

presence, that confers risk. It is extremely difficult to compare groups of patients because of the wide variation between individual patients, but there was nothing in our results to suggest that arrhythmias that occur often and yet do not cause haemodynamic problems are any more dangerous than those that occur only occasionally.

Although our patients were taking sufficient doses of propranolol and atenolol to reduce their maximum and mean heart rates, we found little evidence that these drugs had any useful antiarrhythmic action. Beta-blockers have antiarrhythmic properties when administered acutely, and in higher doses than we used they might have a prophylactic effect. A relatively high proportion of our patients, however, suffered sufficient hypotension to necessitate withdrawal from treatment, and we do not believe that in suspected acute myocardial infarction it is practicable routinely to give more than 40 mg propranolol thrice daily or 50 mg atenolol twice daily.

Even if beta-blockers have little antiarrhythmic effect in suspected myocardial infarction they may still reduce mortality by some other means. Beta-blockers are known, for example, to influence platelet behaviour¹⁰ and may limit infarct size.¹¹

Our findings raise grave doubts about the value of studying arrhythmias to assess drugs intended to reduce mortality from myocardial infarction. Only clinical trials with death as an end-point show the value of a drug; once a drug has been found to be effective then studies such as the one we have described may be needed to elucidate its mode of action.

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Decreased serum 24,25-dihydroxy vitamin D concentrations in children receiving chronic anticonvulsant therapy

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Summary and conclusions

Serum 24,25-dihydroxy vitamin D (24,25(OH)₂D) and 25-hydroxy vitamin D (25-OHD) concentrations and the ratio between the two were measured in 31 Israeli children and adolescents receiving long-term treatment with phenobarbitone or phenytoin and in controls. 24,25(OH)₂D concentrations were significantly depressed in the patients, although the 25-OHD concentrations were similar to those in the healthy controls. In four patients with radiological evidence of osteopenia very low serum 24,25(OH)₂D concentrations and serum 24,25(OH)₂D: 25-OHD ratios were recorded.

The findings suggest that 24,25(OH)₂D deficiency may play an important part in the pathogenesis of osteomalacia in patients treated with anticonvulsant drugs and provide further indirect evidence that 24,25(OH)₂D is important for normal bone structure.

Introduction

Anticonvulsant drugs, particularly phenytoin and phenobarbitone, are thought to affect calcium and vitamin D metabolism and to cause rickets or osteomalacia.¹⁻⁵ The serum concentration of 25-hydroxy vitamin D (25-OHD), the major circulating metabolite of vitamin D, is depressed in many patients receiving anticonvulsant therapy, presumably because of enhanced conversion of 25-OHD to a biologically inactive metabolite.⁶⁻⁷ None the less, the serum concentration of 1,25-dihydroxy vitamin D (1,25(OH)₂D), the active metabolite of vitamin D, is normal or increased in patients on anticonvulsant drugs.⁸ Administration of vitamin D or 25-OHD has been reported to correct anticonvulsant-induced osteomalacia,⁹ which indicates that not all the effects of vitamin D may be due to 1,25(OH)₂D. Indeed, recent studies show the importance of 24,25(OH)₂D, another renal metabolite of vitamin D, in normal bone formation.¹⁰⁻¹¹ We have therefore measured the serum concentrations of 24,25(OH)₂D and 25-OHD in patients on long-term treatment with anticonvulsants and compared the values with those in healthy subjects.

Patients and methods

Serum 25-OHD and 24,25(OH)₂D concentrations were measured by competitive protein binding radioassays¹² in 31 children and adolescents with convulsive disorders treated with phenytoin (n=15) or phenobarbitone (n=16) for over 12 months and in 27 age-matched healthy controls. The patients and controls ranged in age from 2 to 17 years. Neither patients nor controls had any malabsorption or

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hepatic or renal disease. Permission was obtained from the parents of patients and controls. The mean (\pm SD) serum concentrations of phenytoin and phenobarbitone (measured by Gammacoat 125 I phenytoin and phenobarbitone radioimmunoassay kits, Travenol Laboratories) were 12.2 ± 8.3 mg/l and 13.9 ± 8.9 mg/l respectively. Serum calcium and phosphorous concentrations were determined by routine laboratory methods. Radiological studies of wrists and hands were performed in all patients. Data were analysed by the two-tailed unpaired Student's *t* test and by linear regression analysis.

