Therapeutic Drug Monitoring and Evaluation of Therapeutic Effectiveness and Adverse Effects of Antiepileptic Drugs in Iraqi Epileptic Patients

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Abstract

This study was designed to evaluate the therapeutic effectiveness and adverse effects of carbamazepine, valproic acid, topiramate, and their combination in Iraqi epileptic patients. Ninety epileptic patients were participated in this study, their age ranged from (1-45) years. Seventy patients were previously diagnosed with epilepsy and received antiepileptic drugs for at least six months before this study (retrospective groups). The remaining patients were newly diagnosed with epilepsy (prospective groups). Twenty healthy subjects were selected to be a normal group for the purpose of comparison. The results showed that 90

Index terms— TDM, carbamazepine, valproic acid, topiramate, combination therapy, effectiveness, adverse effects, liver function tests.

1 I. INTRODUCTION

pilepsy is a disorder that is best viewed as a symptom of disturbed electrical activity in the brain, which may be caused by a wide variety of etiologies. It is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence, and management. Seizures that are prolonged or repetitive can be life-threatening. The effect of epilepsy on patients' lives can be significant and extremely frustrating (1) . Of note is that seizures in many patients do not remit despite appropriate medication, and lifelong antiepileptic drugs (AEDs) therapy is usually required for those with refractory epilepsy. This practice poses a medical dilemma because prolonged AEDs therapy is often associated with a wide range of chronic adverse effects, including metabolic and endocrine disturbances, behavioral or psychiatric problems, idiosyncratic reactions, negative cognitive effects, and drug interactions (2) . Since AEDs have a narrow therapeutic index and complex pharmacokinetic properties, wide fluctuations in their plasma concentration can lead to either toxic effects or loss of therapeutic efficacy (3) .

Therapeutic Drug Monitoring (TDM) is a concept of individualization of therapy based on drug concentration data, and application of pharmacokinetic and pharmacodynamic principles. It is not only a process of measuring drug concentration levels in biological fluids, but putting them into service of an optimized individual pharmacotherapy. The aim of TDM is to accomplish the optimal therapeutic drug response with minimal adverse drug effects e.g. better pharmaceutical care of patients **??**4, **??**) .

This study was designed to evaluate the therapeutic effectiveness and adverse effects profile of AEDs carbamazepine, valproic acid, topiramate, and their combination through the assessment of the effect of these drugs on the frequency of seizure attack and on liver function tests in Iraqi epileptic patients. Also the present study was conducted to monitor and compare the serum levels of carbamazepine and valproic acid and to relate these levels to therapeutic effectiveness and adverse effects profile.

Therapeutic Drug Monitoring and Evaluation of Therapeutic Effectiveness and Adverse Effects of Antiepileptic Drugs in Iraqi Epileptic Patients courses of the study successfully. Seventy patients were previously diagnosed with epilepsy and received AEDs for at least six months before this study (retrospective groups) and these

patients had poorly controlled epilepsy. Their age ranged from 1 -45 years (mean ± SEM = 18.85 ± 1.25), of them 32 (45.71%) patients were male and 38 (54.28%) patients were female. The remaining patients were newly diagnosed with epilepsy and did not receive any AED before this study (prospective groups). Their age ranged from 2 -32 years (14.95 ± 2.11), of them 9 (45%) patients were male and 11 (55%) patients were female.

The previously diagnosed patients were recruited into the following retrospective groups: Group 1 : Includes 20 epileptic patients tested at baseline and after three months of treatment with carbamazepine (at dose 431.57 ± 16.75 mg/day) (mean ± SEM).

Group 2 : Includes 20 epileptic patients tested at baseline and after three months of treatment with valproic acid (at dose 492.10 ± 35.01 mg/day). Group 3 : Includes 10 epileptic patients tested at baseline and after three months of treatment with topiramate (at dose 57.50 ± 7.49 mg/day).

Group 4 : Includes 20 epileptic patients tested at baseline and after three months of treatment with combination therapy as following: i.

Sixteen patients receiving carbamazepine and topiramate (at dose 787.5 ± 67.00 mg/day and 73.43 ± 12.80 mg/day respectively). ii.

Two patients receiving carbamazepine and valproic acid (at dose 600.00 ± 199.99 mg/day and 800.0 ± 0.0 mg/day respectively). iii.

Two patients receiving valproic acid and topiramate (at dose 800.00 ± 0.0 mg/day and 50.0 ± 0.0 mg/day respectively).

The newly diagnosed patients were recruited into the following prospective groups: Group 1 : Includes 10 epileptic patients tested at baseline and after three months of treatment with carbamazepine (at dose 400 ± 29.81 mg/day) (mean ± SEM).

Group 2 : Includes 10 epileptic patients tested at baseline and after three months of treatment with valproic acid (at dose 430 ± 29.99 mg/day).

2 b) Healthy Subjects

Twenty subjects who were apparently healthy selected for the purpose of comparison. These subjects were selected from the medical staff and some relative volunteers, of them 9 were male (45%) and 11 were

3 d) Sample Collection And Preparation

Six mil liliters of venous blood sample were drawn from each patient in the morning at 8:30 -9:30 AM after 8-12 hours fasting by vein puncture, before starting drug treatment (as baseline sample) and then after 3 months of treatment. Serum was used for the measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), ?-glutamyl transferase (GGT), and concentration of carbamazepine and valproic acid. One blood sample was drawn from each healthy subject.

4 e) Serum Drug Determination

Concentrations of carbamazepine and valproic acid in this study were determined by using high performance liquid chromatography with ultra violet detector (HPLC-UV). The HPLC system comprised the following: Waters 1500 series HPLC pump (USA), Waters 2487 dual ? absorbance detector (USA), and a computer with Waters Breeze software as data collecting system. i. Determination of serum carbamazepine concentration:

? Chrom atographic condition:

The chromatographic column C18 (4.6 mm × 250 mm, 5 ?m) was used. Mobile phase was water, methanol, and acetonitrile (45:45:10). The system operated at ambient temperature. The flow rate was 1.0 ml.min ?1 . An aliquot of 20 ?l was injected for HPLC analysis. Monitoring was performed at 254nm (6). female (55%). Their ages were ranged from 1 -49 years (19.55 ± 4.50).

5 c) Exclusion Criteria :

-Diabetic patients.

Liver enzymes were measured in serum by colorimetric method using the kit from Randox, (UK) for ALT & AST, Biomérieux, (France) for ALP, and Human, (Germany) for GGT. All the assays were performed on spectrophotometer.

