

Study of effects of antiepileptic therapy on various biochemical and hematological parameters patients suffering of epilepsy

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ABSTRACT

Background: Low therapeutic index of established antiepileptic drugs (AEDs) coupled with better understanding of the pathophysiology of seizure has encouraged the development of several novel AEDs. The conventional antiepileptics like phenytoin, phenobarbitone, valproate and carbamazepine and newer antiepileptics like levetiracetam, lamotrigine and topiramate etc. are used for epilepsy. AEDs induce potentially toxic effects over a period of time which remains undetermined over very long time. Earlier studies in this regard, states uneven results about biochemical (i.e. blood sugar level, lipid profile) and hematological (Hb%, blood cell count etc.) toxicity of AEDs. Aims: To unveil the toxic effects of AEDs when given singly or as combinations.

Methods: Adult epileptics of either sex taking antiepileptic monotherapy or combination therapy for \geq six months were enrolled. Biochemical and hematological parameters studied were compared with their age and sex matched controls, baseline and amongst groups. Statistical Analysis Used: Student's 't'-test & One way ANOVA followed by *posthoc* Tukey HSD test for pair wise comparison; $p < 0.05$ was considered significant.

Results: Conventional antiepileptic combination therapy was found more toxic; $p < 0.01$ for lipid profile. Combination groups showed significant reduction in Hb% ($p < 0.05$) with no significant difference among them ($p > 0.05$). Monotherapy and conventional combination therapy caused significant reduction in platelet count ($p < 0.01$), but conventional combination therapy was found more toxic in this regard ($p < 0.05$).

Conclusions: Monotherapy found less toxic with no significant effects on lipid profile, Hb%, RBC count and O₂ carrying capacity and less impact on platelets while combination therapy did not show any advantage over monotherapy and its use must be reserved only for refractory cases.

Keywords: Antiepileptics, Pharmacovigilance, Monotherapy, Combinations

INTRODUCTION

A seizure or convulsion is a paroxysmal time-limited change in motor activity and/or behavior that results from abnormal electrical activity in the brain. It is one of the most common neurological disorders which know no geographical, racial or social boundaries. The incidence is approximately 0.3 – 0.5% in different world populations with a prevalence rate of five to ten per thousand people.¹ Since 1850, antiepileptic drugs (AEDs) are in use. Majority of patients can be treated with conventional drugs like phenytoin (PHT), phenobarbitone

(PB), valproate (VPA) and carbamazepine (CBZ) & many new drugs like levetiracetam (LEV), lamotrigine (LTG) and topiramate (TPR), tiagabine (TBG) etc. are currently used as add-on or alternative therapy.¹

Patients with epilepsy may manifest metabolic adverse effects through the course of their management with AEDs. Such effects may be subtle, insidious, take many years to become clinically apparent, and may have a negative impact on general health for many decades. Unfortunately, many neurologists are unaware of such AED-related side-effects.² According to previous studies,

conventional drug therapy & also their combination therapy are responsible for increase in total serum cholesterol levels^{3,4} & blood sugar level (BSL).^{5,6} Also antiepileptic drugs are hematotoxic i.e. there is decrease in haemoglobin concentration, RBC & WBC counts after long term antiepileptic therapy.⁷ In contrast to these findings some studies mention that AEDs do not have any effect on the biochemical and hematological parameters of epileptic patients.⁸

Screening for adverse reactions to AEDs is not systematically included in everyday clinical practice; and it is very likely that it remains underestimated. Hence present study was undertaken to unveil the potential toxic effects of antiepileptics with reference to biochemical and hematological parameters. It's an attempt to comparatively explore future avenues for clinical research in the pharmacological management of the epilepsies involving rational use of AEDs, both singly and in combination.

METHODS

The study protocol has been approved by Institutional Ethics Committee (Approval letter no: Ref. SKNMC No/Ethics/App/2011/90; date: 15/12/2011).

