Effects Of Anti-Epileptic Drugs (AEDs) on Biochemical Levels in Epileptic Children: A Prospective Study

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ABSTRACT

A prospective study of 225 epileptic patients (male = 154, female = 71) was carried out between August 1998 to July 2000, to access the effects of anti-epileptic drugs on the serum Glucose, Aspartate Amino Transferase (AST), Alanin Amino Transferase (ALT), Alkaline Phosphatase (ALP), Total Bilirubin (TBIL), and Direct Bilirubin (DBIL) levels. The patients were on anti-convulsant drug therapy such as: Carbamazepine (CBZ), Phenobarbitone (PHB), Valproic Acid (VPA), and Poly drug therapy (PDT). The levels were evaluated in epileptic children in the range of 4 months to 14 years, admitted to Pediatric Neurology Division of Riyadh Medical Complex (Saudi Arabia). A group of 22 healthy volunteer children was taken as Normal Control (male = 12, female = 10). The total patient sample was divided into four groups: Group1, Carbamazepine, CBZ, (n = 87); Group 2, Phenobarbitone, PHB, (n = 33); Group 3, Valproic Acid, VPA, (n = 86); and Group 4, Poly drug therapy, PDT, (n = 19).

Elevation of the levels of ALP was found highly significant in Group 1 and Group 2, ($P<0.0001$); Group 3 ($P<0.001$); and Group 4 ($P<0.05$) respectively as compared to control. The levels of AST were found significantly higher ($P<0.001$) in Groups 3 and 4. Similarly a significant increase in ALT levels was observed in Groups 1 and 3 ($P<0.0001$) and Group 2 ($P<0.001$), respectively. However, serum Glucose, TBIL, and DBIL did not show significant change as compared to control.

The significant increase in the levels of serum enzymes such as: ALP, AST, and ALT suggest that all AEDs, either as mono- or poly-therapy have adverse effects that should be considered by the clinician.

(Key words: epilepsy, seizures, glucose, aspartate amino transferase, alanin amino transferase, alkaline phosphatase, bilirubin).

INTRODUCTION

Epilepsy is one of the most common serious neurological problems and is a condition in which seizures recur, usually spontaneously (O'Charles 1996). Therefore, early diagnosis and appropriate treatment of biochemical abnormalities, accompanying seizures is important for seizure control and to avoid further brain damage (Kumar et al. 1995). 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 significance of therapeutic drug monitoring (TDM). Although scientific

work on these issues has resulted in a better understanding of the disease and its treatment, different researchers have reported side effects of AEDs, especially on body liver enzymes, which play a vital role in the maintenance of normal biochemical functions (Dreir et al. 1998; Pellock 1999; Dost et al. 2000). According to Zupanc (1996), most children with epilepsy have well-controlled seizures with the use of AEDs, even though some children have medically refractory seizures. As liver function abnormalities are consistent with a direct, dose-related hepatotoxicity (Sussman et al. 1979), treatment with some anti-convulsants is known to lead to liver enzyme induction (Andersen 2001).

It has been observed from various studies that determination of biochemical parameters is necessary only if there are clinical grounds for it such as suspicion of side effects, the occurrence of epileptic attacks despite therapy, or change from one drug to another (Doppelbauer et al. 1991). Some studies have described that ALP may not be a sensitive indicator of hepatocellular damage in patients on anticonvulsant therapy, as elevated levels may only reflect enzyme induction. Similarly AST is a specific, but relatively insensitive marker of liver damage, and has a poor correlation with liver histology (Callaghan et al. 1994).

Based on a review of the current literature, it was concluded that a comprehensive work with particular reference in hepatic enzymes 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 serum levels of different enzymes in children suffering from epileptic seizures, and to observe the effects of anti-epileptic drugs on these levels.

We investigated the effects of clinically employed anti-convulsants such as Carbamazepine (CBZ), Phenobarbitone (PHB), Valproic acid (VPA), and poly-drugs on serum biochemical parameters of epileptic children. The body serum levels of Glucose, AST, ALT, ALP, TBIL, and DBIL, levels were observed. Serum enzymes ALP, AST, and ALT showed significant changes when compared to the normal control.

MATERIALS AND METHODS

The present study included investigations on 225 children (154 male, 71 female) suffering from different types of epileptic seizures. An analysis and quantitative estimation of serum biochemical levels 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). Among the subjects included in the present study, 177 patients were Saudi nationals while 70 were non-Saudis.

Keeping in view the role of anti-epileptic drug therapy, patients were divided into the following four groups: Group 1) Carbamazepine (CBZ), included 87 patients; Group 2) Phenobarbitone' (PHB), included 33 patients; Group 3) Valproic Acid (VPA) included 86 patients; and Group 4) Poly-Drug Therapy (PDT), included 19 patients.

The biochemical tests included estimation of GLU, AST, ALT, ALP, TBIL, and DBIL levels. All samples were analyzed on Dimension® Clinical Chemistry System 1988; Du Pont Co., Wilmington DE 19898 USA (Shah et al. 2001). The data was analyzed by using a standard spreadsheet program, and was compared with control results by using the Student *t*-test. The minimum level of significance was proposed to be $P < 0.05$.

RESULTS

The results of the biochemical component levels examined for all the groups are shown in Table 1.

Table 1. Biochemical Changes Observed in Different Groups.