Stock solution of carbamazepine (200?g.ml ?1) was prepared in methanol in a 25ml brown glass flask volumetric and stored at -20 ? C. The carbamazepine working solutions at concentrations of (1.6 ?g.ml ?1 , 3.125 ?g.ml ?1 , 6.25 ?g.ml ?1 , 10.0 ?g.ml ?1 , 12.5 ?g.ml ?1 , 15.0 ?g.ml ?1 , and 25.0 ?g.ml ?1) were prepared by serial dilution of carbamazepine stock solution with methanol ? Sample processing and extraction: An accurately sucked test serum 0.2 ml and the extract (chloroform: ethyl acetate = 50:50) 2 ml was successively set into a centrifuge tube on a vortex mixer for 5 min. After centrifuged at 4000 r.min ?1 for 10 min, the organic layer 1.5 ml was transferred to another 5 ml centrifuge tube, and blow-dried with cold air in water bath at 60 ? C. At last, 200 ?l mobile phase was added into the centrifuge tube and 20 ?l solution was injected for HPLC analysis (6) .

6 ? Standard curve drawing :

Standard solutions (1.6 ?g.ml ?1 , 3.125 ?g.ml ?1 , 6.25 ?g.ml ?1 , 10.0 ?g.ml ?1 , 12.5 ?g.ml ?1 , 15.0 ?g.ml ?1 , 25.0 ?g.ml ?1) 200 ?l were took into a centrifuge tube with plug respectively, and then they were blow-dried with cold air in water bath at 60 ? C. Blank serum 200 ?l was added in the centrifuge tube above respectively, making to the corresponding concentrations of standard serum. Serum was extracted according to the performance of the sample processing and extraction. Take the concentration of standard solution as the abscissa, and take the peak area value of standard substance as the vertical axis (6) . Drug concentration in the patient serum can be calculated by this method. The standard curve of carbamazepine is shown in figure 1.

ii. Determination of serum valproic acid concentration: ? Chromatographic condition The chromatographic column C18 (4.6 mm × 250 mm, 5 ?m) was used. Mobile phase consisting of acetonitrile and 0.05 M potassium dihydrogen ortho phosphate (pH adjusted to 3 with ortho phosphoric acid) (45:55 v/v) was used. The system operated at ambient temperature. The flow rate was 1.2 ml.min ?1 . An aliquot of 50 ?l was injected for HPLC analysis. The eluate was monitored at dual wavelength of UV detector at 210 nm from 0 to 10min (7) .

7 ? Solutions preparation:

Stock solution of valproic acid (1000?g.ml ?1) and diazepam (1000?g.ml ?1) was prepared in methanol and acetonitrile respectively in a 25ml brown glass flask volumetric and stored at -4 ? C. The valproic acid working solutions at concentrations of (20.0 ?g.ml ?1 , 50.0 ?g.ml ?1 , 80.0 ?g.ml ?1 , 120.0 ?g.ml ?1 , and 150.0 ?g.ml ?1) were prepared by serial dilution of valproic acid stock solution with methanol from high to low. They were all stored away from light at 4 ? C (7) .

8 ? Sample processing and extraction:

To 250?l serum sample, acetonitrile solution of diazepam equivalent to 2.5 ?g was added as internal standard and shaken well. Then equivalent amount of (250?l) acetonitrile was added for protein precipitation and mixed on a vortex mixer for 1 minutes and centrifuged at 4000 rpm for 20 min. 50 ?l of the supernatant was injected on to HPLC column (7) .

9 ? Standard curve drawing :

Standard solutions (20.0 ?g.ml ?1 , 50.0 ?g.ml ?1 , 80.0 ?g.ml ?1 , 120.0 ?g.ml ?1 , and 150.0 ?g.ml ?1) 250 ?l were taken into a centrifuge tube with plug respectively, and then they were blow-dried with cold air. Blank serum 250 ?l was added in the centrifuge tube above respectively, making to the corresponding concentrations of standard serum. 250 µl of acetonitrile with 2.5 µg diazepam solution was then set into each centrifuge tube on a vortex mixer for 1 min, operated according to the performance of the sample processing and extraction. Plot the peak height ratio between valproic acid and diazepam vs. concentration of the drug to construct the calibration curve using the results from serum standard and serum blank (7) . Drug concentration in the patient serum can be calculated by this method. The standard curve of valproic acid is shown in figure 2.

10 f) Statistical Analysis

All data were expressed as mean ± standard error means (SEM). Statistical analyses were carried out using paired t-test to compare between mean values of parameters. P value < 0.05 was considered statistically significant. Descriptive analysis was carried out by Microsoft Office Excel 2007 software.

11 III. Results

a) Efficacy Of Treatment With Carbamazepine, Valproic Acid, Topiramate, And Combination Therapy : i. Retrospective groups:

Table (1) shows the frequency of seizure in retrospective groups receiving carbamazepine, valproic acid, topiramate, and combination therapy after three months of treatment.

On the other hand, only (45%) of patients receiving combination therapy were seizure free, whereas the remaining (55%) patients had poor seizure control after treatment.

ii. Prospective groups: Table (2) shows the frequency of seizure in prospective groups receiving carbamazepine and valproic acid after three months of treatment. from high to low. They were all stored away from light at 4 ? C (6) .

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The data show that (90%) of the patients treated with carbamazepine mono-therapy did not have any seizure attack after treatment, whereas, (75%) of patients treated with valproic acid mono-therapy did not suffer from any seizure attack after treatment, and (60%) of the patients treated with the topiramate mono-therapy had an excellent control of their seizures after treatment.

The data in this table show that all the patients treated with valproic acid did not suffer from any seizure b) Therapeutic Drug Monitoring: i. Serum carbamazepine:

Table **??**3) shows serum carbamazepine concentration in prospective and retrospective groups receiving carbamazepine as mono-therapy or in combination therapy after three months of treatment.

The data show that the mean of the values of serum carbamazepine after treatment was within normal therapeutic range (10.75 ± 2.96, 10.24 ± 1.82, and 8.47 ± 0.99 µg/ml in prospective, retrospective, and retrospective with combination therapy respectively). No significant differences were observed among these groups.

Table **??**4) shows serum carbamazepine range in prospective and retrospective groups receiving carbamazepine as mono-therapy or in combination therapy after three months of treatment.

