EFFECT OF EPIVAL ON THE CHANGES IN BONE MINERAL LEVEL IN CHILDREN

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ABSTRACT

Objective: To assess the mean change in bone mineral level in children with treatment of epival for management of epilepsy

Study Design: Quasi experimental study

Material and Method: The present study was carried out in the Paediatric department, Services hospital Lahore. Duration of study was 6 months from 02-03-2017 to 02-09-2017. 110 children suffering from epilepsy and taking epival were enrolled in the study from OPD of Department of Pediatrics, Services Hospital, Lahore. Informed consent was obtained from parents. Demographic profile (name, age, gender, address and contact) were also noted. Their blood samples were collected for assessing serum ALP and calcium. Reports were assessed and baseline values were noted. Children were followed-up in OPD for 90 days. After 90 days, calcium and ALP were assessed again. All this information will be recorded in pre-designed proforma. Data was analyzed by using SPSS-20 software.

Results: The results showed that average age of children was 7.68±4.05years. There were 56(50.91%) males while 54(49.09%) females. The mean BMI of patients was 22.40±2.60kg/m^2. The mean calcium level at baseline was 9.34±0.53mg/dl which was decreased to 8.56±0.77mg/dl after 09 days of treatment with epival. The mean change in calcium was 0.78±0.43mg/dl which was significant (P<0.05). The mean ALP level at baseline was 96.20±30.47U/L which was increased to 118.07±38.41U/L after 09 days of treatment with epival. The mean change in ALP level was 21.87±9.38U/L which was significant (P<0.05).

Conclusion: There is significant impact of epival on bone mineral density of epileptic children

Key words: Epilepsy, Epival, Bone Mineral Density, Calcium, Alkaline Phosphate

INTRODUCTION

Epilepsy is 4th most common neurological condition in the general population. In the developed countries its prevalence is 5 to 8 individuals per 1000 people. It is present mostly in children and elderly [1]. Most of the pediatrician prescribes Epival for its treatment. One of the deleterious effect of Epival is decreased bone density. That is why continuous skeleton monitoring is necessary in children receiving antiepileptic treatment[2].

Continuous use of antiepileptic drugs (AEDs causes metabolic changes in bone metabolism with the reduction in bone mineral density and increased incidence of fractures[1]. The association between AEDs and disorders in bone metabolism was first detected in the late 1960s. On one side of the spectrum there may be only bone pain while on the other side there is severe reduction in bone density leading to osteoporosis and fractures on minor trauma. This problem was detected in most of the patients taking AEDs. The most severe manifestations of these disorders are osteopenia/osteoporosis, osteomalacia and fractures. Bone disease has been described in several groups of patients receiving AEDs.[3] Valproic acid (epival) is reported to be effective for the control of absence seizures in 75% of children.[4] Valproic acid (epival) is often considered to be the drug of choice for the treatment of childhood epilepsy.[4]

Our study has found that with epival (n=10 cases), there was significant (p<0.05) change in calcium, ALP and vitamin D i.e. calcium [baseline:9.45±0.15, 90 days:9.08±0.18, change=0.37±0.16], ALP [baseline:188.47±14.12, 90 days:243.33±13.35, change=54.86±13.74], vitamin D [baseline:10.55±1.56, 90 days:7.34±1.08, change=3.21±0.48] but insignificant for phosphorus (p>0.05) i.e. phosphorus [baseline:4.00±0.20, 90 days:4.00±0.25, 0±0.22].[5]

It is seen that sodium valproate can cause osteoporosis in children only when it is used in higher dose and for longer period of time. Those patients should be easily monitored by measuring bone mineral density.[6] Studies shows that not only sodium valproate but also other AEDS like Carbamazepine and Oxcarbazepine when used for prolonged period can affect bone metabolism.[7]

Rationale of this study is to assess the change in bone mineral level in children on treatment with epival for management of epilepsy. Literature is evident that AEDs can alter the bone minerals level which may result in bone weakness and loss of bone structure and easy fracture in children. There is controversy exists but appropriate evidence has been found in this regard. Moreover, no local evidence has been found in literature as well as the reported study was conducted on very small sample size. So, we want to conduct this study to get precise results. Furthermore, we will also get local data which will help us in future to implement the screening of bone mineral density of epileptic children who are taking epival, to identify the bone mineral changes on early basis and can be advised supplements to prevent the loss.

