ORIGINAL REPORT

Chronic Effect of Gabapentin on Liver Function in Adult Male Rats

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Abstract- Gabapentin (GPN) is a new antiepileptic agent currently in used as add-on therapy in adult patients suffering from partial seizures. The extent of liver damage at different dosage and long term treatment with GPN is not yet clear. Therefore this study was undertaken to find out the possibility of liver damage by this drug. Adult male (Wistar) rats of 180-220 g were administered intraperitoneally with GPN (20 or 100 mg/kg) for 45 days. After the experimental period, the liver function tests were carried out in control and experimental groups. The activity of liver enzymes, with 20 mg/kg of GPN were not significantly different from the control group but, the serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, direct bilirubin and total bilirubin were enhanced significantly with 100 mg/kg of GPN. Total protein and albumin decreased in this group as compared with control animals. The histopathology of the liver parenchymal cells also showed minute foci of necrosis in a few rats treated with high dose of GPN, whereas, at therapeutic dose the histopathology and biochemical indices showed almost normal values. At therapeutic dose GPN is a safer drug with regards to liver function and hepatocellular damage as compared with other antiepileptic drugs.

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Keywords: Antiepileptic; Gabapentin; Liver function test

Introduction

Epilepsy is one of the most common serious neurological conditions affecting approximately 1% of the word population at any one time. For the effective therapy, long term therapy is advised with antiepileptic drugs. However, long term treatment frequently causes adverse drug reaction. Generally available traditional anti epileptic drugs such as phenobarbitone, phenytoin, carbamazepine, ethosuximide, sodium valproate administered as mono or poly therapy regimens usually cause hepatotoxicity (1,2). To overcome this problem, there is a need for one substitution of a drug which may have least adverse drug reaction. Therefore, it is necessary to study the effect of individual new anti epileptic drugs on liver function separately.

Gabapentin (GPN) chemically 1-(Amino methyl) cyclohexane acetic acid $C_9H_{17}NO_2$ is one of the new antiepileptic drugs that has been approved as adjunctive therapy in adult patients suffered from partial seizures, with or without secondary generalization. Also used in patients who have not achieved satisfactory control with or who are intolerant of usual anti epileptic drugs. GPN is well absorbed orally and circulates mostly unbound in the plasma and excreted unchanged in the kidneys without appreciable metabolism in the body. Oral bioavailability is approximately 60 percent and is not affected by food. The half-life is five to seven hours and is related to the creatinine clearance. Therefore, excretion is decreased in patients with renal impairment and decreased cardiac function (2).

Liver particularly is vulnerable to drug-induced toxicity mainly because of its role as a primary organ of drug elimination and its subsequent exposure to potential toxins. Since most of the antiepileptic drugs have a kind of adverse drug reaction in response to liver functions. This study was designed to find out the changes in the liver function, if any, after chronic exposure of rats to different doses of GPN.

Materials and Methods

GPN was obtained from HEXAL CO., (Germany). The rats were obtained from Fasa University of Medical Sciences Animal Research Center, and the device used for biochemical analysis was an auto analyzer, ($RA_{1000,}$ Japan).

A total of sixty adult male Wistar rats weighting

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200-225 g had *ad libitum* access to water and semi synthetic balanced diet obtained from a local company, with occasional supply of green vegetables (lettuce leaves and carrot) (3).

Rats were caged four per Perspex experimental cages at room temperature (22-24 ºC) twelve hours of light and dark cycles were strictly followed in a fully ventilated room. The rats were divided into 3 groups of control and experimental 1 and 2. The control group received normal saline (0.9%) intraperitoneally whereas; the experimental groups received GPN (20 or 100 mg /kg) by the same route for 45 days (Table 1).

After 45 days of the experimental period, the blood samples were collected by heart puncture within 4 to 6 hrs of last dose of GPN, liver function tests were carried out immediately after separation of serum using auto-analyzer (the kits were supplied by Pars Azemoon Co., Iran).

