Chronic Toxicity of Antiepileptic Drugs

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Interrelationships Between Serum 25-Hydroxycalciferol and Bone Mass in Adults on Long-Term Antiepileptic Drug Therapy

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Using photon absorptiometry, which seems to be a better diagnostic instrument for detecting osteomalacia than x-ray examination (3), several investigators found a decrease of bone mass in epileptics on chronic antiepileptic drug therapy (4, 7, 9, 10). Antiepileptic drug induced osteomalacia has been explained by a disturbance of vitamin D metabolism (1, 5, 6, 8, 19), which leads to a lowering of 25-hydroxycalciferol concentrations in the serum of chronically treated epileptics. As yet the diagnostic value of serum 25-hydroxycalciferol levels in detecting antiepileptic drug induced osteomalacia remains unclear. The aim of the present study was to evaluate possible relationships between serum 25-hydroxycalciferol concentrations and bone mass in adult epileptics on chronic antiepileptic drug therapy.

PATIENTS AND METHODS

277 epileptic outpatients (157 males, 120 females), aged 20 to 40 years, treated with antiepileptic drugs for at least one year and taking no vitamin D supplement, were examined between December 1980 and July 1981. Most patients received combination therapy. The average daily intake of antiepileptic drugs was calculated in equivalent units per day (1 equivalent unit ≙ 50mg phenytoin, 30mg phenobarbital, 125mg primidone, 50mg CHP-phenobarbital, 200mg carbamazepine, 50mg mephenytoin, 250mg ethosuximide, 300mg sodium valproate, 2mg clonazepam, 300mg methsuximide, 100mg sulthiame, 250mg trimethadione). 20 patients (13 males, 7 females) were taking phenytoin in monotherapy, 47 (26 males, 21

females) primidone, 30 (12 males, 18 females) carbamazepine, and 20 (11 males, 9 females) sodium valproate. Bone mass was measured in each patient at the midshaft of the radius of the right arm using a Norland-Cameron Bone Mineral Analyzer (Norland Instrument Company, Fort Atkinson, Wisconsin). Serum 25-hydroxy calciferol concentrations were determined by a radioassay in a modification of the method described by Belsey et al (2) ; 25-hydroxycalciferol standards were prepared in vitamin D-deficient charcoal treated serum instead of ethanol as described by the authors. The statistical comparison of bone mass and serum 25-hydroxycalciferol employed linear regression analysis. Variance analysis of bone mass values in patients undergoing monotherapy was carried out. Furthermore, a linear regression analysis was performed for the bone mass and the average daily intake of anti-epileptic drugs. The patients were divided into three groups according to the duration of therapy : 1 to 3, 4 to 10 and over 10 years of treatment. Bone mass values as well as 25-hydroxy-calciferol levels of these groups were compared by variance analysis, considering sex differences in bone mass and seasonal differences in 25-hydroxycalciferol levels.

RESULTS

The bone mass (mean ± SD) was 0.82 ± 0.08g cm^{-2} in the males and 0.72 ± 0.07g cm^{-2} in the females. The serum 25-hydroxy-calciferol concentration (mean ± SD) was 73.1 ± 68.2 nmol/l in the males and 72.7 ± 70.7 nmol/l in the females. There was no significant correlation between these parameters (correlation coefficient R = - 0.047 in males and R = 0.027 in females). For both sexes, serum 25-hydroxycalciferol levels were clearly higher in the summer months (Fig. 1). Therefore, a regression analysis between bone mass and 25-hydroxycalciferol was carried out for each month. The results are shown in Table 1 ; no significant correlation was found.

25.4% (n = 40) of the males had a lowered bone mass < 0.76g cm^{-2} whereas 20.8% (n = 25) of the females had lowered values < 0.67g cm^{-2}. The mean serum 25-hydroxycalciferol levels in these patients were higher than in the whole epileptic population (82.4 ± 74.8 nmol/l in males and 79.0 ± 62.4 nmol/l in females). The values of bone mass and 25-hydroxycalciferol in relation to duration of therapy are given in Table 2. The 25-hydroxy-calciferol concentrations were higher in patients treated for up to 3 years compared with the other groups, as well in the summer months, but there were no significant differences. The duration of therapy had no influence on the mean values of bone mass, but the percentage of patients with lowered bone mass in the groups treated for 1 to 3 and over 10 years was higher than in those treated for 4 to 10 years (Fig. 2). However, the number of affected epileptics in each group was too small for statistical evaluation. No relationship was found between the bone mass and the average daily intake of antiepileptic drugs, neither in

TABLE 1. Correlation coefficients of regression analysis of bone mass and 25-hydroxycalciferol for each month

