis were studied.

Patients, methods, and results

Blood samples were taken from seven euthyroid female patients before starting treatment (day 1) and at midday on days 2, 4, 7, and 14. Each sample was analysed for total serum thyroxine (T4) and triiodothyronine (T3) concentrations by radioimmunoassay and for free serum T4 and T3 concentrations by an equilibrium dialysis method.[1] A thyroid hormone binding test (Thyopac 3) was also done and a derived free thyroxine index calculated. At midday on days 1, 2, and 14 200-μg thyrotrophin releasing hormone (TRH) tests were performed. Fenclofenac 600 mg was taken at 6 pm on day 1 and at 8 am and 6 pm thereafter. There had been no change in drug treatment immediately before the study and no other drugs known to interfere with thyroid function tests were being given during the study.

The mean total T4 concentration fell rapidly to 24 nmol/l (1·86 μg/100 ml) and the total serum T3 concentration fell similarly but to only about half of the initial value (figure). The Thyopac 3 test result suggested that the



Mean (±SEM) change in thyroid function tests after the start of fenclofenac treatment in seven women with rheumatoid arthritis.

Conversion[8] *SI to traditional units*— Thyroxine: 1 nmol/l ≈ 0·078 μg/100 ml. Triiodothyronine: 1 nmol/l ≈ 65·1 ng/100 ml.

number of free or unoccupied binding sites decreased over the first three days and then stabilised. The free thyroxine index fell in parallel with the total T4. The free serum T4 concentration did not change significantly until after the fourth day, when it fell sharply, and the mean value at day 14 was just below the normal range (11·6-33·5 pmol/l (0·90-2·60 ng/100 ml)). The free serum T3 concentration fell from 5·5 to 4·0 pmol/l (350-260 pg/100 ml) ($p = 0·05$) but remained within the normal range of 3·7-7·0 pmol/l (0·24-0·46 pg/100 ml). The thyrotrophin response to TRH was blunted 18 hours after the start of treatment ($p = 0·005$) and was still depressed on day 14 ($p = 0·01$).

Comment

This study shows that fenclofenac rapidly depresses the total serum T4 concentration and, to a lesser extent, total serum T3. The magnitude of the fall is similar to that seen during phenytoin treatment.[2] The result of the thyroid hormone binding test suggests that this effect is caused by the drug competing for binding sites. The total serum concentrations of thyroxine-binding globulin and thyroxine-binding prealbumin were not measured, but the rate of fall in total serum T4 concentration makes it unlikely that these were affected. The low serum T4 and T3 concentrations and a low normal free serum T4 concentration during long-term fenclofenac treatment have been reported.[3]

The rapid fall in total thyroid hormone concentrations and the blunted TRH response might have been expected to be associated with a rise in free T4 and T3 concentrations. But there was a fall in free hormone concentrations. Conceivably a short-lived peak of free