Statistical analysis

The results were subjected to statistical analysis and significance of differences between the mean levels of control and experimental groups was calculated by using Kruskal-Wallis test and ANOVA (two-tailed) with SPSS software.

Results

The experimental rats exposed to GPN (20 mg/kg) looked apparently normal with no behavioral abnormalities of any kind, whereas, the other group treated with 100 mg/kg of GPN showed some kind of somnolence and aggressive behavior. The statistical analysis of the results showed the body weight (growth rate) of the low dose group were not significantly different from control group, whereas, the high dose group showed a significant (P<0.01) increase. In body weight as compared to control group, the average weight gain of control and experimental 1 and 2 groups were 43.47, 45.89 and 62.23 g respectively. The results of biochemical indices (Table 2) indicate that the liver enzymes, in first group were not significantly different from control group. However, the serum levels of, alkaline phosphatase (ALP, P<0.01), aspartate aminotransferase (AST, P<0.001), alanine aminotransferase (ALT, P<0.001), lactate dehydrogenase (LDH, P<0.001), total bilirubin (P<0.001) and direct Bilirubin (P<0.001) were enhanced significantly with higher dose of GPN, whereas, total protein (P<0.05) and albumin (P<0.01) decreased in this group.

The histopathology of liver parenchymal cells with lower doses of GPN showed no abnormalities of any kind as compared with control group (Figure 1) whereas, the higher dose showed a few scattered necrotic foci in more than 80 % 0f high dose group (Figures 2 and 3).

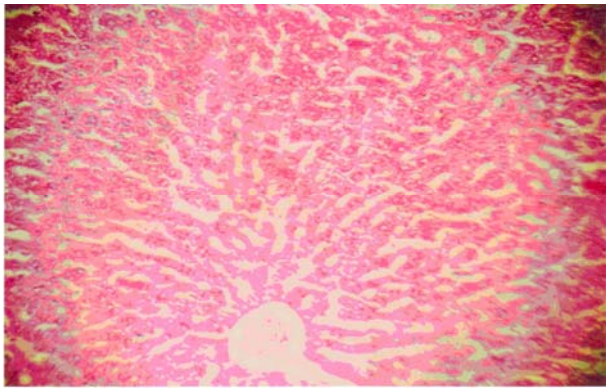

Figure1. Minimal portal inflammation hepatic tissue, Therapeutic dose of GPN, H&E X100.

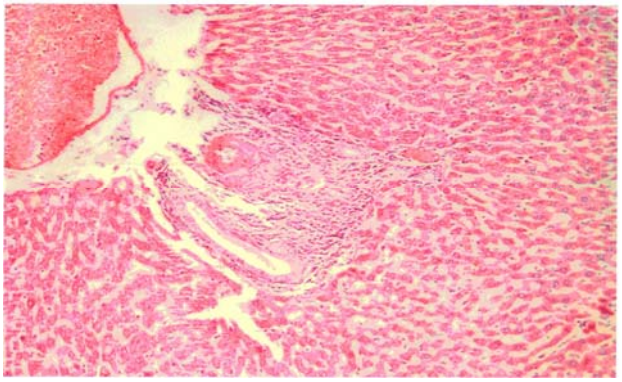

Figure 2. Chronic persistent hepatitis, with toxic dose of GPN, H&E X100.

Table1. Study design.

Group	1st day	2nd day	3rd day onwards
Control (0.9% normal saline)	250 µl saline	250 µl saline	250 µl saline
Therapeutic dose group (20 mg/kg of Gabapentin)	5 mg/kg	10 mg/kg body wt./ day	20 mg/kg body wt./ day
Toxic dose group (100 mg/kg of Gabapentin)	25 mg/kg	50 mg/kg body wt./ day	100 mg/kg body wt./ day

Table 2. Biochemical changes in rat serum exposed to Gabapentin (20 & 100 mg/kg body weight) for 45 days.

