Anti-Epileptic Drugs (AEDs) and Anemia:

A Prospective Study in Epileptic Children

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ABSTRACT

This study was performed to evaluate the influence of anti-convulsants on hematological routine values such as: white blood cells (WBC), hemoglobin (Hb), red blood cells (RBC), platelets (PLT), hematocrit ratio (HCT), poly-neutrophils (NE), lymphocytes (LY), monocytes (MO), and eosinophils (EO) in epileptic children. A total of 225 patients (male = 154, female = 71) age-ranged from 4 months to 14 years were studied. A group of 22 healthy volunteer children was taken as Normal Control (male = 12, female = 10). All the patients were receiving anti-epileptics. Depending upon the mono- or poly-drug therapy, the subjects were divided into four study groups: 1) Carbamazepine (CBZ); 2) Phenobarbitone (PHB); 3) Valproic Acid (VPA); and 4) Poly-drug Therapy (PDT). Reduction in Hb, RBC, and HCT, was found to be highly significant ($P<0.0001$), indicating Anemia, in all the study groups as compared to control. Similarly the decrease in poly-neutrophil and eosinophil levels was significant ($P<0.0001$) in all the study groups. The increase of monocytes ($P<0.0001$, $P<0.05$) in study Groups 3 and 4 was found statistically significant as compared to control. However, white blood cells and platelets did not show a statistically significant change as compared to control.

We concluded that the reduction in the levels of blood Hb, RBC, HCT, and changes in NE, EO, LY, MO, in the patients are adversely affected, due to different type of AEDs, indicating anemia, in epileptic children.

(Key words: seizures, hematological parameters, white blood cells, hemoglobin, red blood cells, platelets, hematocrit ratio, poly neutrophils, lymphocytes, monocytes, and eosinophils.).

INTRODUCTION

Hematological parameters play several critically important roles in many biochemical processes such as enzyme biosynthesis in circulating blood cells, production of hemoglobin, activities of anti-oxidant enzymes like super oxide dismutase (SOD), platelet activation, liver synthetic function, bleeding, and clotting times.

Any biochemical abnormality and/or alteration in hematological levels accompanying seizures is important for seizure control. That is why different researchers have been working 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 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. Similarly, side effects of AEDs have been reported, especially on blood levels, which play a vital role in the maintenance of normal biochemical functions (Dreir et al. 1998; Pellock 1999; Dost et al. 2000). Although scientific work on these issues has resulted in a better understanding of the disease and its treatment, in earlier studies the hematological changes during anticonvulsant medication were found to be related to changes in folate metabolism and vitamin B12, coagulation disturbances with both impaired and exaggerated clotting, and pure red cell aplasia (Goggin et al. 1987; Isojarvi et al. 1997; Zellar et al. 1999).

Based on a review of the current literature, it was concluded that a comprehensive work, with particular reference to blood levels, was still required to be done on epilepsy in Saudi Arabia. Keeping in view the need to understand these aspects of epilepsy cases in Saudi Arabia, the present study was designed to estimate the hematological levels 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 blood levels of epileptic children. The hematological levels such as white blood cells (WBC), hemoglobin (Hb), red blood cells (RBC), platelets (PLT), hematocrit ratio (HCT), and poly-neutrophils (NE), lymphocytes (LY), monocytes (MO), and eosinophils (EO), were observed. Some blood parameters showed significant changes when compared with the normal control. These alterations in blood parameters may be due to the adverse effects of AEDs being used by the epileptic patients.

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 hematological routine values was undertaken. All subjects were registered patients and admitted to Riyadh Medical Complex (RMC), Riyadh (Saudi Arabia). The Normal Control consisted of data from 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 clinical diagnoses in view, patients were divided into different groups. The study was comprised of following four groups: 1) Carbamazepine CBZ, (n = 87); 2) Phenobarbitone, PHB, (n = 33); 3) Valproic Acid, VPA (n = 86); and 4) Poly-drug Therapy, PDT (n = 19).

The hematological parameters: white blood cells (WBC), hemoglobin (Hb), red blood cells (RBC), platelets (PLT), hematocrit ratio (HCT), poly-neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), were measured in each of the study groups. Complete blood count (CBC) was done on a hematology auto analyzer (Coulter® T540 T- Series) (Shah 2000). The data was analyzed by using a standard spreadsheet program, and was compared

with control data by using student *t*-test. The minimum level of significance was proposed to be $P < 0.05$.

RESULTS

The changes of hematological parameters of epileptic patients as compared to the control in different groups are shown in Table 1.

Table.1 Changes of Hematological Parameters of Epileptic Patients as Compared to the Control (Mean ± SE).