About half of the patients (50%, 65%, and 50% in prospective, retrospective, and retrospective with combination therapy respectively) had steady state serum concentration of carbamazepine within therapeutic range of (4 -12 µg/ml) when the usual daily dose of carbamazepine was given (400.0 ± 29.81 mg/day prospectively alone, 431.57 ± 16.75 mg/day retrospectively alone, or 777.77 ± 60.65 mg/day retrospectively combined with another drug); however, this daily dose was sub-therapeutic (?4 µg/ml) for at least (20%, 15%, and 27.77% in prospective, retrospective, and retrospective with combination therapy respectively). On the other hand, this dose produced excessive serum concentrations (?12 µg/ml) in (30%, 20%, and 22.22% in prospective, retrospective, and retrospective with combination therapy respectively). Figures (3 -5) show the chromatograms of drug-free serum (blank), serum spiked by standard of carbamazepine, and serum spiked by carbamazepine in patient's sample respectively. Retention time was 6.034 minutes for carbamazepine.

ii. Serum valproic acid: Table **??**3) shows serum valproic acid concentration in prospective and retrospective groups receiving valproic acid as mono-therapy or in combination therapy after three months of treatment.

The data show that the mean of the values of serum valproic acid after three months of treatment was within normal therapeutic range (74.47 ± 17.11, 71.01 ± 12.36, and 67.27 ± 8.67 µg/ml in prospective, retrospective, and retrospective with combination therapy respectively). No significant differences were observed among these groups.

Table (5) shows serum valproic acid range in prospective and retrospective groups receiving valproic acid as mono-therapy or in combination therapy after three months of treatment.

About half of the patients (40%, 50%, and 75% in prospective, retrospective, and retrospective with combination therapy respectively) had steady state serum concentration of valproic acid within therapeutic range of (50 -100 µg/ml) when the usual daily dose of valproic acid was given (430.0 ± 29.99 mg/day prospectively alone, 492.10 ± 35.01 mg/day retrospectively alone, or 800.0 ± 0 mg/day retrospectively combined with another drug); however, this daily dose was sub-therapeutic (?50 µg/ml) for at least (30%, 30%, and 25% in prospective, retrospective, and retrospective with combination therapy respectively). On the other hand, this dose produced toxic serum concentrations of valproic acid (?100 µg/ml) in (30% and 20% in prospective and retrospective groups respectively), while no patient developed toxic concentration when valproic acid administered with another AED. Figures (6 -8) show the chromatograms of drug-free serum (blank), serum spiked by standard of valproic acid, and serum spiked by valproic acid in patient's sample respectively. Retention time was 1.344 and 7.093 minutes for valproic acid and internal standard of diazepam respectively.

13 c) Effect Of Treatment With Carbamazepine, Valproic

Acid, Topiramate, And Combination Therapy On Liver Function: i. Serum (ALT) :

Table (6) shows the serum ALT in retrospective groups. The baseline values of ALT in all groups were significantly higher than the healthy subjects' values. These values after three months of treatment were significantly higher than the baseline values and the healthy subjects' values. The percent increase between the baseline values of serum ALT and after three months values were ranged from 19.28% to 28.81%.

Table (7) shows the serum ALT in prospective groups. The values of ALT were significantly increased in patients receiving carbamazepine for three months when compared with their baseline values and also with the healthy subjects' values. While, no significant increase in ALT values after treatment with valproic acid as compared with their values at baseline. However, there were significant increases in values of serum ALT at baseline and after three months values when compared with the values of healthy subjects. The percent change between the baseline values of serum ALT and after three months values was 85.07% for carbamazepine and 17.88% for valproic acid.

ii. Serum (AST):

Table (8) shows the serum AST in retrospective groups. The baseline values of AST in all groups were significantly higher than the healthy subjects' values. These values after three months of treatment were attack after treatment, whereas only two patients exhibited one attack per month after treatment with carbamazepine.

healthy subjects' values. The percent increase between the baseline values of serum AST and after three months values were ranged from 29.72% to 43.91% .

The percent change between the baseline values of serum AST and after three months values was 25.17% for carbamazepine and 42.58% for valproic acid.

iii. Serum (ALP) : Table (10) shows the serum ALP in retrospective groups. The baseline values of ALP in patients treated with valproic acid and in those treated with combination therapy showed significant increases when compared with the values of healthy subjects; whereas, no significant differences in the those values were existed between carbamazepine and topiramate groups of patients when compared with the values of the healthy

subjects. However, these values after three months of treatment in all groups were significantly higher than the healthy subjects and baseline values. The percent increase between the baseline values of serum ALP and after three months values were ranged from 17.68% to 21.23%.

14 iv. Serum (GGT):

Table (12) shows the serum GGT in retrospective groups. The GGT values after three months of treatment with carbamazepine, valproic acid, and combination therapy were significantly higher than their values at baseline level; whereas, no significant increase in GGT values in patients receiving topiramate therapy was observed.

These values after three months of treatment with carbamazepine, topiramate, and combination therapy showed significant increase as compared with the values of the healthy subjects; whereas, no significant increase in GGT values was observed in patients receiving valproic acid therapy.

At baseline, the values of GGT in the group of patients receiving carbamazepine and the group receiving combination therapy showed a significant increase when compared with the healthy subjects' values. On the other hand, no significant increases in the level of GGT in patients receiving valproic acid and in those receiving topiramate therapies were found. The percent increase between the baseline values of serum GGT and after three months values were ranged from 7.82% to 29.71%.

15 d) Adverse Effects Associated With The Treatment With

Carbamazepine, Valproic Acid, Topiramate, And Combination Therapy i. Retrospective Groups ii. Prospective Groups Table (15) shows the adverse effects associated with the treatment in prospective groups after three months of treatment. Different types of adverse effects were observed in both groups and their incidences were varied between these groups. The following adverse effects were reported more frequently in both groups: headache, fatigue, and loss of appetite.

16 IV. Discussion

17 Efficacy Of Treatment

Controlling seizures with minimal adverse effects and maintaining the patient's ability to perform daily activities are the critical measures of treatment efficacy. In this study, the efficacy of the AED therapy was measured in terms of the number of seizures Table (14) shows the adverse effects associated with the treatment in retrospective groups after three months of treatment. Different types of adverse effects were observed in all groups and the incidence of these effects was varied among these groups. The combination therapy had the higher rate of incidence of these effects than the other groups; whereas, topiramate had the lower rate of incidence. The following adverse effects were reported more frequently among the groups: headache, fatigue, loss of appetite, weight gain, and weight loss.

