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Mathew George
Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla-689107, Kerala, India

Lincy Joseph
Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla-689107, Kerala, India

Preethi Christina Jose
Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla-689107, Kerala, India

Correspondence
Preethi Christina Jose
Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla-689107, Kerala, India

A review article on assessing the effect of antiepileptics and statins on liver enzymes in epileptic patients

Mathew George, Lincy Joseph, Preethi Christina Jose

Abstract
A number of drugs are available in the market causing hepatotoxicity. The present review is aimed on evaluation of effect on liver enzymes induced by anti-epileptics and statins in epileptic patients. Drug-induced liver injury associated with antiepileptic drugs (AED) is well recognized. Statins are among the most widely prescribed medications for primary and secondary prevention of cardiovascular disease around the world. Asymptomatic elevations in liver enzymes are seen in patients treated with statins due to a pharmacodynamic effect of lipid lowering. Co-medication of anti-epileptics and statins may have effect on liver enzymes in epileptic patients. Monitoring or liver enzymes has to be done by liver function tests including tests for ALT, AST, bilirubin, alkaline phosphatase, LDH.

Keywords: Liver, Hepatotoxicity, Epilepsy, Anti-epileptics, Statins

Introduction
The International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) defined an epileptic seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Epilepsy is a syndrome of different cerebral disorders of the Central Nervous System (CNS) which is characterized by excessive discharges of large numbers of neurons [1]. It is very disabling condition, rendered especially disturbing because of its unpredictability and its being a common neurological disorder worldwide.
The risk factors for developing seizure can be broadly classified under three headings.
- ❖ Metabolic Or Chemical Imbalance
- ❖ Structural Defects
- ❖ Infections Or Inflammatory Reactions

Seizures are mainly classified as: generalised seizures and partial seizures. Generalised seizures include absence, myoclonic, tonic-clonic and atonic seizures. Partial seizures include simple partial seizures and complex partial seizures.

Hepatotoxicity
Hepatotoxicity is defined as the damage to the liver caused by drugs or chemicals. There are many substances capable of damaging the liver with several very different mechanisms. There are many chemical agent that cause hepatotoxicity and these agents are called Hepatotoxins. These cause hepatotoxicity by the generation of free radicals and damage the liver cells and cause many liver diseases [2].
The liver is the primary organ for drug metabolism and elimination for many antiepileptic drugs (AEDs) and thus is subjected to drug-induced toxicity. There is a wide range of hepatotoxic reactions, from mild and transient elevations of hepatic enzymes to fatal hepatic failure. Liver enzymes can serve as markers of hepatocellular injury e.g. aspartate aminotransferase (AST), alanine aminotransferase (ALT) or of an obstruction in the bile flow cholestasis e.g. alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT).
Antiepileptic drugs like carbamazepine (CBZ), valproic acid (VPA) and phenytoin (PHT) produce many serious reactions. When compared with other consistently known hepatotoxic drugs, the hepatotoxicity induced by antiepileptic drug can lead to death or an acute liver failure which could imperatively require liver transplantation. The hepatotoxicity induced by antiepileptic drug occurs either because of production of reactive toxic metabolite/s or because of induction of immunoallergic reactions. Carbamazepine, phenytoin and sodium valproate are associated with mild elevations of liver enzymes, which may occur in up to 50% of patients.

Statins are among the most widely prescribed medications for primary and secondary prevention of cardiovascular disease around the world. Asymptomatic elevations in liver enzymes are common in patients treated with statins due to a pharmacodynamic effect of lipid lowering, but clinically significant liver injury is extremely rare.