MATERIAL AND METHODS

This descriptive study was conducted in outpatient department, at Services Hospital, Lahore.110 children were enrolled in the study after informed consent from parents. Inclusion criteria include children of age 1-14years of either gender presenting with epilepsy. While children already on calcium and vitamin D supplements (on medical record), children already having clinical/biochemical evidence of rickets (calcium<8.5mg/dL, serum phosphorus <4.3mg/dl, and ALP<44U/L), growth and neurological impairment (on medical record) and children showing signs of malnutrition (on clinical examination) were excluded from the study. Demographic profile (name, age, gender, address and contact) were also noted. On inclusion, 5ml venous blood samples were collected under aseptic measures by using 5cc BD syringe. Samples were sent to the laboratory for assessing serum ALP and calcium. Standard biochemical methods were used for analyzing the samples. Reports were assessed and baseline values were noted. Then all children were given standard recommended doses of 15mg/Kg/day epival in BID dose. The dose was increased to 40 mg/Kg/day as maintenance therapy. Those children were followed-up in OPD for 90 days. After 90 days, these children were assessed for calcium and ALP. Reports were assessed and levels were noted. All this information was recorded in pre-designed proforma.

Data was analyzed by using SPSS-20 software. Serum calcium, ALP and change in bone mineral levels were calculated as mean and standard deviation. Qualitative variables like gender were calculated as frequency and percentage. Data were stratified for age, gender and BMI. Post-stratification, independent sample t-test was applied to compare the mean change in calcium and ALP level in stratified groups.P-value≤0.05 was taken as significant.

RESULTS

110 children were included in the study with a mean age of 7.68±4.05years. Table 1

There were 56(50.91%) males while 54(49.09%) females in the study. Fig 1

The mean BMI of patients was 22.40±2.60kg/m^2. Table 2

The mean calcium level at baseline was 9.34±0.53mg/dl which was decreased to 8.56±0.77mg/dl after 09 days of treatment with epival. The mean change in calcium was 0.78±0.43mg/dl. This change was significant (P<0.05). Table 3

The mean ALP level at baseline was 96.20±30.47U/L which was increased to 118.07±38.41U/L after 09 days of treatment with epival. The mean change in ALP level was 21.87±9.38U/L. This change was significant (P<0.05). Table 4

Data was stratified for age of children. In children aged 1-5years, mean variation in calcium level was 0.73±0.42mg/dl, in children 6-10 years, mean variation in calcium level was 0.86±0.44mg/dl and in children with age>10years, mean variation in caladium level was 0.72±0.42mg/dl. The difference in all age groups for mean change in calcium level was insignificant (P>0.05). Table 5

Data was stratified for age of children. In children aged 1-5years, mean variation in ALP level was 23.69±10.09U/L, in children 6-10years, mean change in ALP level was 20.84±8.50U/L and in children with age>10years, mean change in ALP level was 21.06±9.53U/L. The difference in all age groups for mean change in ALP level was insignificant (P>0.05). Table 6

Data was stratified for gender of children. In male children, mean variation calcium level was 0.84±0.43mg/dl and in female children, mean change in calcium level was 0.70±0.42mg/dl. The difference between both genders for mean change in calcium level was insignificant (P>0.05). Table 7

Data was stratified for gender of children. In male children, mean change in ALP level was 22.26±8.86U/L and in female children, mean change in ALP level was 21.46±9.96U/L. The difference in all age groups for mean change in ALP level was insignificant (P>0.05). Table 8

Data was stratified for BMI of children. In underweight children, mean change in calcium level was 0.64±0.52mg/dl, in normal BMI children, mean change in calcium level was 0.78±0.40mg/dl and in

overweight children, mean change in calcium level was 0.80±0.47mg/dl. The difference was insignificant (P>0.05). Table 9

Table 1: Descriptive statistics of age of patients

Age (years)	**n**	110
	Mean	7.68
	SD	4.05
	Minimum	1
	Maximum	14

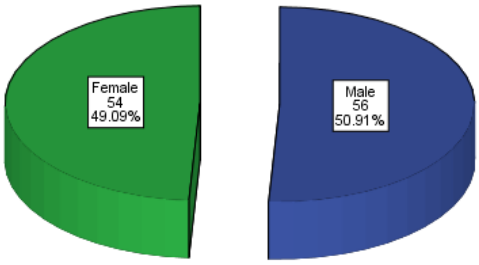

Fig 1: Distribution of gender of patients

Table 2: Descriptive statistics of BMI of patients

BMI (kg/m^2)	**n**	110
	Mean	22.40
	SD	2.60
	Minimum	18.50
	Maximum	27.25

Table 3: Descriptive statistics of calcium level before and after intervention

		Baseline	**After 90 days**	**Change**
Calcium level (mg/dl)	**n**	110	110	110
	Mean	9.34	8.56	0.78
	SD	0.53	0.77	0.43

