Scientia Pharmaceutica (Sci. Pharm.) **70**, 135–145 (2002)

Effect of prolonged vigabatrin treatment on hematological and biochemical parameters in plasma, liver and kidney of Swiss albino mice

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Abstract

We have evaluated vigabatrin (γ-vinyl γ-aminobutyric acid), an irreversible inhibitor of γ-aminobutyric acid (GABA)-transaminase responsible for GABA degradation, for its effects on food consumption, body weight changes, fluid intake, changes in hematological and biochemical parameters in plasma liver and kidney of Swiss albino mice. Mice received vigabatrin 0.26% w/v chronically in drinking water for 7, 14 and 21 days. Changes in all the parameters were recorded after 7, 14 and 21 days respectively in different groups. Food consumption was comparable to the control group with minor fluctuations. The body weight declined significantly but only after 3-week treatment with no appreciable change in organ indices or relative organ indices. There were essentially no adverse effects on hematological parameters (RBC, WBC, HGB, neutrophils, eosinophils, monocytes, lymphocytes and basophils) with this treatment. However, there was a decrease in monocyte counts during the first week and an increase in the neutrophil counts during the third week of vigabatrin treatment. In one part plasma biochemical parameters like AST, ALT, CK-MB, creatinine, glucose and urea were also assessed with the same dose regimen. It was observed that only CK-MB and GPT activity levels were altered slightly significantly and are thought to be a result of cross enzyme inhibitions. In this experiment it was observed that lipid peroxide levels measured, as malondialdehyde did not change appreciably in both liver and kidney tissues. However, the levels of glutathione (non-protein sulfhydryl; GSH) declined significantly in comparison to control in liver and kidney. A comparison of level of GSH in liver and kidney shows that this depletion was at early time points in the former. The depletion of GSH suggests the possible involvement of GSH in detoxification process and corroborates its role in protection.

Keywords: Vigabatrin, hematology, plasma, liver, kidney, biochemistry.

Introduction

Vigabatrin is an enzyme-activated irreversible inhibitor of γ-aminobutyric acid -transaminase (GABA-T; EC, 2.6.1.19),[1] the enzyme responsible for degrading of the neurotransmitter GABA. During the past few years many workers have investigated the correlation of vigabatrin therapy and central GABA systems in various physiological and pathological states. It is fairly understood that stimulation of GABA-ergic system leads to gradual, but significant, changes in the biochemical and functional activity of other neurotransmitter pathways. The interconnection/interaction enhance the side effect potential of GABA-ergics and multiplicity of action broadens the spectrum of therapeutic activity. Evidence from the literature indicates that GABA-ergic agents have some

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peripheral effects and as a consequence measurable quantities of GABA were found in the peripheral organs and fluids suggesting that this inhibitory neurotransmitter may regulate some functions outside the central nervous system.[2-4]

Recently vigabatrin has been shown to induce antinociception, reduce locomotor activity and produce hypothermia in normal and hyperthermic mice.[5] From the same laboratory it was also demonstrated to possess anti-inflammatory properties and sharing anti-migration effect with indomethacin on leukocytes to the inflamed peritoneal cavity in rats.[6] Unlike other antiepileptic drugs, vigabatrin is not metabolized, does not induce liver enzymes or bind to plasma and is rapidly cleared by renal clearance. This may increase direct drug load on liver and kidney. The literature has kept silence on the chronic vigabatrin therapy and as a consequence its impact on liver and kidney is yet to know. It is clearly necessary to establish whether animal models and humans were sensitive to vigabatrin related toxic changes if any. These studies were also undertaken to explore the effect of vigabatrin subacute treatment on the levels of glutathione and lipid peroxides (as a measure of its toxicity) in the liver and kidney tissues of mice at different intervals in a 21-day treatment.

Materials and Methods

Drugs and Chemicals

Vigabatrin (Marion Merrell Dow Ltd. Uxbridge, Middlesex, UK) and the kits for CK-MB, GOT, GPT, Urea, creatinine (Boehringer Mannheim GmbH, Mannheim Germany) and glucose and urea (BioMerieux, France) were purchased from the commercial sources. All the other chemicals and reagents were of analytical reagent grade procured from the commercial suppliers.

