Article *NIMHANS Journal*

Comparative Effect of Single and Poly Therapy on Liver Enzymes in Epileptic Patients Under Long-term Treatment

Volume: 13 Issue: 02 JULY 1995 Page: 141-146

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Reprints request
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Abstract

A number of antilepileptic drugs are currently in use. Despite extensive use of these drugs it has not been possible to predict the side-effects, especially the hepatotoxic reactions noted with these drugs. The problem is more complicated with polytherapy. The present study was undertaken to find out alterations in liver enzyme activities in epileptic patients treated with single or multiple antiepileptic drugs. The levels of Serum Alkaline phosphatase (ALP), Asparatate amino transferase (AST), Alanine amino transferase (ALT), Lactate dehydrogenase (DH) and Gamma glutamyl transferase (GGT) were elevated in patients receiving either a single or multiple antiepileptic drugs for a period of two years. However, it was noted that the levels of these enzymes were higher in those receiving polytherapy than those receiving single drug. The elevation if liver enzymes after chronic antiepileptic medication would reflect hepatocellular damage.

Key words -
Antiepileptics,
Single and Polytherapy,
Liver enzymes,
Blood,
Epilepsy

Patients receiving chronic treatment with antiepileptic drugs are at high risk of developing signs and symptoms of drug toxicity. The problem of drug toxicity in these patients has been repeatedly emphasized [1], [2]. However, the most common sources of information on drug toxicity are case reports and clinical trials [3], which is a better reflection of the prevalence and clinical implications of drug toxicity. 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. Many commonly prescribed medications including virtually all of the major antiepileptic drugs (AED) can cause hepatotoxicity. Hepatic reactions to AEDs ranged from transient elevations of hepatic enzymes, without clinical signs or symptoms of hepatic dysfunctions, to fatal hepatotoxicity. In light of the potential toxicity, clinicians prescribing AEDs must be alert to

the possibility of serious hepatic reactions particularly in case of anticonvulsant polytherapy, each of which may contribute to the overall risk of hepatic reaction. The reactive role of different anticonvulsants in elevation of liver enzymes as a whole is difficult to assess on the basis of case reports alone. Previous studies have been undertaken in groups of epileptic patients most, if not all, of whom have been receiving polytherapy, with reference to one or two liver enzymes. In this study, we have examined the potential for hepatotoxicity with not only polytherapy but also single drug therapy with four major anti epileptic drugs in previously untreated epileptics, with reference to various liver enzymes, namely Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), Alanine Aminotransferase (ALT), Lactate dehydrogenase (LDH) and Gamma glutamyl transferase (GGT). We compared the chronic metabolic effects of these drugs on liver enzymes in five groups of patients treated with either phenytoin D(PH), phenobarbitone (PB), carbamazepine (CBZ) or valproic acid (VPA) alone and also in combination of two or there of these drugs in order to find out the comparative effect of mono and polytherapy and also to study which anticonvulsants most strongly affects the elevation of these enzymes and possibly cause liver damage and hepatotoxicity.

Material and Methods

A total of 225 subjects including 25 normals and 200 non alcoholic epileptic patients were selected from NIMHANS Outpatient Department. The epileptic patients were divided into 5 groups according to their medication. The groups included four single drug treatment cohorts; DPH, PB, CBZ, VPA and a multiple treatment cohort which included combinations of two or three drugs used in single drug treatment (Table I). The control group included volunteers from the staff of NIMHANS, who were age and sex-matched with the outpatient groups. Control group having any systemic disorder of receiving any drugs were excluded from the study since many drugs induce hepatic enzymes [4]. The patients were assessed clinically and type of seizure was assigned. However, before starting antiepileptic drug therapy the patients were referred for biochemical test to rule out any systemic disorder. The patients were put on various antiepileptic drugs and maintained regularly considering the efficacy of AED treatment with dose regimen.