Paired sample t-test = 19.056
p-value = 0.000 (Significant)

Table 4: Descriptive statistics of ALP level before and after intervention

		Baseline	**After 90 days**	**Change**
ALP level (U/L)	**n**	110	110	110
	Mean	96.20	118.07	21.87
	SD	30.47	38.41	9.38

Paired sample t-test = 24.455
p-value = 0.000 (Significant)

Data was stratified for BMI of children. In underweight children, mean change in ALP level was 16.04±6.02U/L, in normal BMI children, mean change in ALP level was 22.23±8.87U/L and in overweight children, mean change in ALP level was 22.88±11.75U/L. The difference was insignificant (P>0.05). Table 10

Table 5: Descriptive statistics of change in calcium level stratified for age

		Age (years)		
		1-5	**6-10**	**>10**
Calcium (mg/dl)	**Mean**	0.73	0.86	0.72
	SD	0.42	0.44	0.42

ANOVA = 1.193
p-value = 0.307 (Insignificant)

Table 6: Descriptive statistics of change in ALP level stratified for age

		Age (years)		
		1-5	**6-10**	**>10**
ALP (U/L)	**Mean**	23.69	20.84	21.06
	SD	10.09	8.50	9.53

ANOVA = 1.060
p-value = 0.350 (Insignificant)

Table 7: Descriptive statistics of change in calcium level stratified for gender

		Gender	
		Male	**Female**
Calcium (mg/dl)	**Mean**	0.84	0.70
	SD	0.43	0.42

Independent sample t-test = 1.727
p-value = 0.087 (Insignificant)

Table 8: Descriptive statistics of change in ALP level stratified for gender

		Gender	
		Male	**Female**
ALP (U/L)	**Mean**	22.26	21.46
	SD	8.86	9.96

Independent sample t-test = 0.443
p-value = 0.659 (Insignificant)

Table 9: Descriptive statistics of change in calcium level stratified for BMI

		BMI		
		Under-weight	**Normal**	**Overweight**
Calcium (mg/dl)	**Mean**	0.64	0.78	0.80
	SD	0.52	0.40	0.47

ANOVA = 0.480
p-value = 0.620 (Insignificant)

Table 10: Descriptive statistics of change in ALP level stratified for BMI

		BMI		
		Underweight	**Normal**	**Overweight**
ALP (U/L)	**Mean**	16.04	22.23	22.88
	SD	6.02	8.72	11.75

ANOVA = 1.968
p-value = 0.145 (Insignificant)

DISCUSSION

Childhood and adolescence are critical periods of skeletal mineralization. Peak bone mineral density achieved by the end of adolescence determines the risk for later pathological fractures and osteoporosis. Chronic disease and medication often adversely affect bone health. Epilepsy is one of the most common neurological conditions occurring in persons under the age of 21. Epilepsy may affect bone in a number of ways. Restrictions of physical activity imposed by seizures; limitations on physical activity resulting from cerebral palsy, frequently present in patients with symptomatic epilepsy; and medications used to treat seizures can all adversely affect bone health. It has long been observed that treatment with phenytoin and phenobarbital can be associated with rickets.[8]

Evidence from different studies showed that AEDs cause alteration in bone metabolism, so there is need of time to have a better understanding about this important subject. Furthermore other modalities should be developed to treat this disorder[9]. Since AEDs have known to cause decreased bone density but many other studies especially in adults lack this important fact [12].

In spite of data about the possible effects of the AEDs on calcium metabolism, the mechanisms of this important side effect remain to be defined. The abnormalities of calcium metabolism were thought to result from the cytochrome P450 enzyme-inducing properties of some AEDs and the resultant reduction in vitamin D levels, but the effect of many medications (e.g., valproate) cannot be readily explained by vitamin D metabolism.[11]

In this study 110 children were included with an average age of 7.68±4.05years. There were 56(50.91%) males while 54(49.09%) females in the study. The mean BMI of children was 22.40±2.60kg/m^2.

The mean calcium level at baseline was 9.34±0.53mg/dl which was decreased to 8.56±0.77mg/dl after 09 days of treatment with epival. The mean change in calcium was 0.78±0.43mg/dl. This change was significant (P<0.05).

The mean ALP level at baseline was 96.20±30.47U/L which was increased to 118.07±38.41U/L after 09 days of treatment with epival. The mean change in ALP level was 21.87±9.38U/L. This change was significant (P<0.05).