Biochemical Parameters	Control group	Experimental group 1 (Therapeutic)		Experimental group 2 (Toxic dose)	
		(20 mg/kg)	% changes	(100 mg/kg)	% changes
ALP (U/L)	340.24 ±16.64	341.24±16.35	0.3	[b] 417.00±18.22	22.6
AST (U/L)	180.24±11.31	190.76±16.18	5.8	[c] 228.00±09.77	26.5
ALT (U/L)	64.88±9.52	69.82±9.17	7.6	[c] 89.53±06.14	38.0
LDH	902.08±105.60	976.94±142.85	8.3	[c]1172.71±133.80	30.0
Total Bilirubin (mg/dl)	0.45±0.05	0.48±0.06	6.7	[c] 0.60±0.07	33.3
Direct Bilirubin (mg/dl)	0.114±0.013	0.118±0.013	3.5	[c] 0.235±0.029	106
Total Proteins (g/dl)	6.44±0.26	6.39±0.21	-0.8	[a] 6.21±0.20	- 03.6
Albumin (g/dl)	3.02±0.17	2.98±0.11	-1.3	[b] 2.87±0.14	-05.0

a $P<0.05$, b $P<0.01$, c $P<0.001$ in comparison with control group

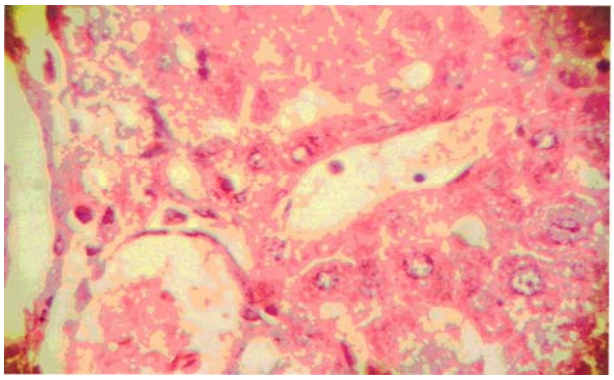

Figure 3. Periportal individual hepatocyte necrosis, in one case of rats, treated with toxic dose of GPN, H&E X400.

Discussion

A gamma-aminobutiric acid (GABA) analog, Gabapentin does not interact with GABA receptors (4) and has no effect on GABA uptake. GPN has been found to interact with the alpha-2-delta subunit of voltage-gated calcium channels. But its mechanism of action is not yet clears (5).

Following oral ingestion of GPN it is rapidly absorbed which is dose-dependent, percentage of absorption of GPN decreases with increasing dose. This is because its absorption from the gut is via an L-Amino acid transport (6) despite this, these are a linear relationship between dose and plasma concentrations over the therapeutically effective dose range (7). Because GPN has no known pharmacokinetic interactions with any other antiepileptic drugs, it can be useful in patients taking other antiepileptic medications (2).

There are various reports that the elevation of liver enzymes after chronic antiepileptic medication would reflect hepatocellular damage. Our previous and several other studies shows that long term treatment with old or new anti epileptic drugs affect liver function from transient state to a fatal liver damage (1,8-10). But when considered GPN such an effect is quite less and no report of death or fatal liver damage. A recent study with low-dose of GPN-antidepressant combination with opioids was effective in managing neuropathic cancer pain without severe adverse effects (11). Though there is a report of GPN induced cholestasis after 15 days of treatment with GPN (900 mg/day) in a fifty years old patient who were on several other drugs for one year and with the history of peripheral diabetic neuropathy (12).