Study Design

Adult epileptics of either sex taking antiepileptic monotherapy (PHT/CBZ/PB/VPA) or combination therapy (conventional AEDs and conventional with newer AEDs like LEV, LTG & TPR etc.) for more than six months were enrolled in the study. The patients with diabetes, HTN, IHD, stroke, malignancy, arthritis, renal/hepatic disease and any disease other than epilepsy for which medicine was taken over long time excluded from study. The old (at least 6 months) records of biochemical and hematological parameters of these epileptics were noted as baseline records and compared with the parameters recorded at the time of enrollment. For the patients with no such old records, investigations were carried out on the day of enrolment and these results considered as their baseline records; six months later investigations were repeated and results compared with baseline. The biochemical and hematological parameters studied were also compared with their age and sex matched controls. The study was further extended to comparatively explore the impact of monotherapy and combination therapy on biochemical and hematological parameters in epileptic patients.

Sample collection

5ml of blood sample was collected; out of that 4ml was taken in sterile plain bulbs and 1ml in EDTA bulb. The samples in sterile plain bulbs were sent to central clinical laboratory on the same day for estimation of BSL random (R) and lipid profile and in EDTA bulb for complete blood count (CBC).

Methods

- Height and weight was measured to calculate BMI using online calculator.
- Blood samples were collected from epileptic patients attending medicine OPD and admitted in medicine wards; BSL(R), lipid profile and CBC were checked by routine laboratory methods. O₂ carrying capacity was calculated by following formula,

$$\text{O}_2 \text{ carrying capacity} = \text{Hb \% (g/dl)} \times 1.34^9$$

Statistical analysis

Data obtained was analyzed using Vassar-stats software. Statistical tests used were student's 't'-test and ANOVA followed by *posthoc* Tukey HSD test for pair wise comparison.

RESULTS

Baseline demographic characteristics at the time of screening were found uniform in all groups (Table 1).

Table 1: Baseline demographic characteristics at screening.

Sr. No.	Character	Control	Antiepileptic group
1.	Sex		
	Male	11(36.7)	11(36.7)
	Female	19 (63.3)	19 (63.3)
2.	Age (years)	43.1±1.8	43.1±1.8
3.	Height (cm)	150±3.7	158±7
4.	Weight (Kg)	52.3±2.4	50.6±4
5.	BMI(kg/cm ²)	23.3±3.3	22.4±1

CBZ and PHT were amongst most prescribed AEDs as monotherapy and as combination therapy as well with VPA; while LEV and LTG were found frequently prescribed amongst newer AEDs (Table 2, Figure 1). This study clearly revealed that all of the AEDs are potential toxic drugs; as all have significantly impaired lipid and hematological profile of the epileptics when compared to their controls and baseline records (Table 3 & 4). However the conventional antiepileptic combination therapy was found more toxic in this regard; $p < 0.01$ for total cholesterol, triglycerides and LDL (see figure 2). HDL levels were significantly reduced in both combination therapy groups; $p < 0.01$, but this was significantly more in conventional combination group; $p < 0.05$. BSL nevertheless showed no significant increase in any of the group (Table 3 & Figure 2). Both combination therapy groups showed significant reduction in Hb%; $p < 0.05$ but no significant difference was found between these groups; $p > 0.05$. Monotherapy and conventional antiepileptic combination therapy both caused significant reduction in platelet count; $p < 0.01$ but conventional antiepileptic combination therapy was found more toxic in this regard; $p < 0.05$.

Table 2: Categorization of patients on the basis of antiepileptic therapy given.

Sr. No.	Therapy	Drugs	No of patients %	Duration (yrs)
1	Monotherapy	1. Carbamazepine	50	4-6
		2. Phenytoin	30	2-5
		3. Phenobarbitone	10	06
		4. Valproate	10	02
2	Conventional antiepileptic combination therapy	1. Phenytoin+ Phenobarbitone	10	15
		2. Carbamazepine+ Phenobarbitone	20	5-8
		3. Valproate + Phenytoin	30	5-8
		4. Valproate + Carbamazepine	40	4-10
3	Newer + conventional antiepileptic combination therapy	1. Carbamazepine + clobazam + topiramate	20	02
		2. Carbamazepine + clobazam + levetiracetam	30	2-4
		3. Carbamazepine + phenobarbitone+ levetiracetam	10	1-2
		4. Valproate + lamotrigine	40	3-5

