Effect of antiepileptic drugs on plasma fibrinogen level

El-AshryR, El-AyuotyM M, Azzam HA,El- Naggar MA

Department of pediatrics and clinical pathology
Faculty of medicine,
Mansoura University,
Egypt

Corresponding author:

Rasha Abd El Malk El-Ashry
Professor of Pediatrics (Pediatric Hematology and Oncology)
Faculty of Medicine – Mansoura University, Egypt.
Tel.0201001559244
E-mail:Rasha_elashery@yahoo.com

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ABSTRACT

Background: Childhood epilepsy is one of the most common neurological disorders in pediatrics. The prevalence of active epilepsy is 5–8 per 1000 population in developed countries and 10 per 1000 population in developing nations. There is a significant relationship between epilepsy and cognitive deficits.

Aim of study: prospective study to evaluate the effect of the most commonly used anti-epileptics drugs on plasma fibrinogen level.

Patient and methods 100 newly diagnosed patients (2months to 15 years old) selected from Outpatient Clinic of Neurology attending Mansoura University Children's Hospital for plasma fibrinogen level evaluation by taking basal sample and second sample after six months after the basal one.

Results: This study showed that, significant positive correlation between plasma fibrinogen level and the use of antiepileptic drugs.

Conclusion: epileptic patient should be closely monitored during Antiepileptic drugs treatment and prior to surgical procedures as they can affect plasma fibrinogen level and coagulation profile.

INTRODUCTION

Epilepsy is a common illness worldwide. It is estimated that 0.5-1% of all children have epilepsy, with the majority presenting during infancy or early childhood (1).

Epileptic seizures result from abnormal, excessive or hypersynchronous neuronal activity in the brain. About 50 million people worldwide have epilepsy, and nearly 80% of epilepsy occurs in developing countries(2).

Antiepileptic drugs (AED) have been associated with adverse effects on the coagulation system. Carbamazepine, phenytoin and valproic acid can cause thrombocytopenia, Additionally, valproic acid and gabapentin have been associated with acquired von Willebrand disease type 1, hypofibrinogenemia, decreased factor XIII and abnormal platelet function. (3).

Coagulopathies were reported in children treated with VPA (>4%), but this is likely to be significantly underestimated. These children were reported with platelet dysfunction, thrombocytopenia, hypofibrinogenemia, acquired Von Willebrand disease, Factor XIII deficiency and vitamin K-dependent factor deficiency (4).

Little is known about the hematological side effects of the newer antiepileptic drugs (AEDs), but recent case reports have raised concerns regarding the possibility of altered coagulation profile, thrombocyte counts or function in some patients during levetiracetam (LEV) treatment. (5)

Carbamazepines have been reported to be associated with clotting defects including: elevated prothrombin time, elevated partial thromboplastin time, though the exact mechanism is not known yet (6).

PATIENT AND METHODS

In this Observational Prospective Study, One hundred newly diagnosed patients will be included. They will be selected from the patients attended to Mansoura University Children Hospital at Outpatient Clinic of Neurology.

This study was conducted on One hundred newly diagnosed patients with age ranging from 2 months to 15 years. In This study, we search for plasma fibrinogen level and coagulation profile. We do a basal sample then another follow up sample after six months of starting treatment with antiepileptic therapy.

Inclusion criteria:

1. Newly diagnosed Epileptic children by criteria of epilepsy ,
At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.

One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.

2. All patients to be in good health, free of a history of bleeding or thrombosis.

3. Patients will receive antiepileptic drugs.

Exclusion criteria:

- Hematological problems affecting fibrinogen [disseminated intravascular coagulation, hemolytic uremic syndrome].
- Patients known to have renal or hepatic diseases.
- Patients receiving other drugs that affect coagulation profile (salicylate or anticoagulants).

