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-$(OH)_2D_3$ concentration in our patient was just below the lower limit of normal, but the total plasma 1,25-$(OH)_2D$ (1,25-$(OH)_2D_2$ + 1,25-$(OH)_2D_3$) concentration was probably normal since she was taking vitamin D_2 and the radioimmunoassay did not measure plasma 1,25-$(OH)_2D_2$.

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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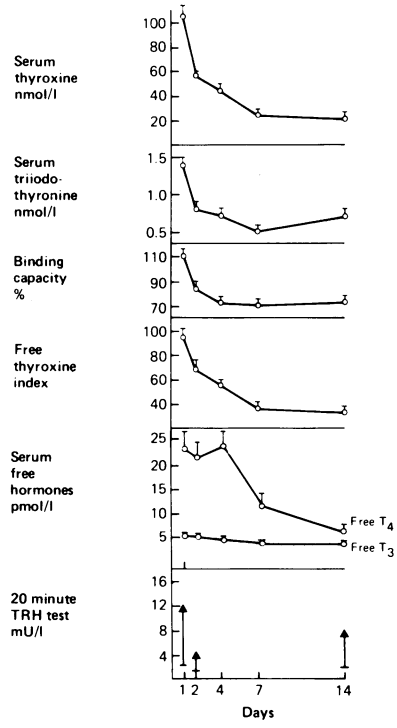
Prospective study of effect of fenclofenac on thyroid function tests

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

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T4 and T3 occurred after the first dose of fenclofenac, but this would not explain the depressed TRH response seen on day 14. The repeated administration of TRH is unlikely to be responsible for this effect.[4 5] It appears that fenclofenac, in addition to displacing thyroxine from its binding sites, has a thyroxine-like effect on the pituitary gland causing partial inhibition of the thyrotrophin response to TRH. We conclude that care must be taken to avoid a spurious diagnosis of hypothyroidism during fenclofenac treatment. The postulated effect of fenclofenac on the pituitary gland is being investigated.

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Are reflectance meters necessary for home blood glucose monitoring?

Tattersall recently discussed the role of reflectance meters in home blood glucose monitoring.[1] A major factor limiting their wider use is their high cost.[2] The Haemoglukotest 20-800 reagent strip (Boehringer Mannheim) offers a considerable saving in capital outlay, since it can be read by eye alone.[3 4] We discuss its possible role in home blood glucose monitoring.

Patients, methods, and results

The Haemoglukotest is specific for glucose. It has two separate test areas, whose indicators permit differentiation of eight pairs of colours corresponding to 1·1, 2·2, 4·4, 6·7, 10·0, 13·3, 22·2, and 44·4 mmol glucose/l blood (20, 40, 80, 121·8, 181·8, 241·8, 403·6, and 807·3 mg/100 ml).

Five diabetic patients, experienced in monitoring blood glucose concentrations at home using a Glucocheck reflectance meter (Medistron) and Dextrostix reagent strips (Ames), were asked to make an independent assessment of their blood glucose concentration at each test using the Haemoglukotest. Results of 242 pairs of tests were recorded by these five patients.

The table shows the number of tests performed in the clinic and at home corresponding to each Haemoglukotest value and the range of blood glucose concentrations (mmol/l; within 95% confidence limits) of these same samples tested by the autoanalyser and Glucocheck reflectance meter respectively.

Comment

A high overall correlation was obtained between the concentrations determined with the Haemoglukotest and the mean values measured by the autoanalyser and reflectance meter (mean value determined by autoanalyser $=1+0{\cdot}88\times$ Haemoglukotest value, $r=0{\cdot}98$; mean value determined by reflectance meter $=0{\cdot}2+1{\cdot}08\times$ Haemoglukotest value, $r=0{\cdot}99$). The main disadvantage of the Haemoglukotest was its inability precisely to identify hypoglycaemia and hyperglycaemia at concentrations of 2·2 and 10·0 mmol/l (40 and 181·8 mg/100 ml) respectively.

The Haemoglukotest value of 2·2 mmol/l (40 mg/100 ml) corresponded to a range in blood glucose concentrations of 1·9-4·1 mmol/l (34·5-74·5 mg/100 ml; $p<0{\cdot}05$) as measured by the autoanalyser and 2·1-4·3 mmol/l (38·2-78·2 mg/100 ml; $p<0{\cdot}05$) as measured by the reflectance meter. Similarly, the Haemoglukotest value of 10·0 mmol/l (181·8 mg/100 ml) corresponded to a range of 7-14·2 mmol/l (127·3-258·2 mg/100 ml; $p<0{\cdot}05$) and 7·3-13·7 mmol/l (132·8-249·1 mg/100 ml; $p<0{\cdot}05$) as measured by the autoanalyser and reflectance meter respectively. This need not be a major drawback if these values are interpreted in a clinical context. The values of 13·3 and 22·2 mmol/l (241·8 and 403·6 mg/100 ml) constantly represented blood glucose concentrations in the hyperglycaemic range while that of 1·1 mmol/l (20 mg/100 ml) represented four samples all of which had concentrations under 2·2 mmol/l (40 mg/100 ml). On the other hand, the values of 4·4 and 6·7 mmol/l (80 and 121·8 mg/100 ml) almost always corresponded to blood glucose concentrations (as measured by the autoanalyser and reflectance meter) within the normal range.

The main advantages of the Haemoglukotest were simplicity and convenience. Furthermore, 25 strips cost £2·90 compared with a cost of £91·00 for a Glucocheck meter and £2·65 for 25 Dextrostix strips. We conclude that the Haemoglukotest 20-800 offers a simple, cheap alternative method of monitoring blood glucose concentrations at home.

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Estimations of blood glucose concentrations (mmol/l) performed at clinic and at home with Haemoglukotest, and mean (±95% confidence limits) blood glucose concentrations (mmol/l) determined by autoanalyser and reflectance meter in these test samples

Haemoglukotest value	1·1	2·2	4·4	6·7	10·0	13·3	22·2	44·4
No of clinic tests having value	4	12	23	19	15	22	7	0
Mean concentrations by autoanalyser	1·1±2·9	3·0±1·1	4·6±2·3	7·6±2·8	10·6±3·6	14·4±4·1	19·4±3·4	
No of home tests having value	0	18	54	66	72	28	4	0
Mean concentrations by reflectance meter		3·2±1·1	4·8±2·0	6·9±3·4	10·5±3·2	15·2±5·2	23·6±10·0	

Conversion: SI to traditional units—Blood glucose: 1 mmol ≈ 18 mg/100 ml.

Random venous blood samples were taken from 32 diabetic children, 24 non-diabetic children, and three small-for-dates babies who were transiently hypoglycaemic at birth. Part of the sample was tested by the patient, his parent, or both independently using the Haemoglukotest. If the test colour did not exactly correspond to any of the eight values, the tester was asked to choose the nearest match. A total of 102 assessments were made on 59 blood samples, which were then tested in the laboratory autoanalyser by a modified glucose oxidase method.

Correction

Jet injection of insulin

A printing error occurred in this paper by Dr R Worth and others (13 September, p 713). The age range mentioned in the first sentence of Patients, methods, and results should have read "17-78."

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