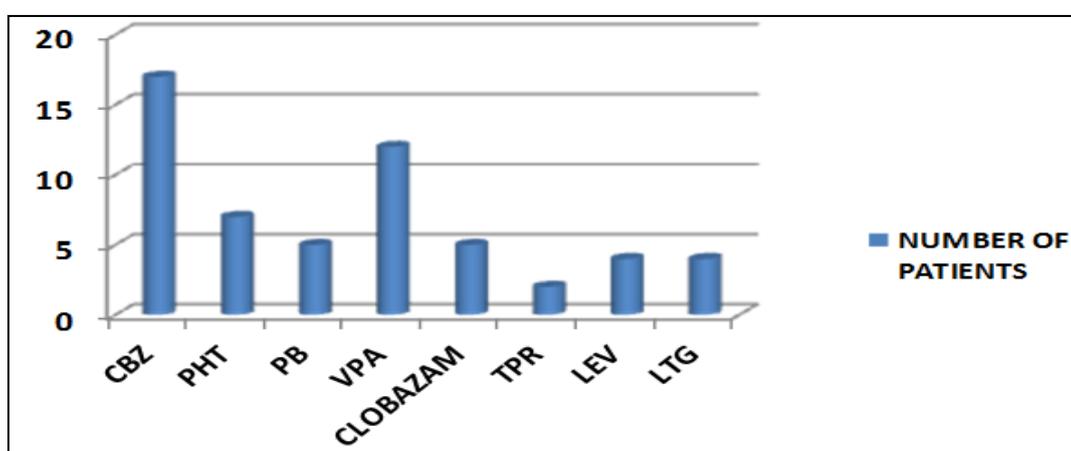


Figure 1: Types and frequencies of AEDs (n=30).

Table 3: Categorization of patients on the basis of antiepileptic therapy given.

Sr. No.	Observations (mg/dl)	Control	Antiepileptic group (baseline)	Antiepileptic group (after ≥ 6 months)
1.	BSL(R)	100.0±1.2	101.2±1.4	104.4±1.3
2.	Total Cholesterol	118.4±10.2	142.5±4.3	†148.4±7*
3.	Sr. Triglycerides	72.4±5.4	76.5±3.7	†††140.3±2.4*
4.	Sr.HDL	49±3	52±2.6	†37.9±4.4**
5.	Sr. LDL	84.9±6.4	90.9±2.9	†109.81±4.4*
6.	Sr. VLDL	14.5±0.5	18.3±1.8	†††28.1±1.1**

n=30, Values are mean±SD; †p<0.05, ††p<0.01 and †††p<0.001 compared to control

*p<0.05, **p<0.01 and ***p<0.001 compared to baseline records

O₂ carrying capacity was found to be reduced in combination therapy groups; p<0.05 for both. Monotherapy found less toxic with no significant effects on lipid profile, Hb%, RBC count and O₂ carrying capacity; p>0.05 and less impact on platelet count

compared to conventional combination therapy; while the WBC count was significantly reduced in monotherapy group; p<0.01 (Figure 3), this toxicity was found to be prominent in PHT and PB treated patients over a period of time.

Table 2: Effects of antiepileptics on hematological parameters.

Sr. No.	Observations	Control group	Antiepileptic group (baseline)	Antiepileptic group (after ≥ 6 months)
1.	Hb % (g/dl)	13.4±0.6	13.8±0.8	†12.5±0.4***
2.	RBC count (x10 ⁶ /mm ³)	8.8±0.5	5.2±0.6	4.6±0.4
3.	WBC count (10 ³ /mm ³)	7.8±0.3	7.9±0.8	†††6±0.1***
4.	Platelets (x 10 ⁵ /mm ³)	2.2±.3	2.8±.2	1.95±.3*
5.	O ₂ carrying capacity (ml/dl)	18±0.8	18.5±0.8	†16.7±0.5*

n=30, Values are mean±SD; †p<0.05, ††p<0.01 and †††p<0.001 compared to control

*p<0.05, **p<0.01 and ***p<0.001 compared to baseline records (Thrombocytopenia was seen in patients treated with VPA, PHE and PB singly or as combination, while leucopenia was prominent in PHT and CBZ treated patients)

