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Short Report

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Monitoring of Laboratory Parameters During Valproic Acidcarbamazepine Combination Therapy

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Introduction

A number of anticonvulsant drugs such as phenytoin, phenobarbital and primidone cause disturbances in bone mineral metabolism (1,2). Side effects of carbamazepine (CBZ) seem to be fewer than with other antiepileptic drugs (3). However CBZ is metabolized to carbamazepine 10-11 epoxide (CE) (4). It is shown that the drug interaction between valproic acid (VPA) and CBZ may result elevated with CE concentrations and thereby clinically relevant side effects (5). To our knowledge, CE has not been reported to cause of anticonvulsant rickets.

We determined antiepileptic rickets in a patient who has been on combination therapy with CBZ and VPA. We suggested that this finding might be due to a high CE level, but we were unable to serum levels of CE .

An 11 year old girl with generalized tonic and clonic seizure was treated with CBZ 15 mg/kg/day. Laboratory examination ,EEG and cranial MRI of the patient was normal at initial examination. She was diagnosed to have idiopatic epilepsy. Nine months later the girl was admitted to our clinic because of recurring seizures. Interictal EEG revealed generalised, bilateral, synchronous and symmetric spike and wave discharge. Serum CBZ level and biochemical analyses were normal. VPA (10 mg/kg/day) was added to treatment regimen continuing CBZ with the previous doses. Nine months later she came with knee pain during walking. Physical examination of the patient was normal.

On laboratory examination Hb 12 gr/dl, white blood cells 5600/mm^3, calcium (Ca) 8.0 mg/dl, phosphate (P) 3.9 mg/dl, alkaline phosphatase 1222 IU, serum alanin and aspartate aminotransferase levels were normal. X-Ray of the hand and wrist revealed irregularity on the radius and ulna (Fig 1). Blood CBZ and VPA levels were within normal therapeutic limits. 25-0H vitamin D level was 5 IU/ml (10-40).

She has been treated with D^3 5000 U/day and calcium-lactate 75 mg/kg/day for three weeks. At the end of the third week, laboratory examination revealed that Ca and P levels were normal and alkaline phosphatase level was 859 IU.

Long term anticonvulsant drug treatment has been associated with clinical osteomalacia and rickets or laboratory abnormalities such as hypocalcemia, elevated serum alkaline phosphatase levels, radiographic evidence of osteopenia, decreased bone minerale dencity and osteomalacia on bone biopsy (2).

The pathogenesis of these disorders are unclear. However altered vitamin D metabolism appears to be of major importance (1). In addition, it has been suggested that antiepileptic drugs may promote hepatic degredation of vitamin D and 25-hydroxy vitamin D with subsequent depletion of vitamin stores (1,6-8). These drugs may modify the synthesis and metabolism of dihydroxy vitamin D metabolites or inhibit intestinal mineral absorbtion by mechanism which are independent of their effects on vitamin D metabolism (9).

The most common side effects of carbamazepine are nause, blurred vision, diplopia and slurred speech (10). It has been shown that carbamazepine decreases

serum calcium and increases serum alkaline phosphatase levels (11-13). In 1984, histological evidence of disturbances in bone mineral metabolism has been demonstrated by Hoikka et al (3).

Side effects of valproate includes gastrointestinal upset, fatal hepatotoxicity, tremor, hyperammonemia, somnolence and thrombocytopenia (10).

Some studies have indicated that CBZ is metabolized to carbamazepine 10-11 epoxide (CE) which is a physiologically inactive metabolite and has an anticonvulsant effect (4). CE seems partially responsible for the side effects of CBZ therapy (5,14). It has been shown that drug interaction between valproic acid (VPA) and CBZ may result in elevated CE concentrations and thereby to clinically relevant side effects (15). Side effects of CE in these studies were vomiting, somnolence, unable to speak, sleeping, but disorder of the bone metabolism has not been reported.

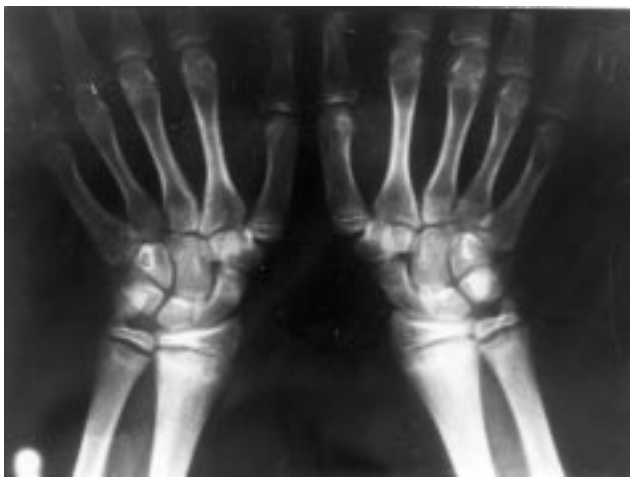

Figure 1. Radioluscent irregularities was seen on hand wrist x-ray belong epifizeal side of the both metaphyses with rickets.