Animals

Male Swiss albino mice (SWR) weighing 20-25 g, bred at Experimental Animal Care and Breeding Center, College of Pharmacy, King Saud University, Riyadh were used in this study. Animals were housed in groups to acclimatize to the laboratory conditions before the start of experiment, as for room temperature (22±1°C), relative humidity and light cycle (7:0 am - 7:0 pm). The animals were fed on food pellets for mice and had free access to water.

Treatment protocols

Vigabatrin (Marion Merrell Dow Ltd. Uxbridge, Middlesex, UK) was administered in the drinking water, as reported previously by Raza *et al.*[7] Mice were given vigabatrin solution with daily increments in concentration, in a logarithmic ratio of 0.11. This procedure enables relatively large increases in concentration to be achieved very quickly.

Different treatment groups of mice were given a 0.12% w/v solution on day 1, increased to 0.15%, 0.20% and 0.26% w/v on days 2, 3 and 4 respectively. Vigabatrin consumption could be increased in this fashion, without greatly impairing fluid intake, until a concentration in excess of 0.26% w/v is achieved. Thus in a 21 days study period, 0.26% w/v vigabatrin was given as a drinking water for days 5-21 and was found to be a quick and reliable way to achieve a high intake of drug in the drinking fluid. The daily intake of the animal was recorded and the dose was calculated in the range of 259.0 ± 7.2 (Mean ± SEM) mg/kg/day (Table 1) of the body weight that has already been reported in the literature.[6-8]

Test procedures

Three sets consisting of two groups each (8 animals in each group, one control and one treatment) were used to see the effects of prolonged vigabatrin on hematological and biochemical parameters in plasma, liver and kidney of Swiss albino mice after 7, 14 and 21 days respectively. All the control groups received tap water instead of drug. In another parallel study three sets of animals were treated by the same protocol and were used to evaluate the changes in food intake, fluid ingestion, body weight variation and in the determination of organ indices at the end of each treatment interval.

Changes in body and organ weights, and plasma biochemical assessment

Three sets of control and vigabatrin-treated animals were used to assess the changes in body weights. Also the individual weight changes were recorded and calculated to see the difference in comparison of control.

All the three sets of treated groups were sacrificed at days 7, 14 and 21, respectively. Each treatment set had its own control (consisting of 8 animals each). Under light diethylether anesthesia one ml blood from each animal was withdrawn and immediately centrifuged at 4.5×10^3 rpm. Plasma was isolated and kept at –20°C until used for biochemical assessment. Deep frozen plasma samples were thawed and used for this study. Biochemical changes for CK-MB, AST (GOT), ALT (GPT), urea, glucose and creatinine were measured by using the standard kits. The standard techniques described with each analysis kit was used and the absorbance of adducts were measured spectrophotometrically and results were calculated as described in the respective literature. Then the body organs (heart, liver, kidney, spleen and lungs) were removed and weighed individually.

Design for the hematological assessment

Another three sets consisting of two groups each (8 animals in each group, one control and one treatment) were used through out this study. Sets 1, 2 and 3 of control and vigabatrin-treated groups, were sacrificed after 7, 14 and 21 days of treatment, respectively. Under diethyl ether anesthesia, blood from each animal was withdrawn by cardiac puncture by using a syringe containing 3.6% sodium citrate (9 volumes of blood to 1 volume of citrate). From each animal 0.5 ml blood was used in hematological studies. An aliquot of blood samples was subjected to a full blood counts which includes important hematological parameters, mainly RBC, hemoglobin (HGB), total and differential counts of white blood cell corpuscles (WBC). Differential WBC count includes determination of percentage of neutrophils, eosinophils, monocytes, lymphocytes, and basophils (out of total count of WBC count) by using Coulter-S Plus® counter (USA).

Isolation of liver and kidney for biochemical assessment

The animals (Five from each group) were killed after the blood collection by cardiac puncture at the end of each treatment period. Liver and kidney tissues were excised from the same animals and stored at -20°C until used in the biochemical analysis for lipid peroxides and glutathione.