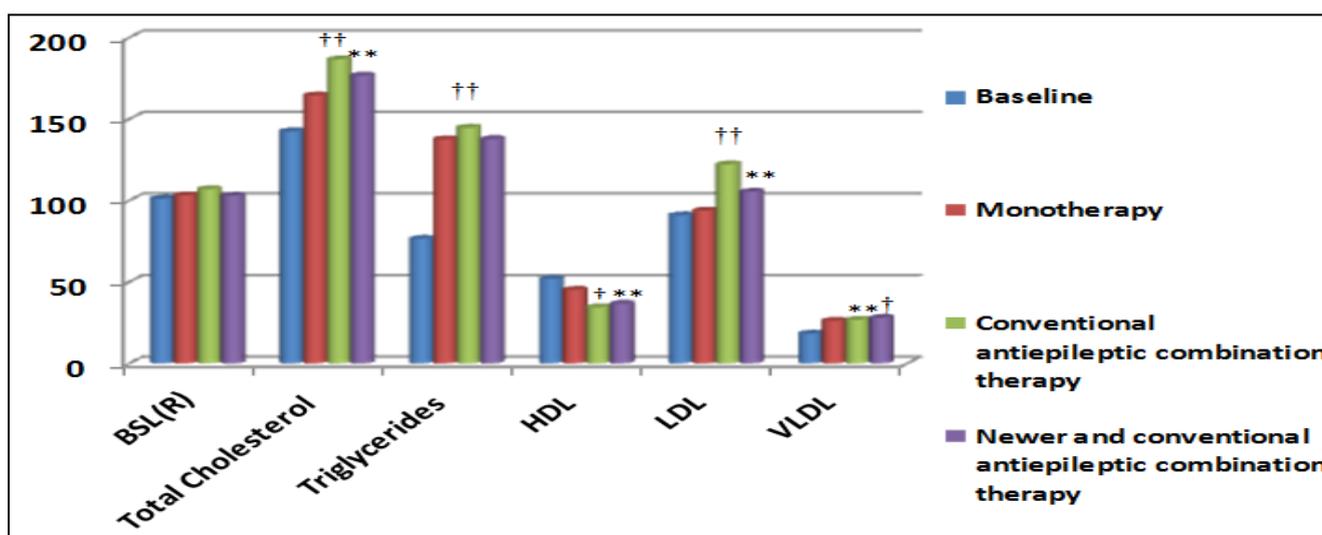


Figure 2: Comparative biochemical toxicity of antiepileptic monotherapy & combination therapy (for ≥6 months).

*p<0.05, **p<0.01, †p<0.05, ††p<0.01; with one way ANOVA followed by posthoc Tukey HSD test for pair wise comparison. (*compared to monotherapy, †comparison between combination therapy)