Table (9) shows the serum AST in prospective groups. The values of AST were significantly increased in patients receiving valproic acid for 3 months as compared with the baseline values and with the healthy subjects' values. While, the carbamazepine's group of patients showed a significant increase in values of serum AST when compared with the healthy subjects' values only without significant increase in these values when compared with their baseline values. Both groups showed a significant increase in the value of AST at baseline level when compared with the healthy subjects' values.

Table (11) shows the serum ALP in prospective groups. There were no significant increases in the serum level of ALP in both groups between baseline values and after three months values. However, there were significant increases in these values at baseline and after three months of treatment in both groups when compared with the values of the healthy subjects. The percent change between the baseline values of serum ALP and after three months values was 27.99% for carbamazepine and 24.00% for valproic acid.

Table (13) shows the serum GGT in prospective groups. The values of GGT after three months of treatment with carbamazepine were increased significantly when compared with these values at baseline and with the values of the healthy subjects. While, no significant changes in the values of GGT were observed in valproic acid treated patients when compared with baseline and with the healthy subjects' values. The percent change between the baseline values of serum GGT and after three months values was 56.74% for carbamazepine and 33.14% for valproic acid.

experienced by the patients throughout the follow up period of three months. Seizure counts are the only reasonable and standard way to evaluate efficacy of treatment (8) .

As shown in tables (1), 48 (68.57%) patients in retrospective groups became seizure free, while 22 (31.42%) experienced different rate of seizure attack during that period. In group treated with carbamazepine, 90% of patients were seizure free after three months of therapy, whereas 75% of patients on valproic acid were seizure free. 60% of patients received topiramate became seizure free after treatment. On the other hand, only 45% of patients on combination therapy were seizure free. Thus, in retrospective groups, carbamazepine showed an excellent control of seizures followed by valproic acid and topiramate mono-therapy, whereas the combination therapy was associated with poor control of seizures.

Whereas in table (2), 18 patients (90%) in prospective groups became seizure free and only two (10%) patients experienced a single seizure attack during the study period. In group treated with carbamazepine, 80% of patients were seizure free and only 20% of patients had a single seizure attack per month, whereas all the patients (100%) on valproic acid became seizure free after treatment. Thus, in prospective groups, valproic acid has a slightly better control of seizures than carbamazepine.

In general, mono-therapy is the ideal strategy for seizure control, and approximately 50% to 70% of all patients with newly diagnosed epilepsy can be maintained on one drug (9,10) . After failure of the first mono-therapy, only 14 to 20% of patients with seizures will be successfully controlled with any alternative single drug; however, many less respond if the first drug was ineffective (11) . This later group represents part of the approximately 20% to 30% of people with persistent seizures and chronic epilepsy even with medical treatment. Overall, persistent seizures are more common in patients with frequent seizures, multiple types of seizures, abnormal neurologic findings, a brain lesion, onset in the first year of life, or abnormal EEG findings (12) . Combining AEDs with different mechanisms of action to achieve freedom from seizures may be advantageous (perhaps allowing synergistic drug effects), although this approach is as yet unproven and typically results in complex and additive side effects (13) . Unfortunately, after failing mono-therapy trials, less than 10% of patients have complete control of seizures with dual therapy (14,1) .

The results gained in this study are in agreement with the results of the other studies. In a study conducted by Ripple T. et al. (2011) to evaluate the effectiveness and safety of AEDs in patients with epilepsy. They reported that carbamazepine had advantages in epilepsy control over newer AEDs as a class, and valproic acid provided epilepsy control similar to newer AEDs (15) . Kowalik A. et al. (2008) studied the effect produced by the conversion from carbamazepine or oxcarbamazepine to topiramate in 140 adolescents and adults with epilepsy. They reported that a seizure reduction of ? 50% was achieved in 91% of patients in the last scheduled period (week 12-26); 62% of patients entering that period remained seizure free (16) . A retrospective review of 1,617 seizure free patients revealed that 21% were on poly-therapy and the remaining patients were on mono-therapy (17) .

18 Therapeutic Drug Monitoring

The data in table (3) showed that the mean of the values of the serum concentrations of carbamazepine and valproic acid after 3 months of treatment in all groups were within normal therapeutic range when the usual daily doses of carbamazepine and valproic acid were given. However, and as shown in table (4), about half of patients taking usual daily doses of carbamazepine had the therapeutic level of drug. While, the remaining patients had their serum levels of carbamazepine either in sub-therapeutic or in toxic level. The lowest concentration of carbamazepine in these patients was 1.8 µg/ml whereas the highest concentration was 27.6 µg/ml.

Carbamazepine has complex physicochemical properties, short half life and narrow therapeutic index. A variety of drugs could inhibit its metabolism and increasing the risk of accumulation. Erythromycin and other macrolides were well recognized to cause significant elevation of carbamazepine concentration (18) . Large inter-individual differences in apparent plasma half life linked to auto induction and narrow therapeutic range make this drug suitable for monitoring **??**19) .

As shown in table (5), therapeutic level of valproic acid was also found in about half of patients taking usual daily doses of valproic acid. The remaining patients had their serum levels of valproic acid either in sub-therapeutic or in toxic level. The lowest concentration of valproic acid in these patients was 22.6 µg/ml whereas the highest concentration was 162.3 µg/ml.

Valproic acid is an inhibitor of certain CYP enzymes and as such can cause drug-drug interactions, including with other AEDs such as carbamazepine. However, valproic acid was devoid of enzyme inducing properties, but a risk of interaction still existed as an inhibitor of oxidative and non oxidative drug metabolism. As a result plasma level of it fluctuates during chronic treatment. Metabolites of valproic acid contribute to both antiepileptic and toxic effects. Considering all these effects, therapeutic monitoring of valproic acid is also quite useful **??**19,20) .

So, TDM of carbamazepine and valproic acid in this study did not show a wide fluctuation in the serum level of each drug as higher proportion of patients taking these drugs individually or combined with other AEDs had their serum drug level within therapeutic range, and the toxic and sub-therapeutic levels were not quite high. However, poor correlation was found between the serum concentration of carbamazepine and valproic acid and their therapeutic effects. It is suggested that monitoring of both drugs would be helpful when their toxicity and efficacy are doubtful.