Parameter	Control Group (n = 22)	Group 1, CBZ (n = 87)	Group 2, PHB (n = 33)	Group 3, VPA (n = 86)	Group 4, PDT (n = 19)
GLU	4.63 ± 0.14	4.84 ± 0.06	4.89 ± 0.11	4.95 ± 0.09	5.06 ± 0.17
AST	28.59 ± 4.43	31.49 ± 0.90*	32.93 ± 1.13	31.32 ± 0.88**	34.09 ± 0.51**
ALT	22.47 ± 2.79	26.24 ± 0.90***	26.33 ± 1.42**	24.63 ± 0.83***	31.40 ± 0.58
ALP	239.76 ± 5.99	313.87 ± 12.05***	348.84± 20.32***	283.47 ± 9.92**	315.47± 763.9*
TBIL	3.82 ± 0.31	3.78 ± 0.28	3.93 ± 0.49	3.96 ± 0.26	4.01 ± 0.47
DBIL	1.48 ± 0.09	1.66 ± 0.07	1.61 ± 0.11	1.61 ± 0.10	1.66 ± 0.13

Group 1= CBZ, Group 2 = PHB, Group 3 = VPA, Group 4 = Poly drug therapy.

GOT/AST = up to 37, GPT/ALT = 15-45

CHANGES IN BIOCHEMICAL PARAMETERS

Elevation in the levels of ALP was found significantly higher in Groups 1 and 2 ($P<0.0001$), Group 3 ($P<0.001$), and Group 4 ($P<0.05$) as compared to control levels. A statistically significant increase ($P<0.001$) was also observed in AST levels in Groups 3 and 4. The ALT serum levels were found significantly higher in Groups 1 and 3 ($P<0.0001$) and Group 2 ($P<0.001$). However, serum Glucose, TBIL, and DBIL, did not show a significant change as compared with the normal control (Table 1).

DISCUSSION

The serum glucose in the present study did not show a statistically significant change in any of the study groups. However, when the sample was re-grouped into different seizure types, it was observed that 17.64% of the patients suffering from Complex Partial Seizures (CPS) and 22.72% of the patients suffering from Complex Partial Seizures-Secondary Generalized (CPS-II-G) showed increased serum glucose levels. Similarly, the percentage of the patients found in Generalized Seizures (GSZ) and Unclassified Seizures (UNC SZ) showing increased glucose levels was 27.39% and 16.66% respectively. All these values were statistically non-significant. The overall observed percentage of the patients showing the trend of increased glucose values in patients suffering from different types of seizures (ranging from 16% to 27%) may be due to effect of AEDs on the liver by increasing glycogenolysis.

Moreover, the review of patients' records showed that some of the patients suffered from infectious diseases or diabetes (hypoglycemic or hyperglycemic states of the patients), which might also be the cause for such abnormalities (Shah 2000).

The levels of liver enzyme Aspartate Amino Transferase AST (SGOT) were found significantly elevated in Groups 3 and 4 as compared with the normal control. Alanine Amino Transferase ALT (SGPT) levels were significantly raised in Groups 1, 2 and 3. These changes may be attributed to the adverse effects of anti-epileptic drugs, being used by patients in these groups.

Our results are supported by earlier studies like Anderson (1998) who described that anti-epileptic drugs have a wide range of drug interactions, including hepatic enzyme induction and inhibition and protein-binding displacement properties. Several researchers showed a serious concern about the elevated AST and ALT levels during Valproic Acid (VPA) treatment (Gram et al. 1985). A dose-dependent elevation of liver enzymes was observed in 44% of the patients receiving VPA in their study.

Carbamazepine (CBZ) therapy is known to cause hepatitis (Snead et al. 1985). In some instances the administration of Phenobabitone was found to induce an elevation of Transaminase activity. This elevation is a consequence of enzyme induction (Aiges et al. 1980). In another study, Cepelak et al. (1998) observed that mean catalytic activity of AST was significantly elevated in epileptic children on VPA, CBZ, and VPA+CBZ therapy. However, ALT activity with maximal increase was observed in CBZ group.

In the present study, the levels of Alkaline Phosphatase (ALP) showed a significant increase in all the study groups. The increase of ALP serum levels was highly significant specifically in Groups 1 and 2. Similar results were obtained earlier by Crosley et al. (1975) and Doppelbauer et al. (1991), according to whom the observed effect on ALP levels may be attributed to the adverse effects of anti-epileptic drugs. Children on Phenobarbitone, Dialentine (Phenytoin) and Carbamazepine were reported to have raised levels of ALP.

However, the levels of Total Bilirubin (TBIL) and Direct Bilirubin (DBIL) did not show any statistically significant change in any of the study groups. The observed normal values for these parameters are in accordance with the earlier reports (Tasaki et al. 1995).

CONCLUSIONS

Based on the present study, it is concluded that these AEDs are known enzyme inducers, which might be reflected by elevated hepatic enzymes. Therefore, hepatic enzyme levels are affected by AED therapy (VPA, CBZ, and PHB) but not by convulsive disorder itself. Poly-drug therapy also shows statistically significant elevations in AST and in ALP serum levels. Long-term anticonvulsant therapy may induce alterations in both metabolism and distribution of the hepatic enzyme levels. Therefore, liver functions should be monitored regularly at 3-4 months intervals to detect bone changes (osteopenia) and rickets in children.

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