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EFFECT OF INDUCING AND NON INDUCING ANTI-EPILEPTIC DRUGS ON LIVER ENZYMES IN EPILEPTIC PATIENTS

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ABSTRACT:

Carbamazepine and levetiracetam are one of the most common anti-epileptic drugs used in clinical practice. This study was conducted to assess the effect of carbamazepine and levetiracetam on serum liver enzymes in 67 epileptic patients. The patients were separated into 2 groups. Group I, 31 patients treated with carbamazepine and group II, 36 patients treated with levetiracetam. Serum liver enzymes AST, ALT and ALP were determined. No patients developed clinical symptoms of liver disease. A significant low elevation of the AST, ALT, ALP were noted in the carbamazepine group and a non significant difference were noted in the levetiracetam group. In conclusion the study showed a lowered proportion of liver enzyme abnormalities and there were no any clinical abnormalities. There is no proven value of routine liver enzyme measurement in asymptomatic patients.

I. INTRODUCTION :

Epilepsy is a common neurological disorder affecting all age groups. Epilepsy affects approximately two millions Americans and 65 million people worldwide (1). Epilepsy is not a disease, but a syndrome of different cerebral disorders of the CNS which is characterized by excessive discharge of large numbers of neurons (2). Epilepsy denotes the occurrence of recurrent, unprovoked seizure (3). Epilepsy is diagnosed when there are recurrent seizure due to chronic underlying process (4).

Carbamazepine was used as anticonvulsant in 1974 under the brand name Tegretol (5). It is an an iminostilbene (dibenzazepine) derivative having a carbamyl group at the 5th position, this provides potent anti-seizure activity (6). Adverse effects are drowsiness, vertigo, diplopia, blurred vision, a plastic anemia, agranlocytosis and hypersensitivity reactions (6).

Levetiracetam is a newer anti-seizure drug with better pharmacokinetic profile, lesser drug interactions and wide therapeutic range (7). It is approved as anti-convulsant agent on 30 November 1999 under brand name Keppra (8).

The liver is the primary organ for drug metabolism and elimination for many anti-epileptic drug and thus subjected to drug induced toxicity reactions, from mild and transient elevations of hepatic enzymes to fatal hepatic failure (9).

Hepatic aminotransferase, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are useful biomarkers for liver injuries (10). Although these enzymes are elevated in liver disease,(19-30) the elevation can also be secondary to enzymes induction without hepatic pathology (11). The hepatotoxicity caused by anti epileptic drugs occurs either because of production of reactive toxic metabolites or because of induction of immunoallergic reactions (12),

The aim of the present work was to study the effect of carbamazepine and levetiracetam on liver enzymes.(ALT, AST, ALP).

Subjects and methods:

This case control study was conducted on 67 newly diagnosed epileptic patients receiving anti-epileptic drugs for 6 months. The patients were selected from neurology private clinic related to Dr. Waseem Hashim Kasim . The patients were separated into 2 groups according to the type of the anti epileptic drug used, 31 patients for carbamazepine group and 36 patients for the levetiracetam group. Another group included in the study as control group consisting of 30 healthy subjects. The method and the purpose of the study were explained to the patients and their approval were obtained at the start of the study.

The study was approved by the ethical committee at the department of pharmacology, college of medicine, Mosul university.

Inclusion criteria :

The study included epileptic patients receiving one of the following anti epileptic drugs (carbamazepine or levetiracetam), the epileptic patients having ages more than 18 years.

Exclusion criteria :

Epileptic patients who had concomitant liver diseases, using other drug causing elevation of liver enzymes (e.g. antibiotics, anti rheumatic drugs, statins and non steroidal anti inflammatory drugs) or those who were alcohol drinkers were excluded from the present study.

Laboratory assessment:

All subjects included in this study were subjected to the following laboratory investigations before and after administration of the anti epileptic drugs. Blood sample was drawn from each patients and control individual before start of drug administration and after duration of three and six months.

Serum liver enzymes including:

1- Alanine aminotransferase (ALT)

2- Aspartate aminotransferase (AST)

3- Alkaline phosphatase (ALP)

Special commercial kits made in were used for the measurement of the above liver enzymes.

II. RESULTS :

A total of 67 patients met the necessary inclusion criteria and were considered for the study and 30 healthy individual as a control group.

