Effect of Vitamin D on Bone Mineral Mass in Normal Subjects and in Epileptic Patients on Anticonvulsants: A Controlled Therapeutic Trial

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Summary

The bone mineral mass was estimated by photon absorptiometry in 23 epileptic patients on long-term treatment with phenytoin and in 20 normal subjects before and during treatment with vitamin D or placebo.

Initially, subnormal values of bone mineral mass were found in the epileptic patients. The group of epileptic patients treated with vitamin D showed a significant increase in bone mineral mass. The group of epileptic patients treated with placebo and the normal subjects treated with vitamin D or placebo showed no change in bone mineral mass.

Introduction

Manifest biochemical osteomalacia (with hypocalcaemia and raised serum alkaline phosphatase) in epileptic patients on long-term treatment with anticonvulsant drugs has been reported several times in the past four years (Schmid, 1967; Kruse, 1968; Dent *et al.*, 1970; Richens and Rowe, 1970; Hunter *et al.*, 1971).

On average, patients without biochemically manifest osteomalacia have a decreased bone mineral mass (Berger and Munde, 1970; Linde *et al.*, 1971; Christiansen *et al.*, 1972), and such patients show an increase in bone mineral mass during treatment with vitamin D (Christiansen *et al.*, 1972).

The effect on bone mineral mass of normal persons by small doses of vitamin D is unknown. We report a controlled therapeutic trial on the effect of the treatment in normal subjects and in epileptic patients on anticonvulsants.

Patients and Methods

Altogether 23 epileptic patients and 20 normal subjects were studied. The epileptic patients were 12 women and 11 men aged 23 to 56 years (mean 38 years). They were all fully able to work and attended the epilepsy clinic at Glostrup Hospital at regular intervals. Long-term treatment with phenytoin had been instituted one to 13 years (mean seven years) previously. During this investigation the mean dose was 5.1 mg (range 3.3 to 6.6 mg) per kg body weight, and on this regimen the serum levels (Larsen, 1971) averaged 7 mg/l. (range 2 to 14 mg/l.) The normal subjects were 10 women and 10 men from the staff of the department aged 21 to 33 years (mean 28 years).

The bone mineral mass was determined by direct photon absorptiometry on both forearms. Cameron *et al.* (1968) showed a direct relation between the absorption of photons from ^{125}I and the bone mineral mass. In our modified version of the method (Jensen *et al.*, 1972; Christiansen and Rødbro, 1973) the bone mineral mass is expressed in arbitrary units as a mean value of six scans from each forearm.

The bone mineral mass was measured and termed "initial value"—100% at time t_0 . This measurement was compared in each case with the values in a group of normal subjects (Christiansen and Rødbro, 1973) matched for age and sex (see chart). The epileptic patients and the normal subjects were then allocated at random to two groups. The first group was treated with calcium lactate (390 mg/ca daily) and vitamin D (2,000 IU daily), both drugs given by mouth, and the second group was treated with calcium lactate (390 mg/ca daily) and placebo. Bone mineral mass was measured one month after the treatment was started, t_1 , and expressed as a percentage of the initial value.

The therapeutic trial was conducted over the months October to November 1972, and Student's t test for pair differences was used to evaluate the effect of treatment.

Bone mineral mass in 23 epileptic patients and in 20 normal subjects before and during treatment with calcium and vitamin D or calcium and placebo. Left. Initial value is compared with mean value and standard deviation in corresponding age and sex groups of normal persons. Right. Average bone mineral mass (as percentage of initial value) as a function of time during treatment is shown. Each point represents mean $\pm$ 1 S.E. of mean. N. S. = Not significant.

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Results

The bone mineral mass of the 23 epileptic patients and the 20 normal subjects compared with the values of other normal subjects matched for age and sex are shown in the chart. The initial values of all the 23 epileptic patients were below the corresponding normal mean value. In the group of epileptic patients treated with calcium lactate and vitamin D the mean bone mineral mass rose significantly. In the other three groups the mean bone mineral mass was unchanged (see chart).

Discussion

As previously found, the epileptic patients as a group had subnormal values (Berger and Munde, 1970; Linde *et al.*, 1971; Christiansen *et al.*, 1972), while the values in the normal subjects scatter around the mean.

This finding, and the unchanged values in both groups of normal subjects and in the placebo groups of epileptic patients, underlines that the method used is well reproducible (Christiansen and Rødbro, 1973). Our earlier findings (Christiansen *et al.*, 1972), that bone mineral mass rises in epileptics during treatment with a small dose of vitamin D, are confirmed.

In this study we have found a 3% increase in bone mineral mass, while we previously found an increase of nearly 7% (Christiansen *et al.*, 1972). Two factors might contribute to this disparity. Firstly, the initial values of our nine patients were higher than the initial values of the patients in our earlier report. Secondly, the two studies were not planned in the same way, as the patients in the earlier study were treated with calcium lactate for one month before the treatment with vitamin D.

Assuming that bone mineral mass in the forearm is representa-

tive of total body calcium (Christiansen and Rødbro 1973), and that the mean value of normal young men corresponds to 1,000 g of total body calcium (Christiansen *et al.*, 1972), it can be calculated that the mean total body calcium in the epileptic patients on vitamin D rose from 699 to 716 g, corresponding to a mean positive calcium balance of 0.5 g per day during the trial.

The present study confirms that the epileptic patients, as a group, have subnormal values of bone mineral mass. Furthermore it shows that epileptic patients treated with vitamin D respond to this treatment, while normal subjects treated with vitamin D and epileptic patients treated with calcium lactate and placebo do not.

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Effects of Clonidine Withdrawal: Possible Mechanisms and Suggestions for Management

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Summary

A severe rebound rise in blood pressure with agitation and insomnia had been noted in five patients when they had previously ceased clonidine (Catapres). This has been shown to be reproducible in these patients and to be associated with a significant increase in urinary catecholamine excretion. The blood pressure can be controlled and the symptoms alleviated promptly by alpha and beta adrenergic receptor blockade using intravenous phentolamine and propranolol.

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Introduction

Clonidine has found use as an antihypertensive agent in moderate (Smet *et al.*, 1969; Parsons and Morledge, 1970) and severe (Raftos, 1969) hypertension, and when side effects such as orthostatic hypotension make adrenergic blocking agents impractical (Hoobler and Sagastume, 1971). It has a largely central site of action, and in rabbits it has been shown to have a central inhibitory action on adrenal catecholamine release (Shaw *et al.*, 1971). A dose-related depression of urinary catecholamine levels has been shown in man (Hököfelt *et al.*, 1970).

Sudden cessation of clonidine has been seen to result in severe rises in blood pressure (Hököfelt *et al.*, 1969 1970; Hoobler, 1969) and a symptom complex of agitation, insomnia, and palpitations. The cause of the symptoms has been suggested to be a large catecholamine release, and some data after short-term therapy support this view (Hököfelt *et al.*, 1970). Identification and further study of this phenomenon is reported.

Materials and Methods

Five patients were studied who had a previously well-documented blood pressure overshoot when clonidine (Catapres)