Prevalence of Hypocalcemia and Elevated Serum Alkaline Phosphatase in Patients Receiving Chronic Anticonvulsant Therapy

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Residents of an institution for the developmentally disabled in northwest Ohio receiving anticonvulsant therapy for six months or more with phenobarbital or phenytoin or both were studied for the prevalence of hypocalcemia and elevated alkaline phosphatase level. Fifty-six residents were identified. Sixteen (29 percent) were hypocalcemic. Fifteen (27 percent) had elevated serum alkaline phosphatase levels. Twenty-three residents received vitamin D supplementation (400 IU/d) in addition to a normal dietary intake of calcium and vitamin D. The mean serum calcium level was identical (8.65 mg/dL) for those receiving and not receiving additional vitamin D. This study corroborates the findings of prior studies suggesting an association between anticonvulsant usage and mineral and bone abnormalities. The causal nature of this association, its clinical significance, and its management require further investigation.

Approximately 2 million Americans are afflicted with a seizure disorder. Many of these individuals require long-term anticonvulsant therapy for control. Family physicians caring for these persons assume an important role in monitoring both therapeutic effectiveness and drug-induced complications. One complication not widely publicized in the family medicine literature is anticonvulsant osteomalacia. Although all commonly used anticonvulsants have been implicated, phenytoin and phenobarbital are the two most frequently associated with this complication.[1-4] Awareness of anticonvulsant osteomalacia is important for two reasons. First, proper treatment of acutely symptomatic patients with significant bone loss or hypocalcemia requires that the problem be suspected and correctly identified. Second, if clinically significant complications occur frequently, then preventive strategies or periodic monitoring become important considerations. Consequently, this study was performed to determine the prevalence of hypocalcemia and elevated serum alkaline phosphatase levels in persons receiving anticonvulsant therapy.

Methods

All residents of an institution for the developmentally disabled in northwest Ohio receiving anticonvulsant therapy for six months or more with phenobarbital or phenytoin or both were screened between June 1982 and December 1982

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for the prevalence of hypocalcemia and elevated serum alkaline phosphatase levels. All residents on chronic therapy had fasting multichannel-automated chemistry (Technicon SMA II) testing ordered by their personal physicians. Total serum calcium results were corrected for albumin as follows: (1) normal albumin = 4 g/dL; (2) each gram of albumin binds 0.8 mg/dL calcium; therefore, (3) for each gram of albumin above or below 4 g/dL, 0.8 mg/dL is subtracted from or added to, respectively, the reported value for serum calcium.[5] For example, if the calcium = 8 mg/dL and the albumin = 3 g/dL, then (4–3) g/dL is a 1 g/dL albumin deficit. Therefore, 8 mg/dL measured calcium + 0.8 mg/dL adjustment for albumin = 8.8 mg/dL adjusted calcium.

All patients with a corrected total serum calcium level less than 8.5 mg/dL were labeled hypocalcemic. A serum alkaline phosphatase level greater than 115 IU was considered elevated in all patients aged 16 years or older. For patients aged less than 16 years, the upper limit of normal was adjusted for age using the reference laboratory ranges. Serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels were also measured to check for evidence of hepatocellular dysfunction as a possible source for an elevated alkaline phosphatase.

The nutritionist for the institution was consulted for an estimate of dietary calcium and vitamin D (excluding supplementation). This estimate was obtained by a review of the menu prepared for the resident patients. The estimate was compared with a computerized assessment performed by the state dietitian. The nutritionist's estimate was similar to the computerized assessment; however, the estimate reflected only the amount of food given to the patient and not necessarily the amount ingested. Vitamin D supplementation was determined by review of the pharmacy records. Names and numbers of anticonvulsants were determined by review of the pharmacy record. Duration of anticonvulsant therapy was assessed by review of the patient's transfer record to the institution in conjunction with the pharmacy record. Nonambulatory patients were identified by staff of the institution. Coexisting diseases were identified by review of the medical record, especially those associated with hypocalcemia (malabsorption, hypoparathyroidism, renal disease). Serum creatinine levels of 2 mg/dL or higher were identified by the SMA II. Those with a coexisting disease associated with hypocalcemia were excluded from analysis.

Table 1. Anticonvulsant Usage (n = 56)

Anticonvulsant	Number
Phenytoin	17
Phenobarbital	9
Phenytoin and phenobarbital	14
Phenytoin and other	7
Phenobarbital and other	3
Phenytoin and phenobarbital and other	6

Results

Of 170 resident patients, 57 received chronic anticonvulsant therapy with phenytoin or phenobarbital or both. One patient was excluded from evaluation because of coexisting documented hypoparathyroidism. The duration of therapy for the remaining 56 residents could not be exactly determined from their transfer records. Most had received anticonvulsant therapy since early childhood, but dates were not recorded. Table 1 presents the number receiving various combinations of anticonvulsant therapy. Sex, age, diet, and activity characteristics are displayed in Table 2. Twenty-three residents received vitamin D supplementation in the form of a multivitamin preparation. The indication for vitamin supplementation could not be identified by chart review.

