Anti-Epileptic Drugs (AEDs) and Body Electrolytes in Childhood Epilepsy: A Prospective Study

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ABSTRACT

A total of 225 epileptic children (male = 154, female = 71) age-ranged from 4 months to 14 years were studied. All the patients were on anti-convulsants. Depending upon the therapy (mono- or poly-drug), the subjects were divided into four study groups: A) Carbamazepine (CBZ); B) Phenobarbitone (PHB); C) Valproic Acid (VPA); and D) Poly-drug Therapy (PDT). The study was carried out to access the effects of these drugs on the blood sodium, potassium, magnesium, calcium, iron, copper, and zinc levels. The ratios of the levels Na/K, Ca/Mg, and Cu/Zn were also calculated. The children in this study were admitted to the Department of Pediatric Neurology, Riyadh Medical Complex (Saudi Arabia). A group of 22 healthy volunteer children was taken as Normal Control (male = 12, female = 10). Reduction in Mg and Fe was found highly significant ($P<0.0001$) in all the study groups as compared to control. The decrease of K ($P<0.05$, $P<0.001$) in the Groups A and C was found statistically significant. A significant decrease ($P<0.001$, $P<0.05$) in Ca was also observed in Groups B and C. Furthermore, Zn was found significantly reduced ($P<0.05$) in Group B as compared to control levels. However, serum Na and Cu did not show any statistically significant change as compared to control.

A significant increase ($P<0.05$, and $P<0.001$) in Na/K ratio was observed in Groups A and C groups as compared to control. The elevation in the Ca/Mg ratio in Groups A and C was also found significant ($P<0.001$) as compared to control. However, Cu/Zn ratio remained unaltered in all the study groups.

These findings suggest that the levels of serum Mg, K, Ca, and Fe levels, in epileptic children might be affected due to different type of AEDs, and supplements of their salts can be arranged during the treatment. The elevation in Na/K and Ca/Mg ratios in different study groups may be the consequence of AED-therapy, and might be correlated with seizure activity.

(Key words: blood serum, seizures, body electrolytes, electrolyte ratios)

INTRODUCTION

Body electrolytes play several critically important roles in many biochemical processes, particularly in maintenance of electrolyte balance, energy production, and normal neuromuscular functions. Magnesium, a prominent intracellular cation required for the function of many enzyme systems, is essential for normal neuromuscular activity and is also responsible for calcium and potassium transport (Rude 1989, 1993). Similarly trace elements such as copper and zinc have their well-defined metabolism (Liu et al. 1998). Any biochemical abnormality/electrolyte imbalance, accompanying seizures is important for seizure control and to avoid further brain

damage (Kumar et al. 1995). That is why the necessity of appropriate treatment has attracted different physicians and scientists to work on the role of anti-epileptic drugs (AEDs) in children, their metabolism and the significance of therapeutic drug monitoring (TDM). According to Podell (1998), successful treatment of seizure disorder requires proper patient assessment and understanding of the principles of AED therapy. Mono-therapy is the initial goal of treating epileptic patients to minimize the possible drug-drug interactions and adverse effects. According to Zupanc (1996), although most children with epilepsy have well-controlled seizures with the use of AEDs, some children have medically refractory seizures.

Although scientific work on these issues has led to better understanding of the disease and its treatment, different researchers have reported side effects of AEDs, especially on body electrolytes, which play a vital role in the maintenance of normal biochemical functions (Dreir et al. 1998; Pellock 1999; Dost et al. 2000). Based on a review of the current literature it was concluded that a comprehensive work with particular reference to electrolytes/trace elements and electrolyte ratios, was still required to be done on epilepsy in Saudi Arabia. Keeping in view the need to understand these aspects of epilepsy in Saudi Arabia, the present study was designed to estimate the electrolyte and trace elemental levels in children suffering from epileptic seizures, observe the effects of anti-epileptic drugs on these levels, and to evaluate the importance of the ratios of electrolytes/metals (such as: Na/k, Ca/Mg, Cu/Zn) as a tool in the diagnosis and understanding of seizures.

We investigated the effects of clinically employed anti-convulsants such as Carbamazepine (CBZ), Phenobarbitone (PHB), Valproic Acid (VPA), and poly-drugs on body electrolytes of epileptic children. The body serum levels of electrolytes such as sodium (Na), potassium (K), calcium (Ca), magnesium (Mg), and iron (Fe), including trace elements copper (Cu) and zinc (Zn), were observed. Some electrolytes showed changed levels when compared with the normal control. These alterations in serum electrolyte levels may be due to the AEDs being used by the epileptic patients. Similarly, changes in electrolyte ratios may be correlated with the activity of AEDs and also with the seizure activity.

MATERIALS AND METHODS

The present study included investigations on 225 children (154 male, 71 female) suffering from different types of epileptic seizures. The analysis and quantitative estimation of serum electrolytes/trace elements was undertaken. All subjects were registered patients and admitted to Riyadh Medical Complex (RMC), Riyadh (Saudi Arabia). The Normal Control consisted of data of 22 healthy children (M = 12, F = 10) with the consent of their parents. Among the subjects included in the present study, 177 patients were Saudi nationals while 70 were non-Saudis.