Raghda *et al.* (2013) [1] conducted a study on "effect of antiepileptic drugs on liver enzymes" to assess the effect of carbamazepine, sodium valproate and phenytoin on serum liver enzymes in 49 epileptic patients admitted to the neurology outpatient clinic at Beni-Suef University between February 2010 and June 2011. The patients were separated into group I (16 patients) treated with 200–1200 mg/day carbamazepine; group II (16 patients) treated with 200–800 mg/day sodium valproate; and group III (17 patients) treated with 200–400 mg/day phenytoin. Serum liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were determined. Hepatic enzymes abnormal values were seen in 51.9% (n = 27) in the three study groups. In group I, the alterations at ALP enzyme were 50% (n = 8). In group II, the alterations at ALT were 6.25% (n = 1) and at ALP were 62.5% (n = 10). In group III, the alterations at AST were 5.88% (n = 1), at ALT were 17.65% (n = 3) and at ALP were 23.53% (n = 4). There was a statistically significant positive correlation between the dose/kg of carbamazepine and the serum level of the drug, a statistically significant positive correlation between the dose/kg of sodium valproate and AST and a statistically significant negative correlation between the duration of administration of sodium valproate and AST. There was also a statistically significant negative correlation between the duration of administration of carbamazepine and AST and ALP. In conclusion, sodium valproate was more hepatotoxic than carbamazepine which was more hepatotoxic than phenytoin. It also concluded that the more is the dose/kg of sodium valproate, the more is the elevation of AST, the more is the dose/kg of carbamazepine and the more is the serum level of carbamazepine. In addition, during the initiation of antiepileptic drugs, the liver enzymes were elevated due to the enzyme inducing property of some of them(1).

Syed *et al*. (2006) [3] conducted a study on "anti epileptic drugs and liver disease" to assess liver functions and hepatotoxicity during anti epileptic drug therapy. A few weeks to a month's therapy with, carbamazepine and phenytoin lead to a modest elevation of ALT, AST, ALP and GGT. Fever, transient skin rash, eosinophilia and lympadenopathy were associated features. A transient and asymptomatic elevation of liver enzymes occured in 25–61% of patients receiving CBZ. Hepatotoxic reactions of CBZ occured within 3–4 weeks after the initiation of therapy. GGT elevated in 50–90% of patients on PHT therapy. Elevation of AST and ALP were considered as more specific markers of liver disease than ALT and GGT. Biochemical features of PHT hepatotoxicity are variable but generally include abnormal serum bilirubin, transaminases, and ALP levels, as well as eosinophilia and leukocytosis. The idiosyncratic hepatic toxicity to VPA usually occured during the first 2–3 months of therapy and lead to reduced alertness, vomiting, hemorrhage, increased seizures, anorexia, jaundice, edema, and ascites. In summary the study concluded that VPA associated hepatotoxicity in adults was rare but potentially serious diagnosis. Study found that mostly hepatic toxicity is idiosyncratic or part of a hypersensitivity reaction. Dose dependent hepatotoxicity is rare and usually reversible with prompt discontinuation of the offending agent.

Dharmesh *et al.* [4] (2013) conducted a study on "liver enzymes activity during sodium valproate therapy on epileptic patients". The study was conducted at Department of Biochemistry, Govt. medical college & Sir Takhtsinhji General Hospital, Bhavnagar Gujarat. In the study 75 known patients of Epilepsy were enrolled and subjected to various biochemical investigations initially and after 3 months of treatment with Sodium Valproate, level of Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase and Pseudocholinesterase were analyzed. The levels of ALT and AST were significantly increased in patients of epilepsy after administration of Sodium Valproate for 3 months. Aminotransferase levels in Epilepsy patients significantly increased and Pseudocholinesterase levels were significantly decreased, but there were no statistical significant changes in the levels of other liver enzymes like alkaline phosphatase. Enzymes activities were expressed as IU/L. Graph pad instat 3 demo version software was used for statistical analysis. Descriptive statistics were shown as mean ± standard deviation. Mean enzyme levels of pre- and post-treatment periods were compared by paired t-test. Normal distribution was tested and data was not found to follow normal distribution. Hence, non-parametric wilcoxan matched –pairs signed ranks test was applied to compare each parameter. *P* value less than 0.05 was considered significant. It was observed that out of 75 patients (67%) of Epilepsy 50 had significant increase in ALT level (P<0.001) & 72 (96%) had significant increase in AST level (P<0.001). On other hand Pseudocholinesterase levels was significantly decreased in 33 patients (44%) of Epilepsy. The study concluded that patients of epilepsy treated with sodium valproate had significantly higher levels of aminotransferases, which suggest a need for monitoring of hepatic enzymes in patients receiving this drug.