Results

There were no significant differences in serum 25-OHD concentrations between patients receiving long-term anticonvulsant treatment and healthy controls (fig 1). But the mean (\pm SD) serum

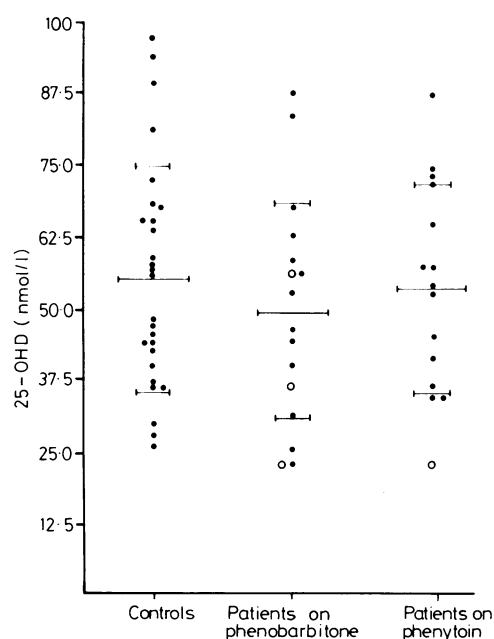


FIG 1—Serum 25-OHD concentrations in patients receiving phenobarbitone and phenytoin and controls. Horizontal lines represent means \pm SD. ○—Patients with radiological evidence of osteopenia.

Conversion: SI to traditional units—25-OHD: 1 nmol/l \approx 0.4 ng/ml.

concentration of radioassayable 24,25(OH) $_2$ D and the mean 24,25(OH) $_2$ D:25-OHD ratios were significantly ($P < 0.01$) lower in patients receiving phenobarbitone (3.25 ± 1.55 nmol/l (1.30 ± 0.62 ng/ml) and 0.067 ± 0.023 respectively) and in patients receiving phenytoin (3.00 ± 1.22 nmol/l (1.20 ± 0.49 ng/ml) and 0.057 ± 0.026) than in the controls (5.42 ± 2.32 nmol/l (2.17 ± 0.98 ng/ml) and 0.100 ± 0.033) (figs 2 and 3).

Serum 24,25(OH) $_2$ D concentrations were under 1.75 nmol/l (0.7 ng/ml) and the 24,25(OH) $_2$ D:25-OHD ratio less than 0.05 in four patients with radiological evidence of osteopenia.

Serum calcium concentrations were significantly ($P < 0.05$) lower in the patients than in the controls, while serum inorganic phosphate concentrations were significantly lower in the phenytoin group than in either the controls or the patients taking phenobarbitone (see table).

Calcium and phosphate concentrations in patients and controls

	Patients receiving:		Controls
	Phenobarbitone	Phenytoin	
Serum calcium (mmol/l)	2.33 ± 0.11	2.34 ± 0.12	2.47 ± 0.07
Serum phosphate (mmol/l)	1.50 ± 0.20	1.17 ± 0.33	1.53 ± 0.10

Conversion: SI to traditional units—Calcium: 1 mmol/l \approx 4 mg/100 ml. Phosphate: 1 mmol/l \approx 3.1 mg/100 ml.

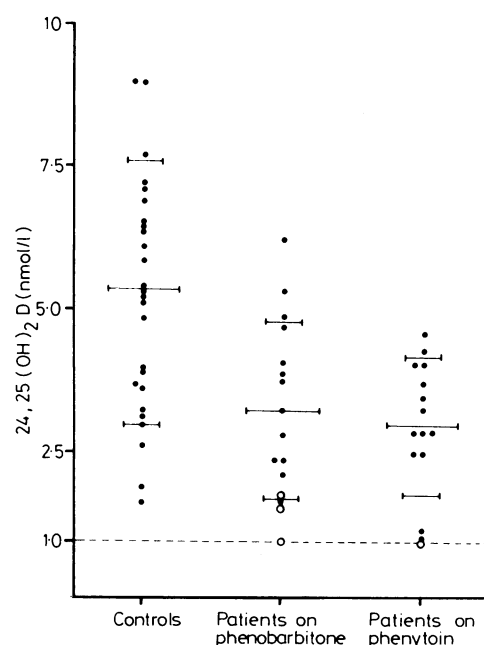


FIG 2—Serum 24,25(OH) $_2$ D concentrations in phenobarbitone- and phenytoin-treated patients and healthy controls.

Conversion: SI to traditional units—24,25(OH) $_2$ D: 1 nmol/l \approx 0.4 ng/ml.

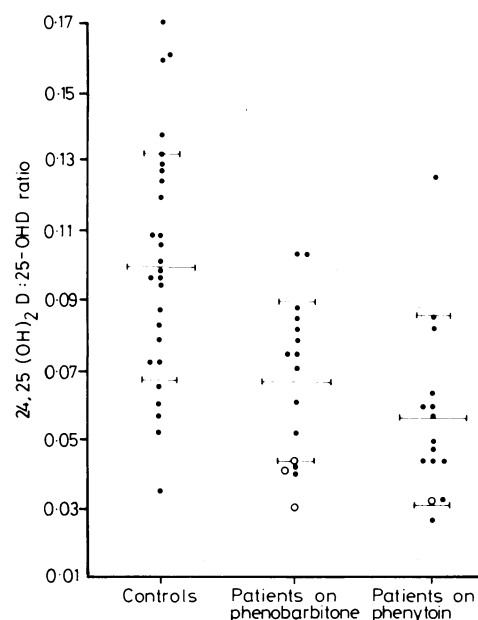


FIG 3—Serum 24,25(OH) $_2$ D:25-OHD ratios in patients receiving phenobarbitone and phenytoin and healthy controls.