Studies on the effect of TDM on outcome in terms of complete seizure control and/or best compromise between improved seizure control and adverse effects are scarce (21) . In randomized controlled trial conducted by Jannuzzi et al. (2000) on the impact of TDM included 180 newly diagnosed patients with epilepsy who were about to start treatment with carbamazepine, valproic acid, phenytoin, phenobarbital, or primidone. Patients were randomized to either treatment with dosage adjusted on clinical grounds alone, or treatment with dosage adjusted to achieve serum concentrations within predefined target ranges. After a follow-up of up to 24 months, there were no significant differences between the two groups with respect to patients achieving 12-month remission (60% in the TDM group vs. 61% in the control group), patients were remaining seizure-free since initiation of treatment, time to first seizure or to 12-month remission, or frequency of adverse effects. Hence, this study could not demonstrate an effect of routine use of TDM on the clinical outcome of early treatment of patients with epilepsy (22) . Subash

V. et al. (2011) were reported that there was poor correlation between daily dose and therapeutic levels of valproic acid after six months of treatment of epileptic children with valproic acid (7) . Imad A. (1992) tried to find the relationship between serum carbamazepine concentration and clinical effect in 111 epileptic patients. He reported that the therapeutic monitoring did not make management of epilepsy easy, but it could improve its therapeutic effect with avoidance of toxicity (23) .

TDM is particularly useful in determination of drug levels and identification of therapeutic failure due to under dosage, and "even in the presence of optimal dosage" for identification of serious toxicity, inter individual pharmacokinetic variability (rapid or slow metabolism of drug) and detection of pharmacokinetic interactions (24) .

One of the most common cause of lower concentration of drug than expected for the prescribed dose in this study is poor patient compliances. Poor compliance is a bigger issue in this set up, which mainly belongs to rural population, due to poor socioeconomic conditions, illiteracy and dependence on free supply of drugs from public hospitals. Assessing compliance on clinical grounds alone can be difficult especially in patients with infrequent seizures or easy to treat epilepsy (25) . Compliance can be improved by limiting to a minimum the number of daily doses and by regular monitoring of the drug level **??**19) .

Toxic levels of carbamazepine and valproic acid were documented in this study and they may be attributed to the significant intra-and inter-individual pharmacokinetic variability of both agents (26,27) . Also, drug levels may be found within the toxic range in patients with uncontrolled seizures as such patients tend to be prescribed increased doses.

19 Effect On Liver Function

As shown in tables (6 and 8), there was a significant elevation in the activity of ALT and AST in all retrospective groups after three months of treatment. Such elevation where also observed in prospective groups as data in tables (7 and 9) showed that the activity of ALT showed a significant elevation after treatment with carbamazepine with a non significant elevation in those treated with valproic acid, and there was a significant elevation in AST activity after treatment with valproic acid with a non significant elevation with carbamazepine. However, these elevations are usually less than twice the upper limit of normal in all groups.

ALT and AST are an excellent marker of hepatocellular injury. Several drugs may cause raised aminotransferase enzymes, and among them are the AEDs (28) , and mild alterations of aminotransferases can occur without clinical significance (29) .

In table (10), the activity of ALP in all retrospective groups showed a significant elevation after three months of treatment, whereas in table (11), the activity of ALP in prospective groups showed a non significant elevation after treatment as compared with baseline values. The results regarding GGT activity showed that there was a significant elevation in all retrospective groups after treatment except the group treated with topiramate which showed a non significant elevation {table (12)}. While in table (13), the activity of GGT in prospective groups showed a significant elevation after treatment with carbamazepine and a non significant elevation after treatment with valproic acid when compared with baseline values. Again, these elevations are usually less than twice the upper limit of normal in all groups.

It has been mentioned that ALP is the most frequently used biochemical marker of bone formation, and increased values were documented both in adults and in children receiving AED therapy in most studies. The reported incidence of this elevation ranges from 19-56% (30) . Carbamazepine is considered to increase vitamin D metabolism, and risk of bone disease. Decreased vitamin D levels in subjects on carbamazepine might result in increased blood levels of ALP (31) . GGT is a sensitive test of hepatobiliary disease; its usefulness is limited by lack of specificity. Medications like carbamazepine may also cause a mild rise in GGT (28) . GGT would confirm hepatic source for a raised ALP. However, hepatic enzymes (GGT and ALP) elevations are frequent and do not have necessarily a pathological meaning (29) .

There is controversy regarding the exact mechanism for increased enzyme activities in treatment with AEDs. Some studies conclude that increase occurs due to enzyme induction along with liver cell damage (32) , while other studies maintain that increase is due to enzyme induction and is mostly mild and clinically insignificant **??**33) . The results in this study indicate that the AEDs used in this study may cause an asymptomatic rise in liver function tests in both retrospective and prospective groups that does not signify liver dysfunction and does not require action, in addition to that, none of the patients suffered from liver disease, thus, mild increase (less than five times the upper limit of normal (34)) found in enzyme levels may only reflect enzyme induction and not hepatocellular damage. Also the results indicate that the short duration of treatment in prospective groups produced approximately the same effect on liver enzyme activities as the long duration of treatment in retrospective groups. The change in enzyme activities produced by the combination therapy is not significantly different from those produced by mono-therapy.

Enzyme induction is one reported iatrogenic effect leading to elevated hepatic serum enzyme levels in patient populations that are not directly indicative of hepatic injury. This has been well documented, especially for AEDs (35) . Hepatic enzyme induction by AEDs in asymptomatic patients was cited by Wall et al. (1992) in a study of 206 adults and children. Of these, serum GGT was elevated in 74.6%, ALP in 29.7%, and ALT in 25.2% (36) . Of 242 patients administered AEDs, 40 exhibited high levels of serum GGT and nearly all cases indicated hepatic microsomal enzyme induction as measured by antipyrine half-life, leading Hirayanagi et

al. (1991) to conclude that, in these patients, elevated serum GGT did not necessarily indicate hepatocellular damage (37) . Similar studies with AED therapy indicated ALT elevations up to three times and AST elevations up to two times the upper limit of normal in more than onequarter of the patient population. These were not considered clinically significant but instead were attributed to enzyme induction. Liver biopsies in similar patients undergoing long-term antiepileptic therapy showed no signs of chronic liver damage (35) .