	Males R	Females R
December	- 0.0358	- 0.3260
January	+ 0.0209	+ 0.0248
February	- 0.0896	- 0.2851
March	- 0.2062	- 0.2049
April	- 0.1792	+ 0.0936
May	- 0.0748	+ 0.0574
June	+ 0.5421	+ 0.3758
July	+ 0.0282	+ 0.2799

TABLE 2. Bone mass and serum 25-hydroxycalciferol levels (mean ± SD) in relation to duration of antiepileptic drug therapy

		Duration of treatment		
		1-3 years	4-10 years	10 years
Bone mass ($g\ cm^{-2}$)	males	0.81 ± 0.08 (n = 24)	0.80 ± 0.06 (n = 46)	0.82 ± 0.08 (n = 87)
	females	0.71 ± 0.06 (n = 24)	0.72 ± 0.06 (n = 26)	0.71 ± 0.08 (n = 70)
25-hydroxy-calciferol (nmol/l) both sexes	December to April	58.7 ± 59.9 (n = 29)	54.4 ± 63.8 (n = 51)	49.9 ± 60.1 (n = 96)
	May to July	132.3 ± 86.1 (n = 19)	90.1 ± 72.6 (n = 21)	112.4 ± 64.8 (n = 61)

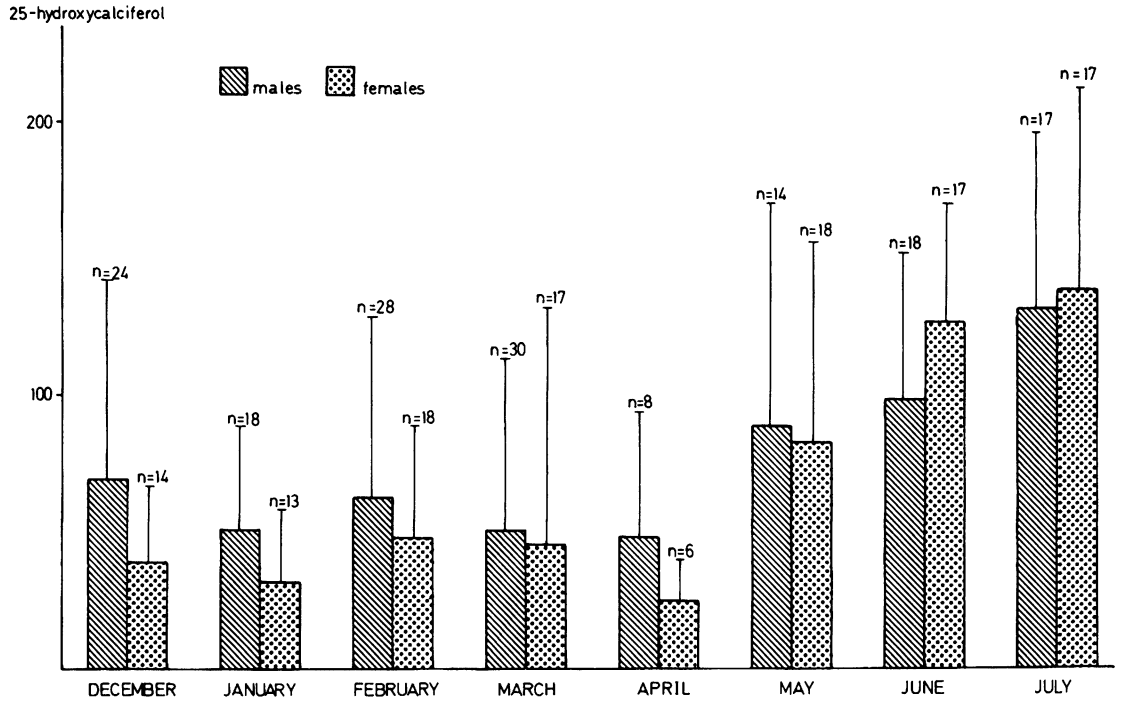

FIG. 1. Seasonal differences of serum 25-hydroxycalciferol levels in nmol/l (mean + SD)

