Influence of anti-epileptic drugs on hematological and biochemical parameters in patients with epilepsy

S. Dwajani1*, G. Ranjana1, G. R. K. Sarma2, Chanda Kulkarni3, B. Ganapathi4

INTRODUCTION

Antiepileptic drugs (AEDs) are the cornerstone of epilepsy treatment. The main treatment goal is freedom from seizures, without side effects and a better quality of life.1 Epileptic seizures can be treated effectively in approximately 60% of patients who become seizure free with first or second AED.2 Although monotherapy is usually recommended,
polytherapy is required for patients with refractory seizures. AEDs have been reported to cause adverse effects on hematological and biochemical parameters.

The conventional AEDs are commonly used as first line drugs and are associated with wide range of side effects. Though newer AED monotherapy is reported to have lesser side effects, AED polytherapy may produce adverse effects due to interactions as a result of variable kinetic profile. Patients with epilepsy (PWE) may manifest metabolic adverse effects during the course of treatment with AEDs. Such effects may be subtle, insidious, take many years to become clinically apparent to have negative impact on general health.

Routine monitoring of hematological and biochemical investigations are currently not recommended in clinical practice in PWE. The present study was carried out to examine the influence of AEDs on hematological and biochemical parameters and to compare the same between AED monotherapy and polytherapy in PWE at a select tertiary care hospital.

METHODS

This was a cross-sectional, observational study conducted in accordance with International Conference on Harmonization-Good Clinical Practice Guidelines, following the approval from Institutional Ethics Review Board, St. John’s Medical College and Hospital, Bangalore. Informed and written consent was taken from all the study participants prior to enrolment. Patients reporting at Neurology outpatient department with confirmed diagnosis of epilepsy receiving AEDs were considered for the study. PWE ≥18 years of age, of both gender, receiving AEDs either as monotherapy or polytherapy for at least 1 month were included. Pregnant and lactating women, comorbidities were excluded from the study. Data were collected in a specially designed case record form.

Data on 255 patients were collected on baseline demographic characteristics such as age, sex, history of smoking/alcohol, family history of epilepsy. Disease and treatment data like type of seizures, duration of disease, AED treatment and adverse drug reactions (ADRs) was also collected. Hematological investigations, including hemoglobin (Hb), white blood count (WBC), platelet count; biochemical investigations for calcium (Ca²⁺), phosphorous (PO⁴⁺) and alkaline phosphatase (ALP) levels were done at the point of contact with patient. The values were compared with the normal lab values.

Data were computed and statistical analysis was done using SPSS version 18. Descriptive statistics like mean, frequencies and mean were used to summarize the data and inferential tests like Chi-square test was used to compare categorical variables between groups with two sided p<0.05 considered as statistically significant.

RESULTS

A total of 255 PWE were enrolled between the age range of 18-65 years (mean±standard deviation [SD]; 28.68±9.29) with 144 (56.54%) males and 111 (43.52%) females during the study period of 2 years from June 2011 to June 2013. Total of 13/255 (5.09%) PWE gave a history of smoking, while 34/255 (13.33%) had family history of epilepsy.

The type of seizures were predominantly focal in 199 (78.04%), generalized in 46 (18.04%) and the remaining 10 (3.92%) were unclassified. The pattern of ADR use showed 113 (44.32%) on monotherapy, 142 (55.69%) on polytherapy with two or more AEDs (Table 1). With regards to ADR profile a total of 46 PWE (18%) showed adverse effects related to bone, central nervous system (CNS) and others (Table 2).

The data on reports of hematological and biochemical parameters were carried out once at the time of enrolment. 23.93% (61/255) of PWE had decrease in Hb levels (g/dl) with mean (±SD) of 10.19 (±1.55). Significant reduction in Hb levels was found in females when compared with males (p=0.000) and patients receiving AED polytherapy when compared to monotherapy (p=0.006) (Table 3). The risk of developing anemia was more likely in female patients and who received AED polytherapy.

About 9.41% (24/255) of PWE had decrease in WBC levels while 3.92% (10/255) of PWE had decrease in platelet count, with the mean (±SD) of 2570 U/L (±20349.44) respectively. There was no statistically significant difference between the genders and between AED monotherapy and polytherapy groups (Table 3) in patients who had decrease in WBC and Platelet levels.

The calcium levels were decreased in 4.70% (12/255) of PWE with mean (±SD) of 7.38 mg/dl (±0.67), while there was 3.13% (8/255) decrease in phosphorous levels with the mean (±SD) value of 1.76 mg/dl (±0.70). There was no statistically significant difference between the genders and between AED monotherapy and polytherapy groups (Table 3) in patients who had decrease in calcium and phosphorous levels.

**Table 1: Pattern of AED use in PWE (N=255)**

<table>
<thead>
<tr>
<th>Type of AED</th>
<th>Number of PWE</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>113</td>
<td>44.32</td>
</tr>
<tr>
<td>Conventional+newer AEDs</td>
<td>81</td>
<td>31.76</td>
</tr>
<tr>
<td>Newer AED combination</td>
<td>36</td>
<td>14.12</td>
</tr>
<tr>
<td>Conventional AED combination</td>
<td>25</td>
<td>9.80</td>
</tr>
</tbody>
</table>

AED: Antiepileptic drug, PWE: Patients with epilepsy
The ALP levels were increased in 20.00% (51/255) of PWE with mean (±SD) value of 212 U/L (±61.90). A significant difference was observed between monotherapy and polytherapy (p=0.003) (Table 3) but not with the genders. Comparison for hematological and biochemical parameters was done between patients receiving monotherapy and polytherapy for age and duration, which did not show statistically significant difference.