During regular follow up once in 3 months, therapeutic drug levels were monitored to get peak therapeutic drug levels and also to avoid possible toxicity. Enzyme multiplied immunoassay technique (EMIT) was used to determine serum levels of AEDs by using SYVA EMIT Kits, Gilford spectrophotometer and auto pipetter diluter following the procedure described in their manual. Venous blood samples were collected from both patients and controls in the morning for biochemical analysis following 12 hours fasting and before the morning dose by the drug. The activity of enzymes like ALP [5], AST [6], ALT [6], LDH [6] and GGT [7] was analysed using Hitachi Auto analyzer-705 (Japan).

Table I

Table I

Statistical analysis

Data obtained from epileptic patients was analysed using student's paired 't' test and students 't' test.

Results

The levels of ALP, AST, ALT, LDH and GGT assayed in 25 normal individuals, 40 epileptics before medication and 200 epileptics during medication at various time intervals have been indicated in Table II. In general, the epileptic patients on medication showed higher serum levels of all the enzymes as compared to controls.

The distribution of patients on various drugs and the mean enzyme activity in epileptics under treatment with various AEDs for two years are indicated in Table III which also gives the levels of various enzymes in patients receiving more than one drug. During monotherapy the serum DPH levels were maintained below 20μ g/ml with an average of 23.2 7mgr g/ml with an average of 6.4μ g/ml and the serum VPA levels were maintained below 100μ g/ml with an average of 58.6μ g/ml. Similarly during polytherapy the serum drug levels were maintained at therapeutic range.

Table II - Comparison of enzyme activities in serum from normal and epileptic patients

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Values are (IU/L) mean ± SD in each group. Comparison using student's 't' test.

Table III - Biochemical indices in serum of patients on AED treatment for a period of 6 months to two years

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Values are in units (IU/L) and are mean ± SD.
Comparison before and after using student's paired 't' test.

During phenytoin therapy, 37% of patients showed elevated levels of ALP (50%, $P < 0.001$), 23% showed elevated AST (50%, $P < 0.001$), 20% showed elevated ALT (27%, $P < 0.05$) and 43% showed elevated levels of GGT (130%, $P < 0.001$).

During PB therapy, ALP levels were increased in 27% of patients (25%, $P < 0.05$), ALT in 15% of patients (46%, $P < 0.01$) and GGT in 27% of patients (108%, $P < 0.001$). During CBZ therapy, ALP levels were increased in 32% of patients (46%, $P < 0.001$), AST in 25% of patients (70%, $P < 0.01$) and GGT in 29% of patients (46%, $P<0.001$). With VPA therapy the elevated levels of ALP was seen in 41% of patients (45%, $P < 0.001$), AST in 33% of patients (84%, $P < 0.01$), LDH in 21% of patients (30% $P < 0.05$) and GGT in 33% of patients (133%, $P < 0.001$). In general, it was observed that the levels of almost all liver enzymes were increased after VPA treatment. During polytherapy, ALP levels were increased in 42% of patients (68%, $P < 0.001$), AST in 38% of patients (103%, $P < 0.0001$), ALT in 22% of patients (87%, $P < 0.01$), LDH in 16% of patients (42%, $P < 0.05$) and GGT in 48% of patients (155%, $P < 0.001$).

In general, the side effects of these drugs in relation to abnormal elevation of various liver enzymes were highest with polytherapy followed by VPA, DPH, CBZ and PB, which is indicated in the flow chart.

ALP Increased in Polytherapy > VPA > DPH > CBZ > PB

AST Increased in Polytherapy > VPA > CBZ > DPH > PB

ALT Increased in Polytherapy > DPH > PB > CBZ > VPA

GGT Increased in Polytherapy > DPH > VPA > CBZ > PB
LDH Increased in VPA > DPH > polytherapy > CBZ > PB