Keeping the clinical diagnosis of the patients in view, subjects were divided into different groups. The study was comprised of following four groups: A) Carbamazepine CBZ, (n = 87); B) Phenobarbitone, PHB, (n = 33); C) Valproic Acid ,VPA (n = 86); and D) Poly-Drug Therapy, PDT(n = 19).

The biochemical tests for this study included estimation of electrolytes such as: sodium (Na), potassium (K), calcium (Ca), magnesium (Mg), and iron (Fe). All samples were analyzed on Dimension® Clinical Chemistry System 1988; Du Pont Co., Wilmington DE 19898 USA, while serum levels of trace elements Cu and Zn were measured by Atomic Absorption Spectrometer GBC 906 AA using flame mode at λ 324.7 nm and 213.9 nm, (Shah et al. 2001). The data was

analyzed by using a standard spreadsheet program, and was compared with control data by using the Student *t*-test. The minimum level of significance was proposed to be $P < 0.05$.

RESULTS

The results of electrolytes in all the groups are shown in Table 1. The Mg and Fe serum levels in all the study group were found significantly lower ($P<0.0001$) than the control group. We observed a significant decrease in the serum K levels in Groups A and C ($P<0.05$, $P<0.001$). A statistically significant decrease was also observed in Ca, levels in Groups B and C ($P<0.001$, $P<0.05$). The zinc serum levels were found to be significantly lower ($P<0.05$) in study Groups A and B. However, Na and Cu levels remained unaltered as compared with the normal control. The changes of serum electrolytes and their ratios in different groups are shown in Tables 1 and 2, respectively.

Table1: Changes of Serum Electrolytes in Different Groups.

Parameters	Normal Control (N = 22)	Group A (N = 87)	Group B (N = 33)	Group C (N = 86)	Group D (N = 19)
Na	140.77 ± 0.45	140.59 ± 0.55	140.39 ± 0.57	139.91 ± 0.38	139.63 ± 0.88
K	4.68 ± 0.05	4.36 ± 0.06*↓	4.51 ± 0.11	4.35 ± 0.04**↓	4.40 ± 0.11
Ca	2.41 ± 0.02	2.38 ± 0.02	2.27 ± 0.03**↓	2.40 ± 0.03*↓	2.38 ± 0.04
Mg	0.89 ± 0.007	0.82 ± 0.009***↓	0.82 ± 0.009***↓	0.81 ± 0.008***↓	0.82 ± 0.01***↓
Cu	0.99 ± 0.02	0.96 ± 0.03	1.01 ± 0.04	0.95 ± 0.03	0.86 ± 0.09
Fe	22.08 ± 0.53	13.85 ± 0.41***↓	13.45 ± 0.48***↓	13.20 ± 0.41***↓	14.25 ± 0.73***↓
Zn	1.06 ± 0.01	0.96 ± 0.02*↓	0.95 ± 0.04*↓	0.99 ± 0.03	1.02 ± 0.10

*P < 0.05, **P < 0.001, ***P < 0.0001 (Students *t*-test).

SE = Standard Error = Increased level ↓ = Decreased level

The internationally accepted values in children for the parameters under study are as follows:

- [Na =133 - 152, K = 3.5 - 5.6 mmol/L]

- [Ca = 2.0 - 2.6, Mg = 0.8 - 1.1 mmol/L]
- [Cu = 0.7 - 1.4, Zn = 0.7 - 1.2 m g/L]

Table 2: Changes of Serum Electrolyte Ratios in Different Groups.

Ratios	Normal Control (N = 22)	Group A (N = 87)	Group B (N = 33)	Group C (N = 86)	Group D (N = 19)
Na/K	30.35 ± 0.35	32.78± 0.46*	31.63 ± 0.62	32.44 ± 0.34**	32.07 ± 0.84
Ca/Mg	2.70 ± 0.03	2.94 ± 0.05**	2.77 ± 0.05	3.01 ± 0.04**	2.89 ± 0.07
Cu/Zn	0.95 ± 0.03	1.08 ± 0.06	1.12 ± 0.06	1.06 ± 0.05	1.07 ± 0.19

*P < 0.05, **P < 0.001, ***P < 0.0001 (Students *t*-test).

SD = Standard Deviation.

The statistically significant elevation (P<0.05, P<0.001) in the mean values of Na/K ratios was observed in the patients of Groups A and C when compared with the control (seen in Table 2). Similarly, a significant increase (P<0.001) was observed in the mean values of Ca/Mg ratios as compared with the control in the patients belonging to Groups A and C. However, the results of Cu/Zn ratio in different groups showed no significant change as compared to the control.

DISCUSSION

Serum Na was found unaltered in all the study groups as compared with the control. The same results were observed in an earlier study in which serum Na levels were not affected with or without anti-convulsants with the exception of CBZ-therapy (Shah et al. 2001; Pellock 1987). Our study was also supported by Koivikko et al. (1983) who found serum Na concentrations within normal range except for the patients with CBZ-therapy showing hyponatremia. This was explained due to inappropriate secretion of anti-diuretic hormone (ADH).