Determination of malondialdehyde (MDA) contents

The method described by Ohkawa *et al.*,[9] was followed. The kidney and liver tissues were homogenized in aqueous KCl solution and incubated with thiobarbituric acid reagent at 90°C for 1 hour. Mixture was allowed to cool and after centrifugation, the optical density of the clear pink

supernatant was read at 532nm. Malondialdehyde bis-(dimethyl acetal) tetra ammonium was used as an external standard.

Quantification of non protein-sulfhydryls (NP-SH)

The levels of NP-SH were determined according to the method described by Sedlak and Lindsay.[10] The kidney and liver tissues were homogenized in ethylenediaminetetra-acetic acid disodium (EDTA-Na_2). Aliquots of homogenate were treated with 50% w/v trichloroacetic acid (TCA) and centrifuged at 3000×g. The supernatant fractions were mixed with Tris buffer and 5,5-dithiobis-(2 nitrobenzoic acid) (DTNB) and the absorbance was read at 412nm against a reagent blank with no homogenate.

Statistical Analysis

The readings shown are means ± SEM. Statistical comparison were made by using analysis of variance (ANOVA, $P<0.05$). In post-hoc analysis mean response of the treatment groups was compared statistically with its control group by using Student's *t*-test and $P < 0.05$ were considered significant.

Results

Drug and fluid intake

Table 1 summarizes the daily fluid intake (ml/kg of body weight/day) and the amount of drug ingested (mg/kg of body weight/day). From days 1-4 the concentration of the drug increased gradually. The daily fluid intake was without any pattern with fluctuations in both groups [control (water) and treatment (vigabatrin)] in first four days. However, fluid intake and drug ingestion remained almost linear at 7, 14 and 21 days of treatment. Since the drug concentration was increasing in the 1st 4 days of treatment so the drug ingested increased gradually till this time but at 7, 14 and 21 days it was in the range of 259.01 ± 7.29 mg/kg of body weight/day and remained unaffected.[7]

Food consumption

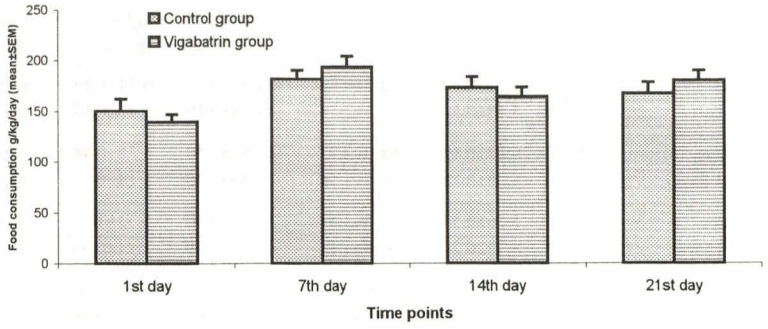
Food consumption in both (treatment and control) groups increased gradually (Figure 1). This increase in food consumption in vigabatrin treatment group was considerable especially at 7, 14 and 21 days of treatment, but there were no significant differences in food consumption between both groups at any time point.

Table 1: Summary of intake of vigabatrin in the drinking water.

Days	Water intake in control group ml/kg/day	Concentration of vigabatrin (%)	Fluid intake in treatment group Ml/kg/day	Vigabatrin intake in treatment group mg/kg/day
1	131	0.12	143	175
2	121	0.15	116	145.3
3	138	0.20	93	165.6
4	125	0.26	106	276.5
5-21	108.6 ± 0.88	0.26	99.6 ± 2.76	259.0 ± 7.2

Readings are the mean of eight animal observations in each group.

Figure 1: Effect of vigabatrin on food consumption during 21 days treatment.

