

ANTICONVULSANT THERAPY-INDUCED ALTERATIONS IN CALCIUM HOMEOSTASIS

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ABSTRACT

35 epileptic patients, aged 10 to 58 years (mean 23), who were taking anticonvulsant drugs were studied. The patients exhibited a 34% reduction in serum calcium levels, a 41% increase in serum alkaline phosphatase activity and a slight but insignificant decrease in serum phosphate, compared to untreated controls. These changes appear to be related to the anticonvulsant drug taken, in the following order of decreasing importance: phenytoin + phenobarbital + carbamazepine; phenytoin + phenobarbital; phenytoin + carbamazepine, and phenobarbital + carbamazepine. It is possible that anticonvulsant drugs alter vitamin D metabolism which results in disturbance of calcium homeostasis. Moreover these changes in serum calcium and alkaline phosphatase activity in anticonvulsant treatment patients are similar to those in patients with osteomalacia.

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INTRODUCTION

During a clinical trial of trinuride (pheneturide, phenytoin and phenobarbitone) Wright observed that serum alkaline phosphatase activity rose in 20% of the patients treated with the test drug.¹² Kruse reported that 15% of young epileptics on anticonvulsant drug therapy showed evidence of osteomalacia.¹¹

More recently, this disorder has been detected in epileptic populations, with the reported incidence varying from 4 to 70%.¹¹ It was therefore of interest to examine the effect of anticonvulsant drug combinations on indicators of calcium homeostasis. This study was undertaken to determine the relationship between anticonvulsant drugs, serum calcium and phosphorous levels and serum alkaline phosphatase activity.

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MATERIAL AND METHODS

Thirty five epileptic patients in the department of neurology of Khorshid hospital (affiliated to Isfahan University of Medical Sciences) were selected for the study. Patients selected had been taking anticonvulsant drugs for one year or longer and they had not received any vitamin D or calcium supplementation. Their ages were between 10 to 58 years (mean 23 years), and had been treated with various combinations of phenytoin, phenobarbital and carbamazepine. These specific treatments and duration of treatment for the patient group are outlined in Table I.

Twenty-eight healthy subjects aged 12 to 54 years (mean 25 years) were selected as controls. They were approximately age- and sex-matched with the patient group. Fasting blood samples were obtained from the patients and the control group between 08:00 and 10:00 hr. Serum was prepared by centrifugation and stored at -10°C until assayed.

Serum calcium was determined with an atomic absorption spectrophotometer (Perkin-Elmer Model 2380)⁷ Serum alkaline phosphatase activity was deter-

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Table I. Summary of patient treatments

treatment	number of patients	mean age (years)	mean duration of treatment (years)
phenytoin+phenobarbital+carbamazepine	11	25.2	4.6
phenytoin+phenobarbital	8	19.2	4.2
phenytoin+carbamazepine	9	29	2.5
phenobarbital+carbamazepine	7	14.8	3.7
Control	28	25	---

mined by the method of Bessey-Lowry-Broch (BLB method), which is a colorimetric technique using par-nitrophenyl phosphate as the substrate.⁴ Serum phosphorus was also measured by a colorimetric method using molybdate and its subsequent reduction.⁷

Statistical significance was determined using the students t test.

RESULTS

The effect of anticonvulsant drug therapy on Ca and P levels and alkaline phosphatase activity is shown in Table II. Patients receiving anticonvulsant therapy exhibited significantly lower serum calcium levels (9.2 ± 0.9 mg/100 ml) compared to that of the control group (10 ± 0.8 ; $p < 0.05$). In addition, serum calcium levels were below the minimum value (9 mg/100 ml) of the normal range in 34% of treated patients. More importantly it can be seen that triple drug therapy (line 3 of Table II) is associated with the lowest serum calcium levels. The other drug combination had a lesser effect on serum calcium levels (Table II).

The serum alkaline phosphatase levels of 35 patients and 28 controls were 66.0 ± 9.2 and 33.7 ± 4.6 mIU/ml respectively, and the difference between them was significant ($P < 0.001$). Serum alkaline phosphatase was above the normal range (13-38 mIU/ml) in 41% of the treated patients. Similar to the situation for calcium, the higher serum alkaline phosphatase activity was found in patients with triple drug therapy (line 3 of Table II). The other drug combinations had a lesser effect on serum alkaline phosphatase activity.