RESULTS

Table(1) pattern of the drug usage among the studied group

Drug	Frequency (N)	Percentage (%)
Na valproate	69	69 %
Na valproate and Topiramate	7	7 %
Carbamazepine	13	13 %
Levetiracetam	11	11 %

Table (1) shows pattern of drug usage among the studied group. The commonest drug in the study is sodium valproate (Depakin), (total number is 76 with percentage 76%), then Carbamazepine (total number 13 with percentage 13 %) then levetiracetam (total number 11 with percentage 11%).

Table (2) plasma fibrinogen of the studied group according to drugs used.

Drugs	Basal fibrinogen level		6 months fibrinogen level		Test of significance
	Mean	SD	Mean	SD	
Sodium valproate	308	59.92	163.78	70.42	T=12.24 P=0.001*
Na valproate plus Topamax	324.43	97	97	76.62	T=4.06 P<0.007*
Carbamazepine	310.38	61.317	272.46	37.15	T=1.67 P=0.119
Levetiracetam	263.8	61.43	232	75.22	T=1.69 P=0.106

Table (2) shows plasma fibrinogen in studied groups according to drugs used, there was statistical decrease in plasma fibrinogen level after 6 months of treatment when compared to initial plasma fibrinogen in groups treated with sodium valproate and groups treated with sodium valproate plus Topiramate.

Figure (1) plasma fibrinogen of the studied group according to drugs used.

(Figure 2): Changes in the Plasma fibrinogen level in the drug-treated groups upon the administration of the drugs for a total period of 6 months

Figure(2) prevalence of bleeding according to drug used

Figure (2) shows prevalence of bleeding according to the drug used.

Bleeding on antiepileptic therapy is statistically significant on patients receiving (sodium valproate) and patients using sodium valproate plus Topiramate.

Table(3) fibrinogen according to gender

	<u>Male</u> <u>N=56</u>	<u>Female</u> <u>N=44</u>	<u>Test</u> <u>of</u> <u>significance</u>
Initial fibrinogen	293 ± 67.19	310.16 ± 52.61	T=1.34 P=0.181
6 months fibrinogen	183.16 ± 80.11	191.84 ± 86.6	T =0.51 P=0.60

Table (3) shows relation of plasma fibrinogen level to gender before and 6 months after treatment with antiepileptic drugs, there was no statistical significance between males and females regarding initial and 6 months fibrinogen level.

Table(4) fibrinogen relation to bleeding

	<u>Bleeding +ve</u> <u>N=4</u>	<u>Bleeding -ve</u> <u>N=96</u>	<u>Test</u> <u>of</u> <u>significance</u>
Initial fibrinogen	360 ± 1.1.54	298.38 ± 58.78	t=1.21 p=0.311
6 months fibrinogen	76.75 ± 56.8	191 ± 80.59	T=3.88 P=0.006

Table (4) shows relation between bleeding and plasma fibrinogen level. There was statistical significant decrease in level of plasma fibrinogen in patients developed bleeding compared to other patients without bleeding.

Figure (3) correlation between fibrinogen at 6 months and liver function at 6 months.

Figure (3) shows correlation between fibrinogen at 6 months and liver function .There is negative correlation between SGPT at 6 months and serum fibrinogen at 6 months.

DISCUSSION

Epilepsy is practically defined by The International League Against Epilepsy (ILAE) as two unprovoked (or reflex) seizures occurring within more than 24 h apart or one unprovoked (or reflex) seizure with probability of further seizures similar to general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years(7).

Antiepileptic drugs (AED) have been associated with adverse effects on the coagulation system. Carbamazepine, phenytoin and valproic acid can cause thrombocytopenia , Additionally, valproic acid and gabapentin have been associated with acquired von Willebrand disease type 1, hypofibrinogenemia ,decreased factorXIII and abnormal platelet function. (8).

Valproic acid (VPA) is a branched short-chain fatty acid derived from naturally occurring valproic acid. It can be administered as either monotherapy or as part of polytherapy regimens comprising several AEDs (9).