The study population were divided according to the medication used: group I consisted of patients who were treated with carbamazepine (31 patients), group II compromised those who were given levetiracetam (36 patients). The age ranged from (19) to (53) years for carbamazepine and from (23) to (63) years for levetiracetam (18) and from to (49) years for control group (18) to (51) years.

Table (1) Demographic differences among the studied groups prior to the treatment are shown in table : the differences between the 3 groups is not significcant

variable	Carbamazepine n=31		Levetiracetam n=36		Control n=30		P value
Age	19-53 years	Mean=34.74 SD=9.628	18-49 years	Mean= 33.38 SD=9.2158	18-51 years	Mean=33.6 SD=9.4817	.818095
sex	Male=13 41.94%	Female=18 58.06%	Male= 19 52.78%	Female=17 47.22%	Male=17 56.6 %	Female=13 43.3%	

The difference in pretreatment liver enzymes among the studied groups is illustrated in table 2, The value are not statistically significant.

Table (2): Comparison in LFT among the study sampled groups at the beginning of the study.

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LFT	At the beginning of the study			P-value*
	Carbamazepine group [n = 31] Mean ± SD	Levetiracetam group [n = 36] Mean ± SD	Control group [n = 30] Mean ± SD	
ALT (U/L)	18.19±1.97^{A}	19.64±3.79^{A}	18.40±1.67^{A}	0.067
AST (U/L)	17.45±2.21^{A}	19.11±3.34^{A}	18.90±3.20 ^{A}	0.057
ALP (U/L)	34.32±8.91^{A}	31.53±7.65^{A}	32.53±8.82^{A}	0.399

* One-way ANOVA-test with Tukey's Pair wise comparisons was applied. Means that do not share a letter are significantly different.

.Table (3): shows theEffect of carbamazepine monotherapy on liver enzymes in epileptic patients during the study period. A significant elevation were noted

LFT	Carbamazepine group [n = 31]			P-value*
	Base line Mean ± SD	After 3 months Mean ± SD	After 6 months Mean ± SD	
ALT (U/L)	18.19±1.97^{A}	19.71 ± 2.52 ^{B}	23.87 ±2.58^{C}	0.001
AST (U/L)	17.45±2.21^{A}	20.26± 2.62^{B}	21.74 ±2.39^{C}	0.001
ALP (U/L)	34.32±8.91^{A}	39.65± 7.26^{B}	44.81± 9.11^{C}	0.001

* One-way ANOVA-test with Tukey's Pair wise comparisons was applied. Means that do not share a letter are significantly different.

Table (4): shows theEffect of levetiracetam monotherapy on Liver enzymes in epileptic patients during the study period. No significant effects were noted.

LFT	Levetiracetamgroup [n = 36]			P-value*
	Base line Mean ± SD	After 3 months Mean ± SD	After 6 months Mean ± SD	
ALT (U/L)	19.64±3.79^{A}	21.89 ±3.38^{A}	21.17 ±5.14^{A}	0.070
AST (U/L)	19.11±3.34^{A}	18.56 ± 3.00 ^{A}	19.36 ±2.72^{A}	0.515
ALP (U/L)	31.53±7.65^{A}	34.03 ±7.43 ^{A}	31.19 ±8.00^{A}	0.238

* One-way ANOVA-test with Tukey's Pair wise comparisons was applied. Means that do not share a letter are significantly different.

Table (5): shows Comparison between carbamazepine and levetiracetam effect on liver enzymes in epileptic patients after 6 months follow-up. A significant difference were noted.

LFT	After 6 months follow-up		P-value*
	Carbamazepine group [n = 31] Mean ± SD	Levetiracetam group [n = 36] Mean ± SD	
ALT (U/L)	23.87 ±2.58	21.17 ±5.14	0.010
AST (U/L)	21.74 ±2.39	19.36 ±2.72	0.001

ALP (U/L)	44.81± 9.11	31.19 ±8.00	0.001

*Independent t test for two means was used.