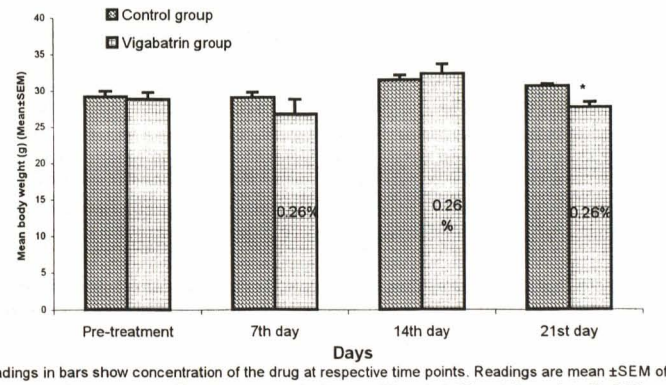


Readings are mean ±SEM of eight observations in a group. Treatments were significantly different at different time points (P<0.05, ANOVA).

Effect on body weight, organ weights and organ indices

The average weight of mice did not change appreciably in both the groups. There were no statistically insignificant changes between weights of mice in both groups, except for a significant (P<0.05) difference (reduction) between the body weights of control group and vigabatrin treated mice after 21 days (Figure 2). The organ (heart, liver, kidney, spleen and lungs) weights did not change in the course of treatment, during 21 days when compared to the control group. The organ index of treatment group was comparable to that of the control group at each interval. Similarly the relative organ indices of all the treatment groups were in a linear range with no significant deviation (Tables 2 and 3).

Figure 2: Effect of vigabatrin on body weight during 21 days treatment.



Readings in bars show concentration of the drug at respective time points. Readings are mean ±SEM of eight observations in a group. Treatments were significantly different at different time points (P<0.05, ANOVA). Post hoc analysis was done by Students t-test, *P<0.01.

Table 2: Effect of vigabatrin on the organ indices of mice in a 21 days treatment.

Treatment/group	Organ Indices (Mean ± SEM)					
	Body weight "g"	Heart "g"×10^{-3}	Liver "g"×10^{-3}	Kidney "g"×10^{-3}	Spleen "g"×10^{-3}	Lungs "g"×10^{-3}
Control 7days	27.42±0.75	6.05±0.40	72.8±6.7	11.32±0.27	6.31±0.87	8.25±0.36
Vigabatrin 7days	26.7±2.04	5.48±0.51	64.1±2.3	11.54±0.19	5.45±0.67	7.93±0.46
Control 14 days	31.42±0.66	6.08±0.42	64.0±3.12	13.87±0.50	5.38±0.48	7.28±0.42
Vigabatrin 14 days	32.24±1.28	5.00±0.33	60.6±2.56	13.59±0.30	5.14±0.39	7.47±0.33
Control 21days	30.54±0.30	5.56±0.31	63.5±3.33	11.62±0.30	5.31±1.31	10.65±2.34
Vigabatrin 21days	27.64±0.70*	5.73±0.23	60.8±1.11	12.32±0.29	3.91±0.40	8.22±0.72

Five animals were used in each group. Each reading is a mean ± SEM of five observations. Treatments were significantly different at different time points ($P<0.05$, ANOVA). In post-hoc analysis treatment groups were compared to its own control group at respective time points. *$P<0.01$ (Student's t-test).

Table 3: Effect of vigabatrin in a 21 days treatment on relative organ indices in mice.

Treatment/group	Body weight	Heart	Liver	Kidney	Spleen	Lungs
7 days vigabatrin	0.97	0.91	0.88	1.02	0.86	0.96
14 days vigabatrin	1.03	0.82	0.95	0.98	0.96	1.03
21 days vigabatrin	0.91	1.03	0.96	1.06	0.74	0.77

Five mice were used in each group. Comparison is made with respective control group after each treatment period.

Table 4: Effect of vigabatrin subacute treatment on some hematological parameters.