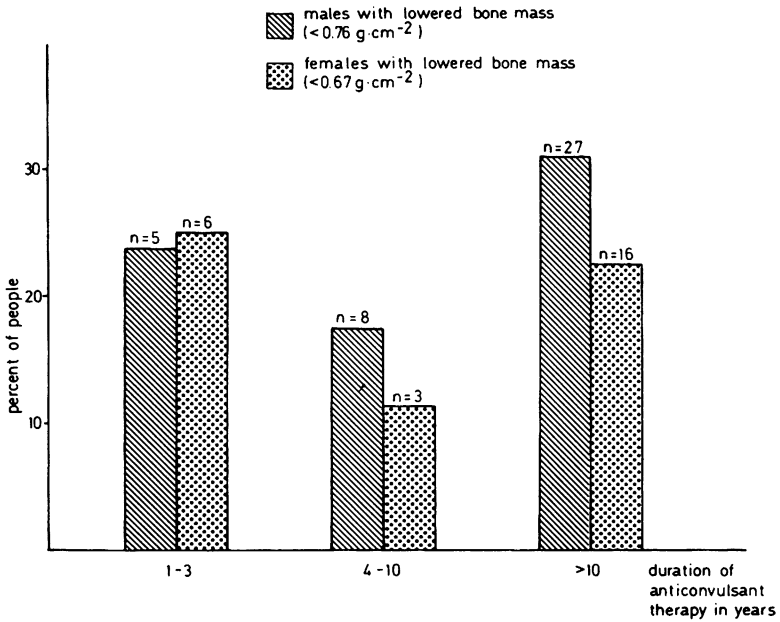

FIG. 2. Percentage of epileptics with lowered bone mass in relation to the duration of antiepileptic drug therapy

males (correlation coefficient R = 0.0487) nor in females (R = - 0.1286). The values of bone mass in epileptics on monotherapy are given in Table 3 ; no significant differences were found.

TABLE 3. Values of bone mass (mean ± SD) in patients on monotherapy

	Males		Females	
	n	bone mass (g cm^{-2})	n	bone mass (g cm^{-2})
phenytoin	13	0.82 ± 0.06	7	0.72 ± 0.03
primidone	26	0.83 ± 0.08	21	0.72 ± 0.07
carbamazepine	12	0.82 ± 0.09	18	0.74 ± 0.10
sodium valproate	11	0.82 ± 0.07	9	0.72 ± 0.05

DISCUSSION

Our data indicate that there is no relationship between serum 25-hydroxycalciferol concentrations and the state of bone mineralisation. Even if the seasonal variation of 25-hydroxycalciferol, which was much more marked in our study than in that of Offerman et al (15), is taken into consideration, there was no correlation between bone mass and serum 25-hydroxycalciferol. These findings are in accordance with the results of Pylypchuk et al (16) and Mosekilde et al (12, 13). The latter authors correlated quantitative morphometric data of iliac crest biopsies with serum 25-hydroxycalciferol levels in epileptics and found no relationships either (12). According to their histopathological findings the authors suspected a difference between antiepileptic drug induced osteomalacia and osteomalacia induced by vitamin D deficiency (13). It might be possible that, not only disturbances of vitamin D metabolism, but also a direct inhibition of membrane uptake of calcium or inhibition of bone resorption may play a role in developing drug induced osteomalacia (1, 17, 18). For practical purposes it is noteworthy that the determination of serum 25-hydroxycalciferol levels is obviously not a suitable instrument for detecting antiepileptic drug induced osteomalacia.

Surprisingly we found no relationship between bone mass and dose of antiepileptic drugs. This fact is in contrast to the findings of Christiansen et al (4) and to own results in a retrospective study with 837 epileptics (11), who had been investigated by X-ray. Probably this difference is due to the kind of calculation of the average daily drug dose. In those patients with an intake of antiepileptic drugs since early childhood the naturally low daily dose in this age decreases the average daily intake of the whole duration of treatment - despite the high doses at the time of examination.

In accordance with the results of Hahn et al (7) and in contrast to those of Christiansen et al (4), in the present study there was no general influence of duration of therapy on bone mass values, but abnormalities were more common in the first 3 years of therapy and in patients receiving antiepileptic drugs for more than 10 years, than in the interval between. We had similar results in our previous study, mentioned above (11). One may guess that there is a disturbance of bone metabolism in some patients soon after the beginning of therapy, followed by a tendency to normalisation as an expression of an adaption process. The group of patients treated for more than 10 years again showed a higher incidence of lowered bone mass ; this may be caused by the fact that there are many epileptics in this group who received medication since childhood, when bone metabolism is more susceptible to drug treatment. The relation of antiepileptic drug induced osteomalacia to duration of therapy seems to be of special interest for long term prospective investigations.

We found no significant differences in bone mass between the patient groups, treated with four major antiepileptic drugs as monotherapy. Similarly, Christiansen et al (4) found comparable patterns of bone mineral content in patients treated with phenytoin and primidone as monotherapy as well as in combination. Recently biochemical evidence of a disturbance in bone metabolism under monotherapy with carbamazepine has been presented (14). However, to our knowledge, sodium valproate as monotherapy has not been incriminated in producing these changes.

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