One study has found that with epival (n=10 cases), there was significant (p<0.05) change in calcium, ALP and vitamin D i.e. calcium [baseline:9.45±0.15, 90 days:9.08±0.18, change=0.37±0.16], ALP [baseline:188.47±14.12, 90 days:243.33±13.35, change=54.86±13.74], vitamin D [baseline:10.55±1.56, 90 days:7.34±1.08, change=3.21±0.48] but insignificant for phosphorus (p>0.05) i.e. phosphorus [baseline:4.00±0.20, 90 days:4.00±0.25, 0±0.22].[5] So prolonged use of AEDs therapy especially in young children can disrupt bone metabolism. These children should be closely monitored by measuring bone mineralization [6].

.In another study, the frequency of changes in biochemical markers of bone metabolism in children who are receiving valproic acid, carbamazepine, and oxcarbazepine were assessed. Blood samples were obtained in order to determine biochemical parameters. Bone mineral density was measured with the dual-energy x-ray absorptiometry method. In patients receiving AEDs, bone mineral density values were significantly lower than the healthy control group. In conclusion, long-term AED treatment either with valproic acid, carbamazepine, or with oxcarbazepine which has unknown effects on skeletal mineralization, induces a state of decreased bone mineral density.[7]

Another study done by Erbayat Altay E showed that AEDs have minimal association with decreased bone density. However they suggested that these patient should be regularly monitored and given Vitamin D supplementation [1] .

The association of prolonged use of AEDs and abnormalities in bone metabolism was reported nearly 40 years age and since variety of different studies were done which proved that there are substantial evidence between abnormalities in serum calcium, ALP and bone mineral density with AEDs.[13-17] AEDs were proved to cause decreased bone density and osteopenia. [18]

Low bone mass associated with AED use is largely unrecognized, undetected, and untreated.[108, 109] In a survey of 624 adult and pediatric neurologists designed to assess the awareness of the effects of AED therapy on bone health, among treating physicians, only 28% of adult and 41% of pediatric neurologists reported screening their patients for bone disease. In a cohort of neurologist, only 7% of adult and 9% of pediatric

neurologists prescribed prophylactic calcium and vitamin D for patients receiving AED treatment. [19] These data underscore the need for aggressive educational strategies to increase screening and treatment of metabolic bone disorders associated with AED use by the treating physicians. [20]

Data was stratified for age of children. In children aged 1-5years, mean change in caladium level was 0.73±0.42mg/dl, in children 6-10years, mean change in caladium level was 0.86±0.44mg/dl and in children with age>10years, mean change in caladium level was 0.72±0.42mg/dl. The difference in all age groups for mean change in caladium level was insignificant (P>0.05). Thus the epival has equal impact on any age of children. As from 1-14years of age of children is growing age and bone requires much calcium for proper growth. The epival decrease the calcium level significant and in pediatric age group, epival can cause slow growth or weak bones due to lack of calcium and phosphorus.

Data was stratified for age of children. In children aged 1-5years, mean change in ALP level was 23.69±10.09U/L, in children 6-10years, mean change in ALP level was 20.84±8.50U/L and in children with age>10years, mean change in ALP level was 21.06±9.53U/L. The difference in all age groups for mean change in ALP level was insignificant (P>0.05). This also showed that epival has equal impact in any age group of children. High ALP levels are diagnostic of rickets or osteomalacia in children. The epival causes a significant increase in ALP level in pediatric age group which is a sign of weak bones and slow growth and increases risk of fractures.

Data was stratified for gender of children. In male children, mean change in caladium level was 0.84±0.43mg/dl and in female children, mean change in caladium level was 0.70±0.42mg/dl. The difference between both genders for mean change in caladium level was insignificant (P>0.05). Thus epival is equally effective in both male and female children.

Data was stratified for gender of children. In male children, mean change in ALP level was 22.26±8.86U/L and in female children, mean change in ALP level was 21.46±9.96U/L. The difference in all age groups for mean change in ALP level was insignificant (P>0.05). Thus epival is equally effective in both male and female children.

Data was stratified for BMI of children. In underweight children, mean change in caladium level was 0.64±0.52mg/dl, in normal BMI children, mean change in calcium level was 0.78±0.40mg/dl and in overweight children, mean change in calcium level was 0.80±0.47mg/dl. The difference was insignificant (P>0.05).