Sixteen of 56 resident patients (29 percent) receiving chronic anticonvulsant therapy were hypocalcemic. The degree of hypocalcemia and its relationship to vitamin D supplementation are presented in Table 3. Ten of the 16 hypocalcemic residents were not receiving supplementation. The three residents with serum calcium levels less than 7.9 mg/dL were not on supplementation. However, the mean serum calcium in those receiving vitamin D supplementation (n = 23) was identical (8.5 mg/dL) to those without supplementation (n = 33).

Fifteen of 56 residents (27 percent) receiving chronic anticonvulsant therapy had elevated serum alkaline phosphatase levels. The relationship

Table 2. Population Characteristics (n = 56)

Characteristics	
Sex	
Male	28
Female	28
Age (yr)	
Mean	29.1
Range	12-47 (Only 3 were < 18 years old)
Diet	
Calcium (mg/dL)	1,200-1,400
Vitamin D (mg/dL)	300-400
Vitamin D supplement (number receiving 400 IU/d)	23
Nonambulatory (number)	4

Table 3. Degree of Hypocalcemia Compared With Vitamin D Supplementation

Degree of Hypocalcemia (mg/dL)	Number	Vitamin D
8.3-8.49	8	3
8.1-8.29	5	3
7.9-8.09	0	0
<7.9	3	0
Total	16	6

of elevated serum alkaline phosphatase levels to abnormal liver function test results is shown in Table 4. Of the three patients aged less than 18 years, none had an elevated alkaline phosphatase level. Concomitant hypocalcemia and elevated alkaline phosphatase levels were present in five patients (9 percent). The mean serum calcium level of the five patients was 8.21 mg/dL. None received vitamin D supplementation. None of the four nonambulatory patients was hypocalcemic.

Discussion

Thirty-four percent of the entire resident population received chronic (six months or more) anticonvulsant therapy with phenobarbital or phenytoin. Sixteen residents received additional anticonvulsant therapy. Of those receiving phenytoin, phenobarbital, or both, 29 percent had albumin-adjusted total serum calcium levels below 8.5 mg/dL and 27 percent had elevated serum alkaline phosphatase levels. Nine percent had both hypocalcemia and elevated serum alkaline phosphatase levels. Consequently, seizure disorders were highly prevalent in the population studied, and hypocalcemia or elevated alkaline phosphatase levels or both were highly prevalent in the subpopulation receiving phenobarbital or phenytoin or both.

Table 4. Elevated Serum Alkaline Phosphatase

	Number
Abnormal SGOT and/or SGPT	9
Normal SGOT and/or SGPT	6
Total	15
Both hypocalcemia and elevated alkaline phosphatase (mean Ca++ = 8.21 mg/dL and 0/5 received vitamin D)	5

Were the residents with subnormal calcium truly hypocalcemic? Residents were labeled by comparison of their albumin-adjusted total serum calcium values with the laboratory-generated normal limits for total serum calcium. These normal limits were obtained from a presumably healthy reference population. However, this comparison and the investigator's reliance upon statistically derived normal limits present several problems. First, it is likely that the reference population differed significantly from the population studied. If statistically derived normal limits had been generated from within the institution, it is possible that they would have been lower and fewer residents would have been labeled hypocalcemic. Second, statistically derived normal limits for most biochemical tests do not permit separation of diseased from nondiseased individuals.[6] They only allow the physician to determine the degree to which a given value is unusual for a population. Consequently, finding a subnormal calcium level in this study does not necessarily indicate the presence of a clinical abnormality. Third, it is unclear that any of the formulas recommended in the

Table 5. Effects of Chronic Anticonvulsant Therapy on Calcium, Vitamin D, and Parathormone

Author	Number* (Study)	(Control)	Serum Calcium (mg/dL)	25-Hydroxy-vitamin D (ng/mL)	Parathormone	Bone Mass (% of normal)
Hahn et al[2]	56		9.72 ± 0.06	13.1 ± 1.0	—	90.5 ± 1.6
		51	10.40 ± 0.05	23.6 ± 0.9	—	100.7 ± 1.0
Hahn and Halstead[9]	6		9.08 ± 0.16	8.6 ± 0.8	10.4 ± 1.6 (μEq/mL)	81.7 ± 4.7
		15	9.65 ± 0.11	19.2 ± 1.6	4.5 ± 0.6 (μEq/mL)	101.0 ± 2.1
Bouillon et al[3]	20		9.2 ± 0.4	6.4 ± 3.2	277 ± 165 (pg/mL)	—
		20	9.6 ± 0.3	8.6 ± 3.2	183 ± 95 (pg/mL)	—