Clinical and laboratory examination of our patient was normal 9 th months after the initiation of CBZ therapy. We determined decreased Ca level, increased alkaline phosphatase level after 9 months of combined VPA and CBZ therapy. For that reason we thought that CE might be responsible for the disturbances of bone mineral metabolism ultimately causing anticonvulsant rickets.

Ala Hauhala et al investigated anticonvulsant rickets in 28 adolescents with long-term (over 6 years) anticonvulsant therapy (phenytoin, carbamazepine or combination). They claimed that rutine vitamin D supplementation didn't appear to be indicated in children on anticonvulsant therapy (16). On the other hand our adolescent patient showed typical rickets findings within 9 months of combined therapy with CBZ and VPA.

Anticonvulsant rickets is treated with vitamin $D^{3.}$ Colling et al determined that 78 percent of patients responded to a dose of 2400 IU/day (17). Our patient was cured with dose of 5000 IU/day vitamin $D^{3.}$. We suggest that VPA and CBZ in combination may cause clinical rickets due to elevated levels of CE. This clinical and laboratory experience is to be supported by monitoring serum CE levels.

References

1. Hahn TJ. Drug- induced disorders of vitamin D and mineral metabolism. Clin Endocrinol Metab 9: 107-129, 1980.
2. Pe na Gri nan MJ, Lluch Fernande MD, Montoya Garcia MJ, Ramos Sanchez I, Perez Cano R. Phosphorus - calcium metabolism in children under prolonged treatment with anticonvulsants. An Esp Pediatr 35: 169-172, 1991.
3. Hoikka V, Alhova EM, Karjalainen P, Keranen T, Savolainen KE, Riekkinen P and Korhonen R. Carbamazepine and bone mineral metabolism. Acta Neurol Scand 69:77-80,1984.
4. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine 10-11 epoxide. Clin Pharmacokinet 11: 177-198, 1986.
5. Rambeck B, Treuman AS, May TH, Boenigk HE. Valproic acid- induced carbamazepine 10-11 epoxide toxicity in children and adolescents. Eur Neurol 30: 79-83, 1990.
6. Hahn TJ, Birge SJ, Scharp CR, Aviol LV. Phenobarbital induced alterations in vitamin D metabolism. J Clin Invest 51: 741, 1972.
7. Stamp TCB, Round JM, Rowe DJF, Haddad JG. Plasma levels and therapeutic effect of 25-Hydroxycholecalciferol in epileptic patients taking anticonvulsant drugs. Brit Med J 4: 9-12, 1972.
8. Sheth RD, Wesolowski CA, Penney S, Hobbs GR, Riggs JE, Bodensteiner JB. Effect of carbamazepine and valproate on bone mineral density. J Pediatr . 127: 256-262,1995.
9. Koch HU, Kraft D, Von Hersath D, Schaeffe K. Influence of dyphenylhydantoin and phenobarbital on intestinal calcium transport in the rat. Epilepsia 13: 829, 1972,

10. Pellock JM. Efficacy and adverse effects of antiepileptic drugs. Pediatr Clin North Am 36: 435-448, 1989.

11. Tjellesen L, Christiansen C. Calcium metabolism in epileptic patients treated with carbamazepine. Calcif Tiss Int 35: 62, 1983.

12. Rajantre J, Lamberg Allardl C, Wilsko M. Does carbamazepine treatment lead to a need of extra vitamin D in some mentally retarded children: Acta Paediatr Scand 73: 325-328, 1984.

13. Sommer R, Ryhtmamsborger H, Stobich E, Voinz C, Leblhuber F. Monitoring of laboratory parameters during carbamazepine therapy in psychiatric patients. 25: 150-153, 1992.

14. Patsalos PN, Stephenson TJ, Krishna S, Elyes AA, Lascelles PT, Wiles CM. Side effects by carbamazepine 10-11 epoxide. Lancet I: 496, 1985.

15. Meijer JWA, Binnie CD, Debets RMC, Van Parys JAP, De Beer, Pawlikowski NBK. Possible hazard of valpromid-carbamazepine combination therapy in epilepsy. Lancet i : 802, 1984.

16. Ala-Hauhala M, Korpela R, Koivikko M, Koskinen T, Koskinen M, Koivula T. Long-term anticonvulsant therapy and vitamin D metabolism in ambulatory pubertal children. Neuropediatrics 17: 212-216, 1986.

17. Collins N, Maher J, Cole M, Baker M, Callaghan N. A prospective study to evaluate the dose of vitamin D required to correct low 25- hydroxy vitamin D levels, calcium and alkaline phosphatase in patients at risk of developing antiepileptic drug induced osteomalacia. Q J Med 78: 113-122, 1991.