Data was stratified for ALP of children. In underweight children, mean change in ALP level was 16.04±6.02U/L, in normal BMI children, mean change in ALP level was 22.23±8.87U/L and in overweight children, mean change in ALP level was 22.88±11.75U/L. The difference was insignificant (P>0.05).

Measurement of bone density should be performed out in children treated with prolonged AEDs therapy. Other modalities like bisphosphonate is carried out in patient who are prone to develop fractures[21] .

CONCLUSION

Thus there is significant impact of epival on bone mineral density of epileptic children. Now the controversy resolved and we have got the local evidence and found the epival has significant effect on change in bone mineral density. Now, in future, we can implement the screening of bone mineral density of epileptic children taking epival to identify the bone mineral changes on early basis and can be advised supplementation to prevent the loss.

REFERENCES

1. Meier C, Kraenzlin ME. Antiepileptics and bone health. Therap Adv Musculoskel Dis 2011;3(5):235-43.
2. Farhat G, Yamout B, Mikati M, Demirjian S, Sawaya R, Fuleihan GE-H. Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology 2002;58(9):1348-53.
3. 3. Pack A, Morrell M. Adverse Effects of Antiepileptic Drugs on Bone Structure. CNS Drugs 2001;15(8):633-42.
4. 4. Ollivier ML, Dubois MF, Krajinovic M, Cossette P, Carmant L. Risk factors for valproic acid resistance in childhood absence epilepsy. Seizure 2009;18(10):690-4.
5. 5. Krishnamoorthy G, Karande S, Ahire N, Mathew L, Kulkarni M. Bone metabolism alteration on antiepileptic drug therapy. Indian J Pediatr 2009;76(4):377-83.
6. 6. Öner N, Kaya M, Karasalihoğlu S, Karaca H, Celtik C, Tütüncüler F. Bone mineral metabolism changes in epileptic children receiving valproic acid. J Paediatr Child Health 2004;40(8):470-3.
7. 7. Babayigit A, Dirik E, Bober E, Cakmakcı H. Adverse effects of antiepileptic drugs on bone mineral density. Pediatr Neurol 2006;35(3):177-81.

8. Sheth RD. Bone health in pediatric epilepsy. Epilepsy & Behavior 2004 2004/02/01/;5(Supplement 2):30-5.
9. Petty SJ, O'brien T, Wark J. Anti-epileptic medication and bone health. Osteoporosis international 2007;18(2):129-42.
10. Petty S, Paton L, O'brien T, Makovey J, Erbas B, Sambrook P, et al. Effect of antiepileptic medication on bone mineral measures. Neurology 2005;65(9):1358-65.
11. Verrotti A, Coppola G, Parisi P, Mohn A, Chiarelli F. Bone and calcium metabolism and antiepileptic drugs. Clinical Neurology and Neurosurgery 2010;112(1):1-10.
12. Erbayat Altay E, Serdaroğlu A, Tümer L, Gücüyener K, Hasanoğlu A. Evaluation of bone mineral metabolism in children receiving carbamazepine and valproic acid. Journal of Pediatric Endocrinology and Metabolism 2000;13(7):933-40.
13. Sheth RD. Metabolic concerns associated with antiepileptic medications. Neurology 2004;63(10 suppl 4):S24-S9.
14. Pack AM, Gidal B, Vazquez B. Bone disease associated with antiepileptic drugs. Cleveland clinic journal of medicine 2004;71:S42-8.
15. Kruse R. Osteopathies in antiepileptic long-term therapy (preliminary report). Monatsschrift fur Kinderheilkunde 1968;116(6):378-81.
16. Dent C, Richens A, Rowe D, Stamp T. Osteomalacia with long-term anticonvulsant therapy in epilepsy. Br Med J 1970;4(5727):69-72.
17. Ali II, Schuh L, Barkley GL, Gates JR. Antiepileptic drugs and reduced bone mineral density. Epilepsy & Behavior 2004;5(3):296-300.
18. Fulton J. New guidelines for the prevention and treatment of osteoporosis. National Osteoporosis Foundation. Medicine and Health, Rhode Island 1999;82(3):110-1.
19. Valmadrid C, Voorhees C, Litt B, Schneyer CR. Practice patterns of neurologists regarding bone and mineral effects of antiepileptic drug therapy. Archives of Neurology 2001;58(9):1369-74.
20. Valsamis HA, Arora SK, Labban B, McFarlane SI. Antiepileptic drugs and bone metabolism. Nutrition & metabolism 2006;3(1):36.
21. Meier C, Kraenzlin ME. Antiepileptics and bone health. Therapeutic advances in musculoskeletal disease 2011;3(5):235-43.