*Study group receiving anticonvulsant drugs; control group not receiving anticonvulsant drugs

Table 6. Prevalence of Hypocalcemia and Elevated Serum Alkaline Phosphatase in Patients Receiving Chronic Anticonvulsant Therapy

Author	Year	Sample Size	Population Studied	Percentage With Hypocalcemia	Percentage With Elevated Alkaline Phosphatase	Other
Richens and Rowe[8]	1970	160	Adult, institutionalized	22.5	29	—
Hunter et al[10]	1971	105	Children, institutionalized	30.0	24	—
Kruse[16]	1968	—	Children, noninstitutionalized	15.0	—	—
Hahn et al[2]	1975	56	Children, noninstitutionalized	4.0	—	↓ 25-hydroxy-vitamin D ↓ Bone mass

literature for adjusting serum calcium using protein or albumin directly reflect the underlying state of ionized calcium.[7] This ionized fraction is most important in determining the presence of clinical manifestations.

There are circumstantial data available in the literature that have an impact on these issues (Tables 5 and 6). Some investigators have demonstrated a significant decrease in mean total serum calcium in patients receiving chronic anticonvulsant therapy compared with those in a concomitant control group.[2,3,8,9] In addition, some have shown a higher mean parathormone level and a lower serum 25-hydroxyvitamin D level in those receiving chronic anticonvulsant therapy.[3,9] Others have shown an increase in hepatic microsomal enzyme activity.[10] These studies suggest that altered microsomal enzyme activity produces a reduced serum 25-hydroxyvitamin D level, which may lead to decreased calcium absorption, reduced serum ionized calcium, and a secondary rise in parathormone level. In addition to these biochemical abnormalities, other investigators have demonstrated a decrease in bone mass[2,11-13] and suggested a higher frequency of bone fracture in those receiving anticonvulsants.[14] Consequently, the literature suggests that subnormal calcium levels seen in those taking anticonvulsant medications reflect a lowered ionized fraction and may be associated with underlying bone disease.

The elevated serum alkaline phosphatase in this study is difficult to interpret in view of the liver function abnormalities detected. Nine of the 15 residents with an elevated alkaline phosphatase had an associated SGOT or SGPT abnormality. In a study of ambulatory pediatric patients by Hahn et al,[2] both bone and liver alkaline phosphatase isoenzyme activity was increased in those receiv-

ing phenytoin or phenobarbital. Consequently, it must not be inferred that the elevated alkaline phosphatase in this study indicates increased bone activity.

Although the three residents with total serum calcium levels below 7.9 mg/dL and the five residents with both calcium and alkaline phosphatase abnormalities did not receive a vitamin D supplement, the mean serum calcium in those receiving and not receiving vitamin D was identical. If those receiving and not receiving vitamin D supplementation were compared for the presence or absence of hypocalcemia, a statistically significant difference could not be demonstrated ($\chi^2 = .12$, $P > .5$). However, the amount of vitamin D that residents received may have been inadequate relative to their needs,[1,15] and the variability in duration of supplementation may have obscured any true difference between groups. Others have reported a decrease in fractures using a before-after design and employing a 400 IU vitamin D supplement daily for one year.[14] A prospective randomized controlled trial to answer the question about the efficacy of prophylactic therapy is still needed.

The sample studied is obviously not representative of the epileptic population at large. This sample was composed of a primarily adult, mentally disabled population requiring institutional care. In settings similar to the one used in this study, comparable prevalence figures have been found (Table 6). In noninstitutional and pediatric settings, similar prevalence figures were observed. Although Hahn and colleagues[2] did find significant differences in mean serum calcium and alkaline phosphatase levels between study and control groups, only 4 percent were overtly hypocalcemic. Still, in general, the literature suggests an increased prevalence of hypocalcemia, elevated alkaline phosphatase levels, and decreased bone mass in epileptic patients receiving chronic anticonvulsant therapy. Consequently, primary care physicians who monitor anticonvulsant therapy in epileptic patients should be aware of these bone and biochemical abnormalities.

Whether patients receiving chronic anticonvulsant therapy should be monitored at regular intervals or receive prophylactic vitamin D or both has been the source of ongoing debate. At present, there is still insufficient evidence to warrant preventive strategies. Although biochemical and sensitive absorptiometry measures reveal frequent subclinical abnormalities, their incidence and their relationship to clinical abnormalities have not been determined in a carefully controlled prospective study. Before subjecting large numbers of seizure patients to treatment with potential risk, it is important to clarify these issues further. With funding from the Family Health Foundation, the Department of Family Medicine at the Medical College of Ohio is embarking on a long-term study to determine in an ambulatory setting the incidence and clinical significance of mineral and bone abnormalities. If these complications are frequent and clinically significant, then a randomized controlled trial of vitamin D prophylaxis will be initiated.

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