Discussion

Though, in general, it was observed that long term treatment with AED affects kuver enzymes, it was necessary to study the effect of individual drugs on liver enzymes separately. During this study the most common side effects or clinical symptoms of AEDs hepatotoxicity observed in epileptics were fever, rashes, jaundice and hepatomegaly which was in nearly 2/3rds of the patients. No sex dependence was observed with AEDs hepatotoxicity. With phenytoin, the interval between the initiation of therapy and the biochemical abnormalities was between 3-6 weeks in most of the patients, which indicates that the most likely mechanism is hypersensitivity to this drug. Mullick and Ishak [8] found that acute hepatic injury with phenytoin involved primarily hepatocellular degeneration and/or necrosis, which generally caused abnormal serum levels of bilirubin, transaminases, alkaline phosphatase etc. In this study it was observed that patients under treatment with only DPH for upto two years and who were maintained on therapeutic drug levels, show an abnormal elevation of ALP levels in 37%, AST in 23%, ALT in 20% and LDH in 17% of patients. However serum GGT was significantly elevated in 50% of patients. The elevation in GGT was as high as 200% in some cases. Elevation of GGT has been shown as a measure of hepatic injury. Orlowski [9] pointed out that, the measurement of serum GGT activity is useful as a sensitive indicator of liver disease, as GGT increases in the chronic stages of liver disease, with no change in the acute stage, contrary to the activities of transamines. The increase in GGT, after AED therapy, has been shown to be due to enzyme induction by these drugs causing increased synthesis of microsomal enzymes has come from studies on serum GGT. It has been shown that many epileptics receiving phenobarbitone, phenytoin and similar drugs have elevated serum GGT activity [10]. Spielberg et al [11] in an invitro study have identified arenoxide metabolite of phenytoin as a possible cause for hepatotoxicity. Such electrophilic metabolites may covalently interact with cell macromolecules, causing call death. Moreover, individual susceptibility to the effects of such metabolites may be genetically determined.

It is observed that PB at therapeutic level is not as toxic as DPH. Treatment with PB resulted in elevation of ALP, AST and LDH in about 25% to 35% of the patients. Serum GGT levels, however were increased in about 35% of the patients.

Adverse side effects with CBZ are not infrequent, although most are transient and can be controlled in a manner such that the treatment can be continued and the adverse effects will be outweighed by the benefits. Nevertheless, there are dermatologic, hematologic and hepatic side effects that should be recognised. CBZ induced hepatic abnormalities have been reported by several workers [12], [13], which occur in 5% to 10% of patients and consisted of elevation of liver enzymes. Gram and Bensten [14], reported that hepatitis due to CBZ exposure is a hypersensitivity reaction presumably mediated by immunological mechanisms. However, Horowitz et al [15], have described hepatitis after CBZ treatment in patients, most of whom had granulomatous hepatitis and sometimes associated with cholangitis. Hepatotoxic reactions to CBZ in two females, confirmed by liver biopsy and laboratory analysis, showed significant elevation of ALP, AST and creatinine [15]. In our group of patients this occurred in more than 25% of patients under treatment with CBZ. Biochemical analysis of these

groups of patients showed 40-50% increase in ALP, GGT, AST and ALT activity. However, these increased levels were reversible with withdrawal of medication. Similarly, a significant fall in serum calcium and phosphate concentrations and increased alkaline phosphatase activity has been reported by several workers with DPH, PB and CBZ, when given alone to epileptic patients for two years [16], [17]. Valproic acid, resulted in significant elevation of ALP and GGT levels in about 40% of the patients. In general, the incidence of increased hepatic enzyme levels was more with VPA as compared with DPH, PB and CBZ. A similar finding was observed by Jeavons [13], in which during monotherapy, the highest incidence of hepatotoxicity was reported in association with VPA and the lowest incidence with PB. It has been postulated that 4-en-VPA or one of its further metabolites may be responsible for the hepatic toxicity [18]. Fatal hepatotoxicity during VPA treatment was first reported in 1979 by Donat et al [19], and since then more than 100 such case reports have been published by Scheffner [20]. Abnormal elevation of ALP, AST, ALT and GGT was highest with polytherapy. The incidence of hepatotoxicity with polytherapy has been shown to be more than with monotherapy. This toxicity is directly related to the number of drugs being consumed and leads to problems of chronic toxicity [17], drug interactions, failure to evaluate individual drugs, and sometimes exacerbation of seizures. However, such of the undesirable metabolic and clinical consequences of polytherapy could be avoided by preliminary prospective trials on patients [21]. With this study it is concluded that AED polytherapy and among single drug therapy VPA has greater potential for developing hepatotoxicity. Hence care is needed during therapeutic management of epileptic patients. However, to avert AED induced hepatotoxicity, it is better to avoid prescribing polytherapy with phenytoin and valproate for patients with known hepatic disease; have a regular follow-up to regularly evaluate the liver status and take extreme care while treating children with AEDs, especially with VPA, DPH or combination of these drugs.