The serum Mg was found lower in the epileptic children in all study groups. The low Mg levels along with hypokalemia can be correlated with the administration of AEDs, as first line mono-therapy and combination of other drugs in poly-therapy (Shah 2000). Mg has significant therapeutic potential and plays a role in seizures, especially associated with relative hypocalcaemic states (Swain et al. 1999).

During our study, potassium levels were found significantly reduced in groups A and C. Our results are in agreement with earlier reports where anti-epileptic drugs lead to an inhibition in

potassium currents which are potentially epileptogenic (Ricard-Mousiner et al. 1993). In another study, Natelson et al. (1979) observed potassium levels ranged between normal to low during attacks of seizure. Hypokalemia observed in the present study may be expressed as an increase in ratio of intracellular to extra-cellular potassium concentration, which may result in serious neurological symptoms. Based on the fact that magnesium-deficiency is linked with K^+ activity (Rude 1989), the possible role of low magnesium levels observed in our patients may also not be ruled out in causing hypokalemia.

Reduced levels of calcium observed in the present study groups (B and C) showed that such a change in Ca levels, may be due to toxic effects of AEDs and is directly correlated with hyper-excitability of cell membrane, resulting in enhanced epileptic activity in the children (Shah 2000).

Konig et al. (1999) and Gram et al. (1985) reported that VPA-associated side effects must be considered in patients without any evidence of metabolic defect or underlying neurological disease. In general, an increase in brain and neuromuscular excitability was related to the shifts in calcium concentration across cell membrane (Vein et al. 1988).

The serum iron levels of patients in all study groups were found significantly lower as compared to normal control (Shah et al. 2000). Iron-deficiency anemia was earlier recorded as a common feature in epileptic patients (Kobrinsky et al. 1995; Takeuchi 1996). Our current study also revealed that in general, Saudi children had low hemoglobin levels, which might be a result of decreased total serum iron concentrations (Jamil 2000). The decrease of Fe in the present study may be due to AEDs, like CBZ, PHB, etc., which are enzyme inducers, hypothetically leading to quick depletion of iron stores, resulting in anemia. Severe or moderately severe anemia states may coexist with relative hypoxia of brain, causing low jerks/seizure threshold. This, in turn, warrants the iron supplement therapy in children on AEDs.

The Cu-levels were found unaltered in the present study groups as compared with the normal control. However, we observed a significant decrease in Zn serum levels in the study Groups A and B. Palm et al. (1982, 1986) postulated that AEDs might cause a relative Zn deficiency through a chelate binding between Zn and the drug. Souzer et al. (1995) observed the similar effects of AEDs on serum Zn and Cu levels in children treated either with CBZ and VPA therapy. Their results indicate the serum trace metal homeostasis may be affected by AED therapy, but not by the convulsive disorder itself. A decrease in Zn serum levels in the present study groups may suggest that anti-convulsant therapy may induce alterations in metabolism and the distribution of Zn, influencing the effectiveness of seizure control.

The present study has revealed the significant lowering of Mg and Fe in all the study groups, both in mono-therapy (Groups A-C) and in poly-therapy (Group D). K and Ca, levels were also significantly lower in Groups (A and C) and (B and C) respectively. While Zn was observed in reduced concentration in A and B study groups.

Based on a review of the literature, it is concluded that serum electrolytes/trace elemental homeostasis may be affected by AED therapy but not by convulsive disorder per se. Further, it was observed that long-term anti-convulsant therapy might induce alterations in both metabolism and distribution of the metals (Shah 2000).

Elevation in the Na/K ratios was found highly significant in Groups A and C when compared with mean values of control. Similarly the ratio of Ca/Mg, in the same study groups (A and C), was observed to be significantly higher as compared to the normal control. However, we found no statistically significant alterations in the Cu/Zn ratios in the study groups.

When further clinically studied by Electro Encephalogram (EEG), patients with disturbed electrolyte levels (ratios of Na/K and Ca/Mg) showed epileptic discharges and clinical epileptic seizures (Jamil 2000). An elevation in the electrolyte ratios of Na/K and Ca/Mg might be due to sub-clinical seizure activity (Shah 2000).

CONCLUSIONS

Keeping in view the results of the present study, it can be recommended that routine laboratory tests measuring serum electrolytes should also include the measurement of Mg, K, Ca, and Zn apart from Na, Cu and other serum levels. Patients on AED therapy showing decreased levels of electrolytes, as mentioned, should be given the salts of Mg, K, and Ca as special supplements during the treatment. Likewise coexistent anemia needs to be treated accordingly with iron supplements. The ratios of Ca/Mg and Na/K might be considered as important parameters during follow-up examination of epileptic children. Therapeutic drug monitoring should be emphasized in all clinical laboratories to re-adjust the serum drug levels. Further study with a greater sample size is necessary to evaluate the effect of anti-convulsants on body electrolytes, trace elements and their ratios in epileptic patients in general.

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