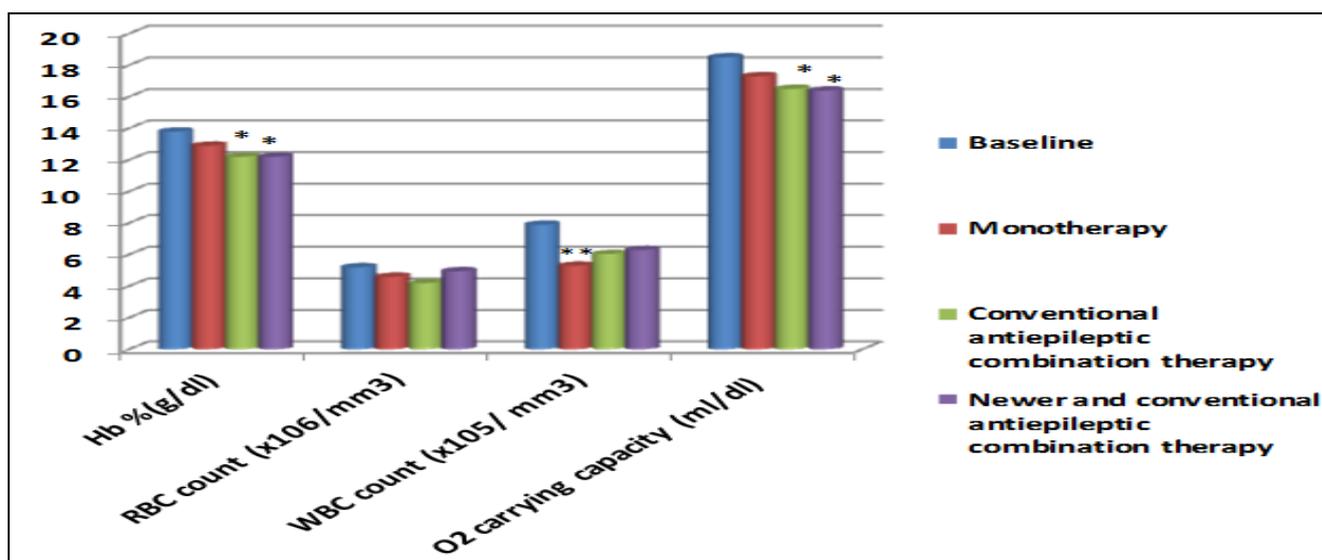


Figure 3A: Comparative hematological toxicity of antiepileptic monotherapy and combination therapy (for ≥6 months).

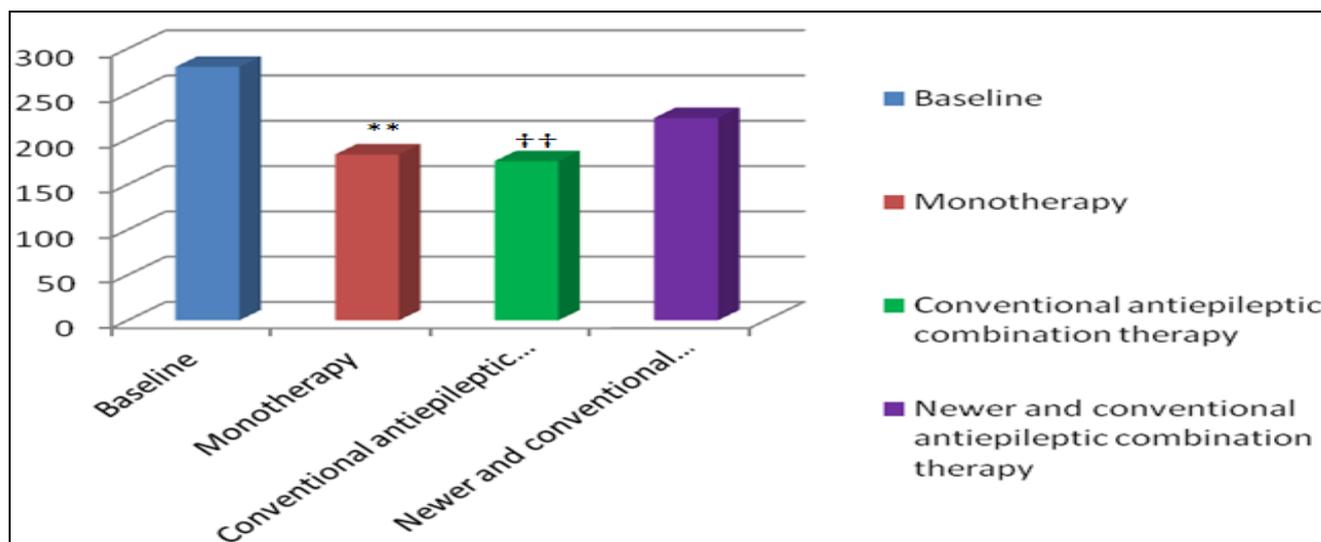


Figure 3B: Platelet count (x10³/mm³).