Coagulopathies were reported in children treated with VPA (>4%) , but this is likely to be significantly underestimated. These children were reported with platelet dysfunction, thrombocytopenia, hypofibrinogenemia , acquired Von Wilbrand disease, Factor XIII deficiency and vitamin K-dependent factor deficiency(10).

Carbamazepines have been reported to be associated with clotting defects including: elevated prothrombin time, elevated partial thromboplastin time, though the exact mechanism is not known yet (11).

Levetiracetam is a novel antiepileptic drug (AED) that is widely used as adjunctive therapy of partial-onset seizures, ecchymosis have been reported in patients when levetiracetam was added to long-term carbamazepine therapy (12).

Our study is observational prospective Study which was done on 100 newly diagnosed patients. They were selected from the patients attended to Mansoura University Children Hospital at Outpatient Clinic of Neurology complaining from epilepsy. This study was conducted on patients with age ranging from 3 months to 15 years with mean age (5.35 $\pm$ 3.99 year).

The drugs in the study are Na valproate (total number is 67 with percentage 67%), then carbamazepine (total number is 13 with percentage 13%), Levetiracetam (total number is 11 with percentage 11%) and then Na valproate plus topiramate (total number is 7 with percentage 7%).

In This study, we searched for plasma fibrinogen level and coagulation profile. Basal sample then the second sample was obtained after six months from basal one.

In our study, bleeding and fibrinogen consumption were not affected by changes in demographic data regarding age and gender of the studied group with insignificant P-value.

Only four patients among our studied group developed bleeding during the period of the study and they represent 4 % of the whole patients involved in study whereas patients with no bleeding were 96 patients representing 96% of all patients with no statistical difference. According to figure number(2) bleeding had occurred in 2 out of 67 patients who received Na valproate and another 2 out of 7 patients received Na valproate plus topirimate with significant statistical difference; However the other two groups did not develop bleeding during our study. These results was concordant with a study done by (13) which was done on 24 patients and showed insignificant bleeding among the patients included in this study. On the other hand, combination between depakin and topirimate increase risk of side effects specially bleeding side effect, in our study there are 2 out of 7 cases receiving this regimen developed bleeding with significant statistical difference this is agreed with a study by (14).

According to data published by (15) there was evidence that VPA can induce hypofibrinogenemia, it was a meta-analysis in which data collected from several studies and revealed this result with significant P value (0.0001). This result is agreed with our study which showed significant decrease in fibrinogen level in patient treated with VPA alone as well as VPA and Topiramate, another study done by (16) on 385 VPA treated patients and has the same results. Gu" Isen and his colleagues had done another study on 24 newly diagnosed epileptic patients and showed that there was a significant decrease in the serum concentration of serum fibrinogen at the first and fourth month of the therapy ($P < 0.05$).

Regarding other patients groups that was maintained on carbamazepine, there was no effect on fibrinogen level which is against a data published by (17) this disagreement may be related to limited number of cases in this study in comparison to our study, in the same time racial differences between the 2 studied groups may play a role in this disconcorodence in the results.

Levetiracetam showed no significant effect in fibrinogen level and this agreed with a study by (18).

The mechanism of fibrinogen consumption with usage of antiepileptic drugs is unknown but according our study there was correlation elevation of liver function and decline of plasma fibrinogen level according to figure number (3).

CONCLUSIONS

- Epilepsy is considered between the most serious and well-known neurological disorders in children.

- Antiepileptic drugs have hematological side effects as they can plasma fibrinogen level and coagulation profile.
- Continuous monitoring clinically and laboratory is needed with special concern prior to surgical operations and in cases of bleeding tendency.

Recommendations

Careful selection for AED as Side effects from AEDs are common, frequently contributing to treatment failure and reduced quality of life, and are therefore deciding which AED has the optimum profile is not always straightforward.

At this time, we cannot recommend controlling all hemostatic parameters in every patient treated with antiepileptic drugs. Whenever an increased bleeding tendency is observed, or before surgical procedures, platelet count, PT, aPTT, and fibrinogen, should be examined. If laboratory findings are pathologic, further examinations must be done.

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