20 Adverse Effects

As shown in tables (14 and 15) carbamazepine was responsible for the incidence of adverse effects in 80% of patients in retrospective group and 50% of patients in prospective group, and the number of types of these effects occurred in retrospective group was higher than that types occurred in prospective group. This may be probably due to long duration of treatment in retrospective group (i.e. more than six months versus only three months in prospective group). The common adverse effects documented in both groups were headache, blurred vision, fatigue, and loss of appetite. Most of the patients (8 out of 11) in both groups with carbamazepine level in toxic range showed these adverse effects. Neurological adverse effects are common with high doses of carbamazepine, particularly when the plasma concentration exceeds 9 µg/ml (38) .

In retrospective group treated with valproic acid mono-therapy, 75% of patients had adverse effects, whereas, 60% of patients in prospective group receiving valproic acid showed adverse effects and the number of types of these effects occurred in retrospective group was higher than the types that occurred in prospective group. Again, the duration of treatment may be responsible for this. The most common adverse effects documented in both groups were headache, fatigue, ataxia, and loss of appetite. Only 4 out of 7 patients in this study with valproic acid level in toxic range showed these adverse effect. CNS adverse effects are more common when plasma concentrations of valproic acid exceed 100 µg/ml although some patients may have plasma concentrations of 150 µg/ml or higher without adverse effects (38) . 80% of patients were suffered from adverse effects after three months of treatment with topiramate mono-therapy; however, it was associated with the incidence of the lower number of adverse effects when compared with other treatment options. The most common adverse effects documented were CNS-related effects including headache, fatigue, and loss of appetite. Whereas combination therapy was responsible for the incidence of a wide range of adverse effects in 85% of patients in retrospective group that received combined AEDs. This is due to the fact that when seizures are poorly controlled; AEDs are used in combination, leading to potential pharmacokinetic or pharmacodynamic interactions, causing more adverse effects than might occur when the AED is taken as mono-therapy. Combination therapy can result in additive or sometimes supra-additive adverse effects (39) . The most common adverse effects documented were headache, fatigue, loss of appetite, blurred vision, and weight loss.

However, these adverse effects were considered to be mild to moderate in nature and did not require discontinuation of the medications and the patients can tolerate them. Ripple T. et al. (2011) reported that carbamazepine had more adverse effects than newer AEDs, and there were adverse events that occurred more commonly with valproic acid. However, these effects did not significantly increase the risk of withdrawals (15) . Also, like what was reported by other researchers, the results from this study showed that there was no relationship between serum levels of carbamazepine or valproic acid and their adverse effects as these effects occurred over a wide range of serum drug level (40)(41)(42) .

A few number of patients in this study did not show any adverse effects after treatment especially in children. There is a fact that some adverse effects, such as diplopia or dizziness, may be difficult in children or nonverbal children and adults who are unable to describe their symptoms to caregivers (43) ; in addition, some adverse effects (like weight change) are insidious because of the slow and incremental increase in severity or impact over time (39) .

21 V. Conclusions

? Carbamazepine was more effective in mono-therapy in retrospective groups than other treatment options; whereas, valproic acid in prospective groups was slightly more effective than carbamazepine in controlling seizures. ? Mono-therapy with AED should always be attempted first in treatment-naive patients as the advantages include excellent control of seizure, fewer adverse drug reactions, easier administration and decreased cost, while the combination therapy was associated with a poorer seizure control and higher incidence of adverse drug reactions. ? Poor correlation was found between the serum concentration of carbamazepine and valproic acid and their therapeutic effects; therefore, TDM of both drugs will be useful only when individuals are nonresponsive to treatment or vulnerable to adverse reactions with standard doses. ? AEDs significantly increase levels of liver enzymes activity; however, these alterations are mostly mild and clinically insignificant and do not justify routine testing. ? AEDs in this study have been shown to be well tolerated with mild to moderate adverse effects in nature. However, no relationship between serum levels of carbamazepine or valproic acid and their adverse effects was observed as these effects occurred over a wide range of serum drug level. **??**———— **??**————

Figure 1:

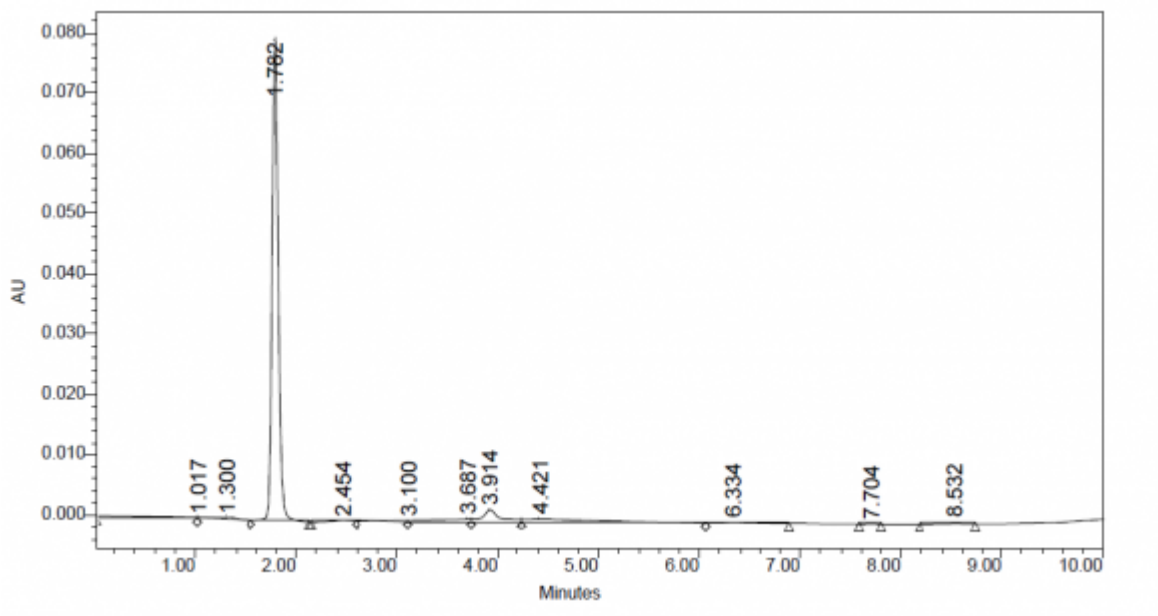

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Figure 2: 2 24 Table 9 :