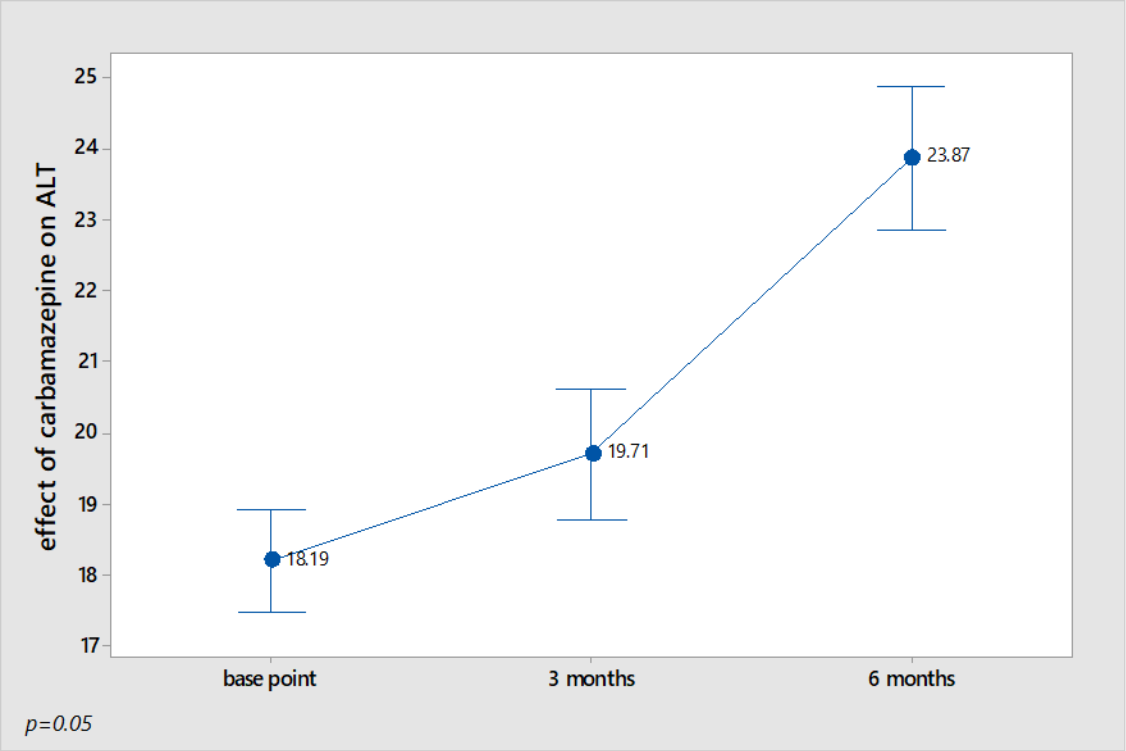

Figure (2): Effect of carbamazepine monotherapy on ALT level in epileptic patients during the study period.

III. DISCUSSION:

Alternation of liver enzymes is a well known phenomenon with anti-epileptic drugs (13). Drug induced liver injury associated with anti-epileptic drugs is well recognized. The frequency of the most common anti epileptic is rare but the consequences can be very serious leading to death or liver transplantation due to acute liver failure induced by these drugs (14).

After 6 months of treatment with carbamazepine and levetiracetam, ALT, AST, ALP liver enzymes were elevated in the carbamazepine group but not in the levetiracetam group. Despite the statistical significance, the observed elevation in the carbamazepine group is benign and did not exceed the normal upper limit of the enzymes. Regarding the enzymes level in carbamazepine group, there is statistically difference after six months.

No clinical symptoms or signs of hepatic dysfunction have been reported for this study, including vomiting, nausea, jaundice or right hypochondrial pain.

The elevation of liver enzymes in the carbamazepine group may be due to that carbamazepine is enzyme inducing agent (15) that cause hepatic enzymes induction such as ALT, AST, ALP (16). The non significant elevation of ALT,AST,ALP in the levetiracetam, may be due to the levetiracetam is not enzyme inducer agent (15).

Hoshino et al. (1995) showed that the routine screening of hepatic enzymes level during the chronic use of anticonvulsant drugs in adults has a questionable value (17). This is in a accordance with Sechmidt and Siemes, who do not support regular repeated monitoring of liver enzymes in a symptomatic patients (18).

IV. CONCLUSION

The results of our study showed that the alteration of liver enzymes was benign, low elevation in the carbamazepine group and no elevation in the levetiracetam group. There is significant enzymes difference between the two group, and there were no clinical abnormalities of hepatic dysfunction. The study showed that the benefit of routine screening in asymptomatic patients has not proved.

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