**DISCUSSION**

AED use among PWE to achieve maximal seizure control with least ADRs is challenging. An optimal seizure control with one AED is often possible in 70% of PWE provided the choice of AED is appropriate. Around 20-30% of epilepsies require dual or triple AED combinations. However, such polytherapy may require close monitoring for ADRs.

From the results obtained in the present study, it was observed that majority of PWE were in younger age group with preponderance among men and the findings are similar to study conducted by Radhakrishnan et al. The treatment pattern with AEDs involved the practice of polytherapy, a trend similar to a study conducted by Tolou-Ghamari et al. The occurrence of partial seizures was seen more frequently than generalized seizures.

The hematological and biochemical findings of our study revealed decrease in levels of Hb, WBC, platelets, calcium, and phosphorous with increase in the ALP levels in PWE. There was a significant reduction in Hb levels, which was observed in female patients and in those patients receiving AED polytherapy. Folate is important and necessary for rapid division of cells and tissues like bone marrow. Anti folic acid activity of antiepileptics, which may be responsible for bone marrow depression resulting in blood dyscrasias like aplastic anemia, leukocytopenia and thrombocytopenia. Though folic acid is not a biologically active substance, its importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in liver by reductase enzyme. This reductase enzyme is said to be inhibited by AEDs which leads to anemia, leukocytopenia and thrombocytopenia. Published literature suggests that changes in hematological parameters such as Hb over 12 months is inversely associated with a subsequent risk of morbidity and mortality, independent of the effects of baseline anemia and other important predictors.

A statistically significant difference was also noticed in ALP levels between monotherapy and polytherapy, where polytherapy had greater influence on ALP levels, a finding similar to the study by Tolou-Ghamari et al. ALP is considered to be the marker for hepatocellular activity. However, an increase in the ALP levels may be due to increase in the osteoblastic activity.

In summary, alterations in hematological and biochemical parameters were observed in a large proportion of patients receiving AED polytherapy. The extent of polytherapy use was seen in >55% of patients who received two or more

### Table 2: ADRs with AEDs (n=46).

<table>
<thead>
<tr>
<th>System affected and ADR’s</th>
<th>Number of PWE with ADR</th>
<th>PWE on monotherapy</th>
<th>PWE on polytherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee pain, back pain and joint pain</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>0.266</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diplopia, slurred speech, migraine, paraesthesia</td>
<td>10</td>
<td>04</td>
<td>06</td>
<td>0.866</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain, indigestion, loss of appetite, acne</td>
<td>06</td>
<td>03</td>
<td>03</td>
<td>0.470</td>
</tr>
</tbody>
</table>

*p≤0.05 is considered to be significant. ADRs: Adverse drug reactions, AEDs: Antiepileptic drugs, CNS: Central nervous system, PWE: Patients with epilepsy

### Table 3: Influence of AEDs on hematological and biochemical parameters in PWE.

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameters</th>
<th>Number of PWE on AED</th>
<th>Monotherapy (113)</th>
<th>Polytherapy (142)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Low Hb levels (Male: &lt;13 g/dl, Female: &lt;11.5 g/dl)</td>
<td>26</td>
<td>35</td>
<td>0.006*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low WBC levels (&lt;4000 U/L)</td>
<td>09</td>
<td>15</td>
<td>0.094</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low Platelet levels (&lt;1.5 lakh/U/L)</td>
<td>07</td>
<td>03</td>
<td>0.123</td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td>Low Ca²⁺ levels (&lt;8.5 mg/dl)</td>
<td>04</td>
<td>07</td>
<td>0.324</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low PO₄⁻ levels (&lt;2.5 mg/dl)</td>
<td>04</td>
<td>04</td>
<td>0.535</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High ALP levels (&gt;136 U/L)</td>
<td>20</td>
<td>31</td>
<td>0.003*</td>
<td></td>
</tr>
</tbody>
</table>

*p≤0.05 is considered to be significant. AEDs: Antiepileptic drugs, PWE: Patients with epilepsy, Hb: Hemoglobin, WBC: White blood count, Ca²⁺: Calcium, PO₄⁻: Phosphorous, ALP: Alkaline phosphatase
AEDs. Therefore, AED polytherapy may be anticipated to produce significant change in Hb and ALP parameters leading to side effects.

Other parameters such as WBC, platelet, calcium and phosphorous did not show significant changes. Further investigations are required with respect to these observations in select patient groups, especially PWE using AED polytherapy and in larger population.

CONCLUSIONS

The limitations of this study are lack of follow up, non-uniformity of data, and small sample size. The results of this study showed significant alterations in the levels of Hb and ALP with the use of AED polytherapy in PWE. It is hence prudent to consider routine monitoring of hematological and biochemical parameters during AED treatment in patients receiving AED polytherapy.

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