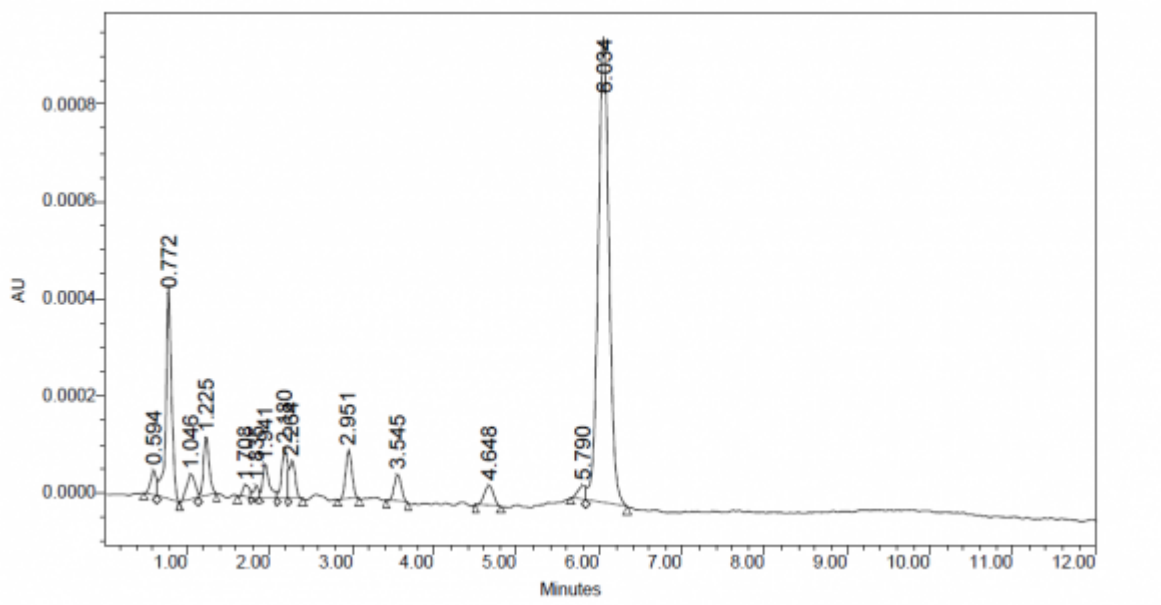

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Figure 3: Table 11 :

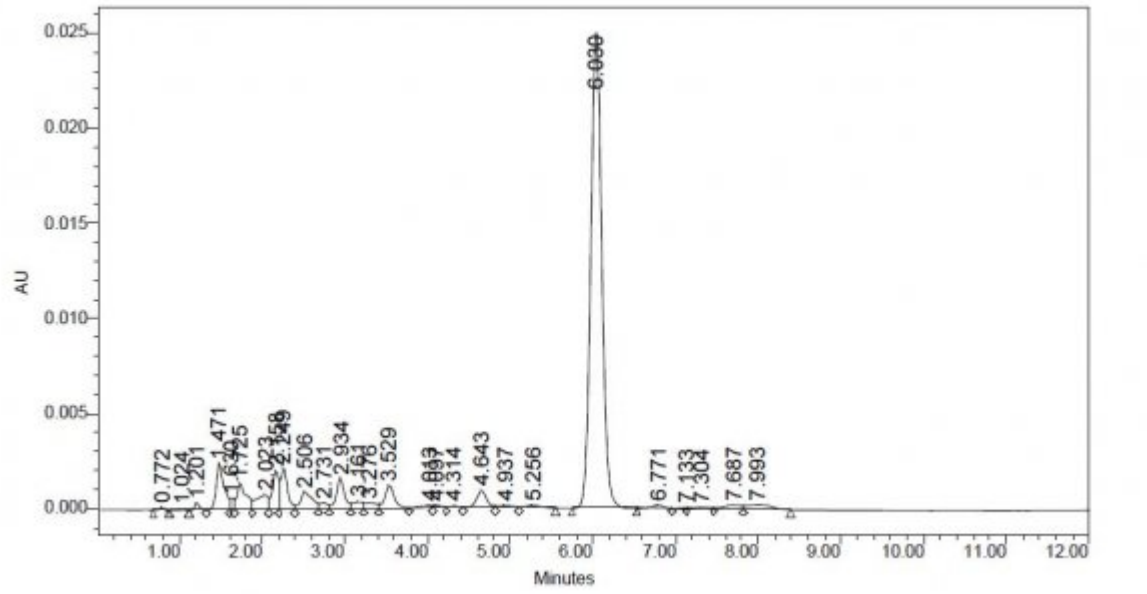

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Figure 4: Table 12 :

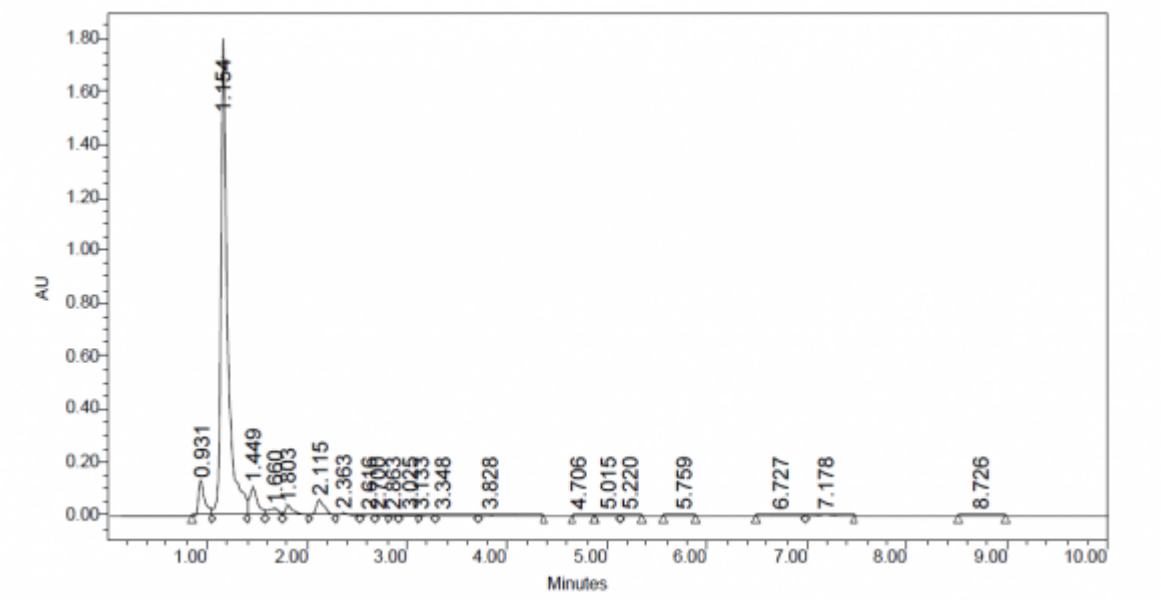

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Figure 5: Table 13 :