Treatment groups	Hematological Parameters (Mean ± SEM)							
	WBC ×10^3	RBC ×10^5	HGB (gm %)	Neutr %	Lymp %	Mono %	Eos %	Baso %
Control 7 days	3.74± 0.87	7.23± 0.29	10.72± 0.31	7.45± 1.79	73.78± 3.1	14.6± 2.16	0.56± 0.17	0.98± 0.56
Vigabatrin 7 days	3.9± 0.4	7.94± 0.19	11.97± 0.34	7.02± 1.22	81.58± 2.45	8.43± 0.76*	0.57± 0.09	0.17± 0.03
Control 14 days	3.77± 0.84	7.37± 0.25	10.78± 0.36	3.16± 0.37	72.2± 5.44	17.28± 2.56	0.16± 0.08	0.43± 0.24
Vigabatrin 14 days	4.83± 0.7	7.05± 0.31	10.37± 0.56	4.86± 0.81	70.73± 6.85	14.48± 2.15	0.50± 0.19	0.33± 0.08
Control 21 days	4.47± 0.8	6.3± 0.49	9.07± 0.71	4.58± 0.39	67.92± 2.34	22.84± 3.93	0.65± 0.28	0.28± 0.08
Vigabatrin 21 days	3.42± 0.66	6.75± 0.28	10.13± 0.36	5.7± 0.27*	66.12± 5.28	20.37± 0.06	0.58± 0.06	0.32± 0.09

The readings are mean ± SEM of five observations in a group. Treatments were significantly different at different time points ($P<0.05$, ANOVA). In post-hoc analysis, treatment groups were compared to their respective controls at each interval. *$P<0.05$, (Student's t-test).

Effect on hematology and blood plasma biochemical parameters

Vigabatrin treatment for 21 days (in drinking water) did not affect RBC, HGB, total or differential counts of WBC at all intervals, except for a significant ($P<0.05$) decrease in monocytes during the

first week and a significant ($P<0.05$) increase in neurtophils during the third week of treatment (Table 4). Vigabatrin given in drinking water for 21 days did not significantly affect creatinine, urea and glucose at all the time points except a significant ($P<0.01$) decrease in plasma glucose levels at 14 days. On the other hand, plasma CK-MB was elevated significantly ($P<0.05$) at all intervals. Plasma GPT levels was significantly ($P<0.05$) decreased during first and second weeks. The GPT decrease was significant ($P<0.01$) during the third week of vigabatrin treatment. However, plasma GOT levels was only altered at 21 days after vigabatrin treatments being significantly ($P<0.05$) elevated (Table 5).

Table 5: Effect of vigabatrin subacute treatment for 21 days on blood plasma biochemical parameters.

Treatment groups	Plasma biochemical parameters (Mean ± SEM)					
	CK-MB	ALT	AST	Creatinine	Urea	Glucose
	U/L	U/L	U/L	Mg/dl	Mg/dl	Mg/dl
Control 7 days	24.14 ± 1.53	7.31 ± 0.82	15.09 ± 0.66	0.532 ± 0.022	408.75 ± 46.70	89.55 ± 7.71
Vigabatrin 7 days	51.63 ± 9.78*	4.68 ± 0.68*	15.09 ± 0.54	0.497 ± 0.037	426.44 ± 51.38	65.93 ± 9.17
Control 14 days	27.48 ± 2.46	7.00 ± 0.51	15.57 ± 1.18	0.543 ± 0.056	395.6 ± 34.53	70.69 ± 6.44
Vigabatrin 14 days	47.19 ± 7.14*	4.75 ± 0.85*	12.85 ± 0.76	0.59 ± 0.056	346.83 ± 40.36	46.60 ± 2.03**
Control 21 days	29.73 ± 4.51	7.78 ± 0.86	13.50 ± 1.16	0.584 ± 0.051	403.85 ± 32.70	81.84 ± 8.91
Vigabatrin 21 days	62.03 ± 10.89*	4.52 ± 0.47**	17.55 ± 1.15*	0.455 ± 0.065	486.46 ± 39.39	105.49 ± 13.03

The readings are mean ± SEM of five observations in a group. Treatments were significantly different at different time points ($P<0.05$, ANOVA). In post-hoc analysis, treatment groups were compared to their respective controls at each interval. *$P<0.05$, **$P<0.01$ (Student's t-test).

Biochemical assessment of liver and kidney

Lipid peroxidation

Treatment of the different animal groups with vigabatrin increased malodialdehyde production in a time dependent fashion in the liver, but these levels were statistically insignificant at any interval. Dissimilar results were seen in the kidney where malodialdehyde contents remained to ground, when compared to control group at all the intervals tested (Table 6).