Serum drug, calcium, and phosphorous concentrations did not appear to be correlated with either serum 25-OHD or 24,25(OH) $_2$ D concentrations.

Discussion

Our findings show that serum 25-OHD concentrations in ambulatory patients receiving anticonvulsants are similar to those of healthy subjects, presumably because of the abundant ultraviolet radiation prevalent in Israel. Nevertheless, the serum concentrations of 24,25(OH) $_2$ D in these patients were significantly depressed, and patients with radiological evidence of

osteopenia had very low serum 24,25(OH)₂D concentrations and 24,25(OH)₂D:25-OHD ratios.

Our data do not identify the site of the drugs' action. Anticonvulsants may affect 24,25(OH)₂D synthesis or catabolism directly. Alternatively, the primary effect of anticonvulsants may be to decrease gastrointestinal calcium absorption through end-organ hyporesponsiveness to 1,25(OH)₂D,^{13,14} leading to hypocalcaemia, secondary hyperparathyroidism,⁵ raised serum 1,25(OH)₂D concentrations, and decreased serum 24,25(OH)₂D concentrations.

A reduction in the circulating concentrations of 25-OHD and possibly of other active metabolites of vitamin D is generally believed to play an important part in the pathogenesis of anticonvulsant-induced osteomalacia.^{1-6,8} Recent studies have shown, however, that the serum concentration of 1,25(OH)₂D is normal or increased in patients on long-term treatment with anticonvulsant drugs.⁸ The fact that the administration of vitamin D or 25-OHD corrects anticonvulsant-induced osteomalacia⁹ raises the question whether another metabolite of vitamin D, essential for normal bone structure, is affected by anticonvulsants. Indeed, our findings suggest that 24,25(OH)₂D deficiency may be implicated in the pathogenesis of osteomalacia in patients receiving anticonvulsant drugs. This assumption is supported by recent observations^{10,11} that 24,25(OH)₂D is important for normal ossification of bone.

Thus in patients in institutions and in northern populations in whom serum 25-OHD values are low the changes in 25-OHD metabolism may produce very low or undetectable concentra-

tions of 24,25(OH)₂D. On the other hand, the administration of vitamin D, which increases serum substrate (25-OHD) concentration, might enhance 24,25(OH)₂D synthesis and subsequently its serum concentrations despite the effect of the anticonvulsants.

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High-carbohydrate diets and insulin-dependent diabetics

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Summary and conclusions

A high-carbohydrate-(HC)-modified fat diet was compared with a standard low-carbohydrate (LC) diabetic diet in 11 insulin-dependent diabetics. Basal and preprandial plasma glucose concentrations were appreciably lower when the patients received the HC diet derived chiefly from readily available cereal and vegetable sources (mean (\pm SE of mean) basal concentrations 6.7 ± 1.2 mmol/l (121 ± 22 mg/100 ml) with the LC diet and 4.3 ± 0.7 mmol/l (77 ± 13 mg/100 ml) with the HC diet; mean preprandial concentrations 11.1 ± 1.2 mmol/l (200 ± 22 mg/100 ml) LC diet and 8.9 ± 1.3 mmol/l (160 ± 23 mg/100 ml) HC diet). Total and low-density lipoprotein cholesterol concentrations were lower when patients took the HC diet (mean 4.4 ± 0.2 and 2.4 ± 0.3

mmol/l (170 ± 8 and 93 ± 12 mg/100 ml) compared with 4.9 ± 0.2 and 3.2 ± 0.2 mmol/l (189 ± 8 and 124 ± 8 mg/100 ml) respectively), and the ratio of high-density lipoprotein cholesterol to total cholesterol tended to rise. The average percentage of glycosylated haemoglobin did not differ between the two diets.

Thus several measures of carbohydrate and lipid metabolism appear to be more satisfactory when patients receive a HC diet, which is an acceptable alternative to that still recommended to most insulin-requiring patients.

Introduction

We have shown in maturity-onset diabetes that a high-carbohydrate (HC) diet composed of readily available cereal foods and tuberous vegetables resulted in lower fasting and preprandial blood glucose concentrations than a standard low-carbohydrate (LC) diet.¹ In the present investigation we carried out a similar comparison in a group of insulin-dependent diabetics.

Patients and methods

After obtaining informed consent we recruited 12 established insulin-dependent diabetics (six men and six women) into this outpatient study. The mean (\pm SE of mean) total insulin requirement was 51 ± 8 U/day (range 21-92 units). Eleven patients were on a twice-daily insulin regimen, and only one received a single daily

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