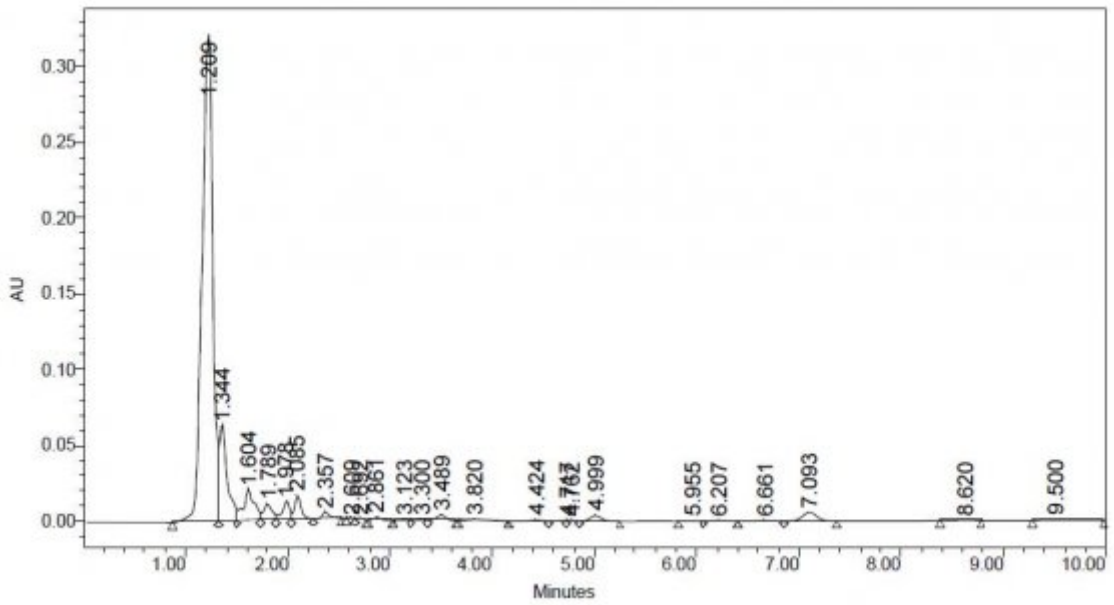

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Figure 6: Figure 1 :

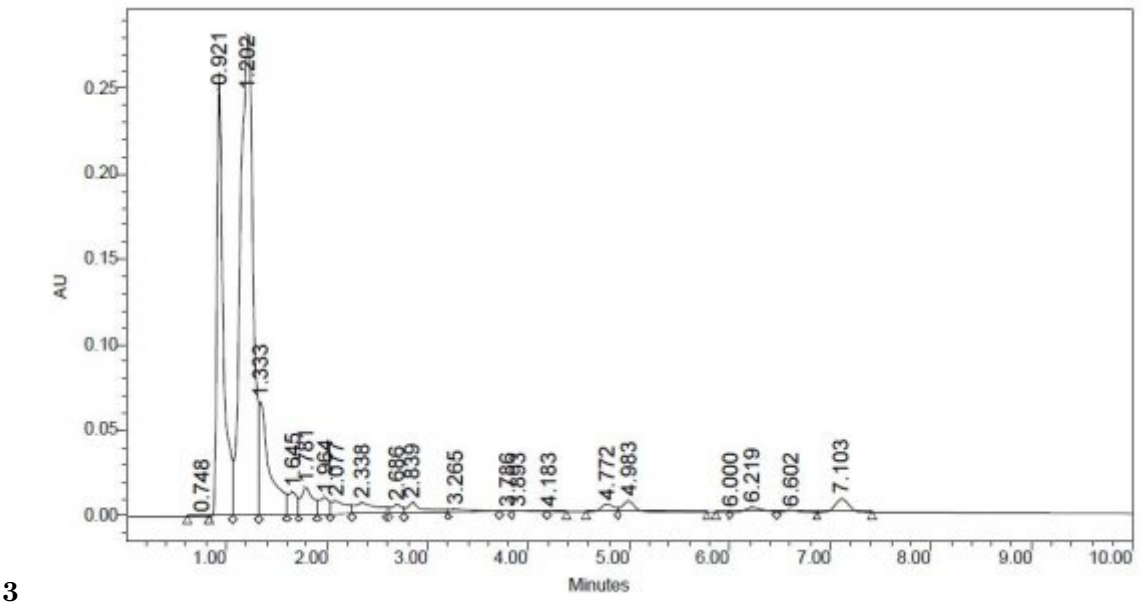

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Figure 7: Figure 3 :

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*[Note: YEach value represents the mean ± standard error of mean. * P ? 0.05 significant difference from baseline values.a P ? 0.05 significant difference from healthy subjects values. b P ? 0.05 significant difference from healthy subjects values.]*

Figure 8:

7

Number of Prospective groups patients	SERUM ALT (U/L)		
	Baseline	After 3 months	% change
			-

Figure 9: Table 7 :

8

Healthy subjects	20	7.00 ± 0.51	–	
Carbamazepine	10	6.70 ± 1.25	12.40 ± 1.57 *a	85.07%
Valproic acid	10	12.30 ± 1.11 b	14.50 ± 2.05 a	17.88%

Each value represents the mean ± standard error of mean.
* P ? 0.05 significant difference from baseline values.
a P ? 0.05 significant difference from healthy subjects values.
b P ? 0.05 significant difference from healthy subjects values.

Retrospective groups	Number of patients	SERUM AST (U/L) Baseline	After 3 months	% change

Figure 10: Table 8 :

?? ?? ?? 1 (5%
) Diplopia 1 (5%) 1 (10%) 2 (10%) 1 (5%) Ataxia 12 (60%) 7 (70%) 6 (30%) 14 (70%) Headache 2 (10%) 1 (10%)
Chest pain ?? ?? ?? Parasthesia Table ??4
: Adverse effects in retrospective groups after three months of treatment. The data were expressed as number (n) and percentage (%).

.1 (15%) -

Table ??5 : Adverse effects in prospective groups after three months of treatment. The data were expressed as number (n) and percentage (%).

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