Table 6: Effect of vigabatrin treatment on malondialdehyde production in the liver and kidney of mice in prolonged treatment at different durations.

Group No	Treatment groups	Liver	Kidney
		nmoles/g wet tissue	nmoles/g wet tissue
1	Control (tap water)	267.55±8.12	214.50±8.72
2	Vigabatrin 7 days	281.39±6.70	212.37±9.65
3	Vigabatrin 7 days	283.95±8.62	229.05±8.48
4	Vigabatrin 7 days	293.76±8.42	227.67±8.92

Readings are Mean ± SEM of five determinations. Treatments were significantly different at different time points ($P<0.05$, ANOVA). In post-hoc analysis, groups 2, 3 and 4 were statistically compared to group 1 for each tissue type (Students t-test). $P>0.05$

Glutathione levels

Hepatic glutathione (GSH), measured as non-protein bound sulfhydryl, levels were altered by vigabatrin at the relatively early time point (7 days) that persisted in the whole study period (21 days). A moderately significant decline ($P<0.01$) in its level was evident in the liver tissue. The same treatment in the same animal resulted in a time dependent depletion of GSH in the renal tissue. This depletion of GSH was 30%, 32% and 33% of the control group after 7, 14 and 21 days of treatment, respectively. A comparison of GSH depletion in liver and kidney shows that vigabatrin treatment promoted this depletion in kidney strongly and at an early time point (Table 7).

Table 7: Effect of vigabatrin treatment on non-protein sulfhydryl levels in the liver and kidney of mice after a prolonged treatment at different durations.

Group No	Treatment groups	Liver nmoles/g wet tissue	Kidney nmoles/g wet tissue
1	Control (tap water)	69.20±3.05	51.74±2.37
2	Vigabatrin 7 days	59.57±2.25*	35.95±3.25**
3	Vigabatrin 7 days	52.61±3.19**	34.90±3.82**
4	Vigabatrin 7 days	53.18±3.06**	34.29±3.49**

Readings are Mean ± SEM of five determinations. Treatments were significantly different at different time points ($P<0.05$, ANOVA). In post-hoc analysis, groups 2, 3 and 4 were statistically compared to group 1 for each tissue type. *$P<0.05$; **$P<0.01$ (Students t-test).

Discussion

The chronic treatment of mice with vigabatrin did not show any considerable change in food intake. As such it does not comply with previous studies[11] that have shown a dose-related reduction of food intake in rats after both single (125-1000 mg/kg; i.p. or 500 mg/kg; p.o.) and repeated (250 mg/kg/day; i.p.) administration. The discrepancies in food consumption during chronic administration might have arisen from different protocols used, different dose regimen, species differences and possibly the development of tolerance to vigabatrin anorexia. However, the literature is lacking any reference to the development of tolerance to its anorectic effects with this dose regimen.

In the present studies, it was also noted that chronic administration at the beginning of treatment arrested any growth as observed by weight changes, and caused a decline in body weight in the last week of treatment. These results are in agreement with the previous report of Singewald *et al.*[12] Singewald and colleagues[12] found that vigabatrin (up to 150 mg/kg, s.c.) in a seven weeks treatment to young rats delayed an increase in body weight, irrespective of their age. In another study, oral administration of the drug (1000 mg/kg/day) for 2-4 weeks caused decreased food consumption and weight loss in rats and dogs.[13]

It is obvious from the results of the present work that chronic treatment with vigabatrin although very slowly reduced the body weights of animals; it did not reflect any change in organ indices or relative organ indices even after 21 days. A possible explanation for this failure to induce any change may reside in the pharmacokinetics of this drug.

This drug is rapidly and completely absorbed after oral administration, uninfluenced by food,[14] quickly enters the CSF,[15,16] rapidly excreted by the kidney without any accumulation in other body organs.[17] Also, the drug circulates freely and does not bind to plasma proteins and is cleared without the induction of liver enzyme. As it does not induce any metabolic changes it is considered a safe drug that does not cause any toxic changes in organ indices and relative organ indices.