Parameters	Control group (N = 22)	Group 1 (N = 87)	Group 2 (N = 33)	Group 3 (N = 86)	Group 4 (N = 19)
WBC	8.05 ± 0.199	7.27 ± 0.21	7.54 ± 0.32	7.70 ± 0.26	7.62 ± 0.44
Hb	12.95 ± 0.07	11.85 ± 0.12***↓	11.33 ± 0.25***↓	11.77 ± 0.11***↓	12.22 ± 0.22**↓
RBC	4.86 ± 0.02	4.45 ± 0.03***↓	4.37 ± 0.06***↓	4.34 ± 0.04***↓	4.39 ± 0.08***↓
PLT	289.81 ± 7.29	274.68 ± 6.96	286.69 ± 13.18	274.88 ± 10.71	291.36 ± 23.93
HCT	39.72 ± 0.22	36.44 ± 0.34***↓	37.00 ± 0.58***↓	35.94 ± 0.30***↓	36.31 ± 0.37***↓
NE	56.90 ± 0.70	45.22 ± 1.24***↓	43.51 ± 1.90***↓	40.78 ± 1.63***↓	43.8 ± 3.06***↓
LY	34.40 ± 0.49	43.63 ± 1.09***	49.09 ± 2.22***	45.49 ± 1.46***	42.95 ± 2.71**
MO	3.81 ± 0.23	5.02 ± 0.33	4.09 ± 0.53	6.74 ± 0.41***	5.92 ± 0.68*
EO	5.30 ± 0.10	3.18 ± 0.24***↓	2.49 ± 0.35***↓	3.69 ± 0.29***↓	3.38 ± 0.50**↓

Group 1= CBZ, Group 2 = PHB, Group 3 = VPA, Group 4 = PDT.

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

SE = Standard Error; = Increased level;↓ = Decreased level;

WBC=White blood cell; Hb=Hemoglobin; RBC=Red blood cells; PLT=Platelets; HCT=Hematocrit ratio; NE=Poly neutrophils; LY=Lymphocytes; MO=Monocytes; EO=Eosinophils.

CHANGES IN HEMATOLOGICAL PARAMETERS

It was observed that the mean values of Hb, RBC, HCT, NE, and EO of the patients in different groups were significantly lower ($P<0.0001$) as compared to the control. However, the LY levels were found significantly raised ($P<0.0001$) in all groups while MO levels were found higher in Group 3 ($P<0.0001$) and Group 4 ($P<0.001$) respectively as compared to the control. There were no appreciable changes in WBC and PLT levels.

DISCUSSION

A significant decrease of Hb, RBC, and HCT was found in all study groups as compared to the control. The same results were observed in an earlier study in which the long-term administration of valproate was found to induce hematologic, hepatic, and endocrine abnormalities, causing the reduced number of red blood cells (Szuperan et al. 2000). In another study, the immune mechanism of VPA was found to induce pure red cell aplasia. The drug-induced PRCA (pure red cell aplasia) is caused by toxic or allergic agents, but this case suggests the immune mechanism of VPA-induced PRCA (Anzai et al. 1994). Red cell aplasia was observed during CBZ mono-therapy as well, and by discontinuation of CBZ, the hemoglobin level of patients raised to normal levels within one week (Tagawa et al. 1997).

In an earlier study the mean RBC count was found decreased after two months of CBZ-therapy, and remained at this lower level during 5-years of medication (Isojarvi et al.1997). In hemolysates of patients treated with PHB, the Hb-ASSG (glutathione adduct of hemoglobin) represented 2.4% of the total Hb, while it was totally absent in those treated with VPA (Niketic et al. 1995).

Patients on long-term valproate mono-therapy have also been studied for hematological side effects. Thrombocytopenia and macrocytosis were the most common findings (May et al. 1993; Allarakhia et al. 1996; Zellar et al. 1999). In another set of studies, Crosley et al. (1975), and Ganick et al. (1990), showed hematologic toxicity, including thrombocytopenia, macrocytic red cells with or without anemia, due to VPA-therapy.

The reduced blood cell and platelet counts and elevated MCV, during a study indicates the direct side effect of VPA on a hematopoietic precursor or stem cell in a patient. Goggin T et al. (1987) showed that all anticonvulsant drugs (CBZ, PHY, VPA) interfere with (i.e. reduce) folate metabolism.

The present study also showed a highly significant reduction ($P<0.0001$) in the levels of NE and EO in all the groups as compared to the control. However, the levels of WBC and PLT did not show any significant change. The results of a study performed by Tanindi et al. (1996), were in favor of present findings suggesting that use of VPA does not result in platelet dysfunction within therapeutic limits.

Our findings are supported by the fact that Saudi children in general were found to show low Hb levels (Jamil 2000) indicating anemia during the treatment as compared to the normally accepted range. However, the long-term use of AEDs may be another reason for depletion of hemoglobin (Blackburn et al. 1998). Although neutropenia, agranulocytosis, hemolytic anemia, thrombocytopenia, bicytopenia, pancytopenia, or aplastic anemia is known in patients on AEDs, serious blood dyscrasias are rare in patients taking anti-epileptic agents. Some reports suggested that use of CBZ caused blood count reverse in children (Snead et al. 1985).

The reduction in the levels of Hb, RBC, HCT, NE, and EO was found highly significant in all the study groups as compared to the control. However, the LY levels were found significantly raised in all the groups, while elevation in MO levels was observed in third and fourth groups only. These changes may be attributed to the adverse effects of anti-convulsants being used by the patients. The levels of WBC and PLT did not show any significant change as compared to the control.

CONCLUSIONS

Based on the present study it is concluded that hematological parameters are affected by anti-convulsants (CBZ, PHB, VPA, and PDT), but not by epilepsy. The epileptic patients suffer from anemia, which is due to long-term mono- or poly-drug therapy in our cases. Therefore, it is highly recommended that the children under AEDs-therapy should have a regular monitoring of hematological values such as RBC, Hb, and HCT at 3-6 months interval to avoid serious toxicity of AEDs, leading to anemia. The patients on VPA and CBZ drugs should have blood estimation done every three months to detect the thrombocytopenia and neutropenia respectively.

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