High doses of GPN have caused pancreatic acinar cell carcinoma in laboratory rats; however, in humans, pancreatic carcinoma is usually ducal in origin (4). Increased rate of pancreatic tumor occurrence has not been reported in patients using GPN. Overdoses of 15 times the usual daily dose have resulted in diplopia, slurred speech, drowsiness, lethargy and diarrhea (13), GPN is eliminated unchanged via kidney and its clearance is linearly related creatinine clearance. Drug interactions with GPN is not much reported, since it is not protein-bound or metabolized and dose not induce liver enzymes (14,15) or may metabolized and eliminated via kidney therefore it has no effect on liver cells. Though drug monitoring of GPN in the plasma was necessary, unfortunately was not carried out in this study. However, other studies reported the correlation between the seizure frequency and the current putative target concentration range of 12-120 Îµmol/l (7,16,17).

The present study concludes that the prolonged exposure of rats to therapeutic dose of GPN results in no change in the levels of serum bilirubin and liver enzymes. Therefore it can be a drug of choice for epileptic patients as a safe drug with regards to liver hepatocellular damage as compared with other AED drugs.

References

1. Meshkibaf MH, Subhash MN, Rama Rao BSS, Narayanan CP, Kailashnath KM. Comparative effect of single and poly therapy on liver enzymes in epileptic patients under long-term treatment. Nimhans J 1995;141-6.
2. Patsalos NP. New antiepileptic drugs. Ann Clin Biochem 1999;36(Pt 1):10-9.
3. Harmuth-Hoene AE, Schelenz R. Effect of Dietary Fiber on Mineral Absorption in Growing Rats. Fed Res Cen. J NutR 1980;110(9) 1774-84.
4. Laxer KD. Guidline for treating epilepsy in the age of felbamate, vigabatrin, lamotrigine, and gabapentin. West J Med 1994;161(3):309-14.
5. Sutton KG, Martin DJ, Pinnock RD, Lee K, Scott RH. Gabapentininhibit high-threshold calcium channel currents in cultured rat dorsal root ganglion neurons. Br J pharmacol 2002;135(1):257-65.
6. McLean MJ. Gabapentin. Epilepsia. 1995;36(Supple 2):S73-86.
7. Wilson EA, Sill GJ, Forrest G, Brodie MJ. High dose gabapentin in refractory partial epilepsy: clinical observations in 50 patients. Epilepsy Res 1998;29(2):161-6.
8. Preece N.E, Jackson GD, Houseman JA, Duncan JS, Williams SR. Nuclear magnetic resonance detection of increased GABA in vigabatrin-treated rats in vivo. Epilepsia 1994;35(2):431-6.
9. Beghi E, and Dimascio R. Antiepileptic drug toxic definition and mechanism of action. Neurol Sci 1986;7(2):209-22.
10. 10. Mullick FG, Ishak KG. Hepatic injury associated with diphenyl-hydantion therapy: A clinicopathological study of 20 cases. Am J. Clin. Pathol 1980;74(4):442-52.
11. Arai YC, Matsubara T, Shimo K, Suetomi K, Nishihara M, Ushida T, Kobayashi K, Suzuki C, Kinoshita A, Kondo M, Matsubara S,Hayashi R, Tohyama Y, Nishida K, Arakawa M. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. J Anesth 2010;24(3):407-10.
12. Charles E Richardson. Gaqbapentin indused cholestasis. Br Med J 2002;325(7365):635.
13. Rosner H,Rubin L, Kestenbaum A. Gabapentin adjusnctive therapy in neuropathic pain states. Clin J Pain1996;12(1):56-8.
14. Patsalos PN, Duncan JS. Antiepileptic drugs: a review of clinically significant drug interactions. Drug Saf 1993;9(3):158-84.
15. Patsalos PN. Phenobarbitone to gabapentin: aguid to 82 years of anti-epileptic drug pharmacokinetic interactions. Seizure 1994;3:163-70.
16. Beydoun A, Fakhoury T, Nasreddine W, Abou Khalil B. Conversion to high dose Gabapentin monotherapy in patients with medically refractory partial epilepsy. Epilepsia 1998;39:188-93.
17. Sivenius J, Kalviainen R, Ylinen A, Riekkinen P. Double-blind study of Gabapentin in the treatment of partial seizures. Epilepsia 1991;32:539-42.