Results obtained in this study, did not show any significant change in most of the hematological parameters tested, in response to sub-acute vigabatrin treatment. These findings agreed with Cocito *et al.*[18] study who reported that during a follow up of 23 responder epileptic patients (who continued vigabatrin treatment for 7 years), no significant effect were noted on any of the routine hematologic assessments. Vogt and Krämer[19] have also claimed the data on hematological safety during chronic vigabatrin treatment. However, a significant ($P<0.05$) decrease was noted in monocytes during the first week and a significant ($P<0.05$) increase in neutrophils during the 3rd week of vigabatrin treatment in our study. In one study[20] a slight reduction in RBC count and HGB levels were noted during nine month- vigabatrin treatments of 20 children given 60 mg/kg/day. These findings were thought to be of doubtful clinical significance. The differences in results may be due to differences in species and/or drug administration regimen.

The enzyme tests have proved to be the most helpful tool in the diagnosis of myocardial infarction, liver disease and muscle damage. In the present study the enzyme activities of CK-MB increased early after the start of the treatment and persisted throughout the treatment. There is paucity in literature on this cardiac enzyme activity after treatment with vigabatrin or other GABA-ergic drugs. On the other hand, ALT (GPT) activity declined from the beginning of this treatment. However, AST (GOT) activity increased slightly at the end of 21 days treatment. ALT (GPT) is present moderately in liver but low in cardiac and skeletal muscle and other tissues.

Accompanied by an increase in AST (GOT) activity in these cases, myocardial infarction is suspected. However, when GOT and GPT activities both are elevated in serum, liver ischemia (because of congestive heart failure or other source of liver cell injury) is suspected.[21] Foletti *et al.*[22] have also shown a reduction in alanine aminotransaminase (ALT) activity in plasma during vigabatrin treatment, with a conclusion that perhaps this reduction is an *in vivo* phenomenon due to a possible cross-enzyme inhibition. In the present study plasma glucose level was moderately significantly ($P<0.01$) decreased in the second week of vigabatrin treatment. However, Enna[23] claimed that, agents thought to be GABA agonists have been reported to be effective in certain disorders including diabetes. In one study,[24] exogenous GABA and muscimol did not affect insulin release by isolated mouse or rat islets, but they inhibited glucagon release by inhibiting A-cells, probably by acting on $GABA_A$ receptors in islet cells.

A reduction in alanine aminotransferase (ALT) activity was further supported by the biochemical studies of the liver and kidney tissue for lipid peroxidation that indicated no significant change in its concentrations being an indicator of the oxidative damage. Non-protein sulfhydryls (GSH or glutathione), which is a well-known scavenger of the free radicals and reactive oxygen species,[25,26] on the other hand was found to be reduced significantly at early time points. GSH is also known to play a cytoprotective role in the effects of various drugs.[27,28] Comparison of the depletion of GSH and persistence of MDA levels (lipid peroxides) at all time points both in liver

and kidney show that this effect is either a drug induced epiphenomenon or a cause effect relationship and supports the role of GSH in the detoxification process. It is further suggested that the lipid peroxidation may not become evident until GSH activity is limited[29] and detection and/or accumulation of MDA could proceed only if endogenous levels of lipid peroxides are enough not to be detoxified. These findings of depletion of GSH indicate its possible involvement in the cytoprotection during vigabatrin treatment.

These effects are thought to be a result of neuromediator interaction and a possible direct effect of GABA and drug itself. However, there is considerable evidence favoring the use of vigabatrin in different behavioral changes and pathological problems. This is supported by the hematological and biochemical studies concerning its safety, on whole blood and plasma except a mild increase in plasma CK-MB. The levels of GSH declined significantly at early time points and suggest the possible involvement of GSH in the detoxification process (cytoprotection) and corroborate its role.

It is hoped that future research in this line may offer better understanding of the underlying mechanisms and thus better use of vigabatrin in different epileptic conditions and other pathological states.

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Received December 31st, 2001
Accepted February 20th, 2002