In contrast to apparent drug-induced changes in serum calcium and alkaline phosphatase activity, serum phosphorus levels were unaffected by anticonvulsant drug treatment.

DISCUSSION

This study shows that epileptic patients receiving anticonvulsant drugs exhibit reduced serum calcium

Table II: Effect of anticonvulsant-drug therapy on serum calcium, on serum calcium, phosphorous and alkaline phosphatase levels.

Line	Treatment	Patients	Serum Ca (mg/100ml)	Serum P (mg/100ml)	Serum Alkaline Phosphatase activity (mIU/ml)
1	control	28	10.4 ± 0.8	3.7 ± 0.1	33.7 ± 4.6
2	all patients	35	9.2 ± 0.9	3.5 ± 0.5	66.0 ± 9.2
3	phenytoin+phenobarbital+carbamazepine	11	8.9 ± 1.3	3.6 ± 0.6	81.3 ± 7.3
4	phenobarbital+phenytoin	8	9.0 ± 0.6	3.5 ± 0.6	73.5 ± 8.3
5	phenytoin+carbamazepine	9	9.4 ± 0.6	3.5 ± 0.4	49.1 ± 3.2
6	phenobarbital+carbamazepine	7	9.4 ± 0.7	3.4 ± 0.5	55.6 ± 5.0

* mean values \pm SE

level and elevated serum alkaline phosphatase activity compared to untreated controls. These observations are in agreement with other studies.^{3,8,10} Moreover our results agree with those of Kruse¹¹ in that osteomalacia can be related to the number of anticonvulsant drugs. Table II shows that serum calcium levels were inversely proportional to the number of drugs taken, indicating that the combination of three most common anticonvulsant drugs had the greatest deleterious effect on calcium homeostasis. In addition, phenytoin and phenobarbital appear to impair calcium homeostasis to a greater extent than carbamazepine. Similarly, elevated serum alkaline phosphatase activity was more prominent when the drug treatment contained both phenytoin and phenobarbital compared to treatments composed of only one of these drugs and carbamazepine (compare line 3 and 4 to line 5 and 6 of Table II).

It has been shown that the serum concentration of the active vitamin D metabolites is diminished after administration of phenytoin and other anticonvulsant drugs.¹¹ This effect of these drugs is due to induction of hepatic metabolic enzymes thus resulting in an acceleration of vitamin D metabolism. Thus these drugs have an indirect effect on calcium homeostasis. Further support for the notion that anticonvulsant drugs enhance vitamin D metabolism comes from observation that phenobarbital can stimulate the activity of mitochondrial vitamin D-25 hydroxylase.¹¹ In addition, when phenobarbital and phenytoin were administered to severely vitamin D deficient chicks, there was an enhancement of renal 25, OH-1-hydroxylase activity.¹¹ Several groups of investigators have shown that anticonvulsant therapy increases target organ resistance to vitamin D.⁹

Although anticonvulsant drugs can influence calcium metabolism indirectly via alterations in vitamin D metabolism, the effects of these drugs on calcium homeostasis and bone integrity are probably more complex. In point of fact, phenytoin has been shown to inhibit membrane cation transport,² which suggests

that it has a direct effect on mineral metabolism. In bone tissue, both phenytoin and phenobarbital can block the tissue response to PTH and vitamin D.¹¹ Likewise phenytoin can inhibit collagen synthesis¹ and lysosomal enzyme release¹¹ in cultured bone cells, indicating inhibition of both osteoblast and osteoclast activity. The diminished serum calcium and elevated serum alkaline phosphatase activity in our anticonvulsant-treated patients indicate that both bone and vitamin D metabolizing tissues may be the site of action of these drugs for their adverse effects. The fact that serum phosphorous levels in the treated patients were not different from those in controls, suggests that these anticonvulsant drugs have little effect on the renal handling of phosphorus.

Long-term use of anticonvulsant drugs can cause osteomalacia⁵ and rickets (Jamshidi, unpublished observation). Thus even though a precise mechanism for this drug-induced condition is lacking at present time, we recommend that patients receiving anticonvulsant drugs, particularly phenytoin and phenobarbital, be given vitamin D supplementation in order to prevent their adverse effects. From our own experience, vitamin D and calcium supplementation have reversed the phenytoin-induced rachitic state of a 14 year old patient within 6 months (Jamshidi, unpublished observation).

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