1.Reynolds E H, Chronic antiepileptic toxicity: A review
Epilepsia Page: 16: 319-352, 1975
2.Schmidt D (eds), *Adverse Effects of Antiepileptic Drugs. New York: Raven Press*1982
3.Beghi E & Dimascio R, Antiepileptic drug toxicity: definition and mechanism of action
Neurological Sciences Page: 87: 209-222, 1986
4.Conney A H, Pharmacological implication of microsomal enzyme induction
Pharmacological Reviews Page: 19: 317-366, 1967
5.Bailly M, Phung H T, Pourci M L, Amsellem L, Vassault A & Bretaudiere J B, Criteria for establishing a standardized method for determining alkaline phosphate activity in human serum
Clinical Chemistry Page: 23: 2263-2274, 1977
6.Mauck J C & Davis J E, *In: Clinical Laboratory Methods and Diagnosis. Sonnenwirth A C & Leonard*
Page: pp 305-323, 1980
7.Szasz G, In: Selected Methods of Clinical Chemistry (Eds) Cooper G R. Washington, D.C.
American Association for Clinical Chemistry Page: Vol. 8, 1977
8.Mullick F G & Ishak K G, Hepatic injury associated with diphenyllhydantoin therapy: A clinicopahtological study of 20 cases
American Journal of Clinical Pathology Page: 74: 442-452, 1980
9.Orlowski M, The role of gamma-glutamyl transpeptidase in the internal disease
Archives of Immunological Therapy & Experiment Page: 11: 1-61, 1963
10.Ewen L M & Griffiths J, Gamma-glutamyl transpeptidase elevated activities in certain neurological disease

American Journal of Clinical Pathology Page: 59: 2-9, 1973
11.Spielberg S P, Gordon G B, Blake D A, Goldstein D A & Herlong H F, Predisposition to phenytoin hepatotoxicity assessed in vitro
New England Journal of Medicine Page: 305: 722-727, 1981
12.Pellock J M, Carbamazepine side-effects in children and adults
Epilepsia Page: 28: 564-570, 1987
13.Jeavons P M, Hepatotoxicity of antiepileptic drugs
In: Antiepileptic Therapy: Chronic Toxicity of Antiepileptic Drugs. Oxley J, Janz D & Meinardi H (eds) I Page: 1-45, 1983
14.Gram L & Bensten K D, Hepatic toxicity of antiepileptic drugs: A review
Acta Neurologica Scandinavica Page: 63: 81-90, 1983
15.Horowitz S, Patwardhan R & Marcus E, Hepatoxic reactions associated with carbamazepine therapy
Epilepsia Page: 29: 149-154, 1988
16.Shorvon S D, Chadwick D, Galbraith A W & Reynolds E H, One drug for epilepsy
British Medical Journal Page: 1: 474-476, 1978
17.Reynolds E H & Shorvon S D, Mionotherapy or polytherapy for epilepsy
Epilepsia Page: 22: 1-10, 1981
18.Michael B, Michael V G, Michael D & Robert B D, Valproate metabolites and hepatotoxicity in an epileptic population
Epilepsia Page: 298: 543-547, 1988
19.Donat J F, Bocchini J A, Gonzales E & Schwendiamnn R N, Valproic acid and fatal hepatitis
Neurology Page: 29: 273-274, 1979
20.Scheffner D, St. Konig, Rauterberg R I, Kochen W, Hobmann W J & St. Unkelbch, Fatal liver failure in 16 children with valproate therapy
Epilepsia Page: 29: 530-542, 1988
21.Delaportas C I, Marshall W, Galbraith A W, Sharvon S D & Reynolds E H, The evaluation of chronic toxicity in previously untreated patients on phenytoin or carbamazepine
*Communication to the 11th Epilepsy International Symposium, Florence*1979