*p<0.05, **p<0.01, †p<0.05, ††p<0.01; with one way ANOVA followed by posthoc Tukey HSD test for pair wise comparison. (*compared to monotherapy, †comparison between combination therapy)

DISCUSSION

AEDs are associated with panoply of metabolic and haemopoietic abnormalities; results of our study shore up this statement. Although BSL is spared; lipid profile of epileptic patients was significantly affected by AEDs. Majority of the epileptics (83.33%) were treated with PHT, PB and CBZ either as monotherapy (90%) or as combination therapy (100% conventional and 60% with newer with conventional AEDs). PHT, PB and CBZ are potent enzyme inducers and induce cytochrome P450 system.^{10,11} The CYP450 enzyme system is involved in the synthesis and metabolism of cholesterol¹². In particular, CYP51A1 plays a key role in cholesterol synthesis.¹³ Enzyme-inducing AEDs would therefore be expected to increase cholesterol production. And so are the results i.e. all groups showed impairment in lipid profile to variable extent compared to controls and their baseline records. This impairment was significant with conventional antiepileptic combination with two enzyme inducer AEDs compared to monotherapy and newer antiepileptic combination therapy group. PHT is known to induce hyperglycemia by inhibiting insulin release and by insulin insensitivity that results due to post-binding defect induction in insulin action.^{6,14} In our study PHT was given to relatively less number of epileptics (23.3%), this could be the reason for insignificant effects on BSL. Valproate is reported to cause glucose intolerance exclusively in overweight patients, however in our study groups mean weight was found to be 50.6 kg with BMI 22.4 kg/cm² this could be another reason for insignificant effects on BSL though significant number of patient(40%) were on valproate therapy.¹⁵

Folate is important for cells and tissues that rapidly divide e.g. bone marrow.¹⁶ Anti-folic acid activity of antiepileptics like CBZ, oxaCBZ, PHT, PB, LTG and

VPA etc. is responsible for bone marrow depression that results in blood dyscrasias like thrombocytopenia, leucopenia and aplastic anemia.¹⁷ Platelet count was significantly reduced in epileptic treated with CBZ, PHT, PB and VPA (66.6%) as monotherapy or combination therapy compared to newer AEDs combination therapy (33.3%). This toxicity was prominent in VPA, PHE and PB treated epileptics singly or as combination at the same time leucopenia was significant in PHT and CBZ treated monotherapy group patients (26.6%). Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver by dihydrofolate reductase. This reductase is said to be blocked by AEDs.¹⁸ Anti-folate activity can also lead to decreased Hb% and homocysteine accumulation¹⁹ which further affect lipid metabolism.²⁰ Ultimately resulting into biochemical and hematological toxicity, these results are in agreement with earlier studies stating biochemical and hematological toxicity of AEDs²¹⁻²⁵ and in disagreement with the studies stating AEDs have minimal or no effects on hematological and biochemical parameters.^{8,26} In this study it was found that monotherapy has overall less toxic effects on lipid profile, Hb%, RBC count and O₂ carrying capacity compared to combination therapy; although it found less promising than newer AEDs combination therapy pertaining to platelet count and WBC count.

Epileptic patients in 70% are seizure free with one drug based on cautious drug administration and dosage modification. Judgment to treatment of epilepsy is normally based on monotherapy. AEDs combination therapy may contribute to cause side effects in patients.^{27, 28} Hence it is advisable to start the therapy with single antiepileptic and rather combining an additional conventional AED, combine a newer antiepileptic as an add-on therapy for optimal seizure control with minimal adverse effects unlike conventional AEDs combinations.

CONCLUSION

From the results of this study it can be concluded that, all the antiepileptics are potentially toxic drugs. They produce varied adverse effects, but these are the drugs that improve quality of life of epileptics and their judicious use is necessary for effective and safe treatment of epilepsy. It is reported that combination therapy does not have advantage over monotherapy, hence its must be emphasized that monotherapy is a gold standard in antiepileptic therapy and combination therapy should be advocated with caution only if patient is refractory to monotherapy.

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Conflict of interest: None declared

Ethical approval: Approval was taken from the institutional ethics committee

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