Kashinath *et al.* (2014) [5] conducted a study on the "effect of phenytoin sodium on liver function tests". Thirty seven patients suffering from Grandmal epilepsy who attended the neurology O.P.D. of Wenlock Hospital were selected for study. The patients belonged to age group of 20 to 30 years. There were 20 males and 17 females, 25 patients were receiving 200 mg daily and 12 patients receiving 300 mg daily. Ten healthy volunteers of same age group who were the control for the study. There were five males and five females. The period of exposure to drug varied from one year to five years. 10 ml blood was collected from each patient, 2 ml of serum was extracted from each sample, serum phenytoin level was measured using U.V. spectrophotometer, Bausch and Lamb 21 by the method of Dill. 5 ml of blood was collected to measure following biochemical parameters:

1. Serum Aspartate Transaminase. (AST)
2. Serum Alanine Transaminase. (ALT)
3. Serum Alkaline Phosphatase

The study was conducted to evaluate the effect of Phenytoin sodium on liver function tests using serum AST, serum ALT, serum ALP as parameters. Mean value of serum ALP in epileptic patients receiving Phenytoin sodium wass 186.67 which is significantly higher than control group (106.3) p<0.001. The results of the study showed a significant increase in the levels of serum ALP in the epileptic patients on Phenytoin sodium as compared to control group. This increase in serum ALP could be a result of cholestasis induced by drug or as a consequence of hepatocellular toxicity.

Mark *et al.* (2014) [6] conducted a study on the Spectrum of Statin Hepatotoxicity: Experience of the Drug-Induced Liver

Injury Network. The aim of this study was to report the presenting features and outcomes of 22 patients with clinically apparent liver injury due to statins. Among 1,188 cases of drug-induced liver injury enrolled between 2004 and 2012 in a prospective registry by the U.S. Drug Induced Liver Injury Network, 22 were attributed to a statin. All patients were evaluated in a standard fashion and followed for at least 6 months after onset. The median age was 60 years (range 41-80), and 15 (68%) were female. The latency to onset of liver injury ranged from 34 days to 10 years (median5155 days). Median peak levels were alanine aminotransferase 892 U/L, alkaline phosphatase 358 U/L, and total bilirubin 6.1 mg/dL. Nine patients presented with cholestatic hepatitis and 12 patients presented with hepatocellular injury, of which six had an autoimmune phenotype. Nine patients were hospitalized, four developed evidence of hepatic failure, and one died. All commonly used statins were implicated. Four patients developed chronic liver injury, of which three had an autoimmune phenotype of liver injury. Standard descriptive statistics were used to summarize the data including means and standard deviations (SD), medians, and ranges for continuous variables, and frequencies and percentages for categorical variables. Chi-square tests (or Fisher exact test for situations with small frequencies) and nonparametric tests were used to test the difference between injury types for categorical and continuous variables, respectively. $P<0.05$ was considered statistically significant. All calculations were performed using SAS v. 9.2. Drug-induced liver injury from statins is characterized by variable patterns of injury, a range of latencies to onset, autoimmune features in some cases, and persistent or chronic injury in 18% of patients, most of whom have an autoimmune phenotype.

Bjornsson *et al.* (2012) [7] conducted a study on "hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing". Reports on adverse reactions suspected to be due to statins received by the Swedish Adverse Drug Reactions Advisory Committe 1988–2010 were analyzed. The most common types of ADRs suspected were DILI in 124/217 (57%) cases. A total of 73/124 (59%) cases had at least possible relationship, median age 64 years (57–73), 55% males, whereas 25/124 cases (20%) were excluded due to mild elevations of liver tests and 26 due to unlikely relationship and/or lack of data. A statin-related DILI episode was reported in 1.2/100,000 users. Atorvastatin was implicated in 30/73 (41%) cases, simvastatin in 28 (38%), fluvastatin (15%), and others. Two patients died of acute liver failure, one underwent liver transplantation and 25 (34%) had jaundice. Three patients were rechallenged with the same statin producing similar patterns of liver injury. The median duration of therapy was 90 days (30–120), 120 (39–248) for atorvastatin, and 75 (30–150) for simvastatin (NS). Cholestatic/mixed injury was more common with atorvastatin, 17/30 (56%) than with simvastatin, 7/28 (24%) (p = 0.018). Most patients experienced liver injury 3–4 months after start of therapy. Atorvastatin was mostly associated with cholestatic liver injury whereas hepatocellular injury was more common with simvastatin.

Ramin *et al.* (2015) [8] conducted a study on "Evaluation of Atorvastatin Safety on Liver Function Tests, a Prospective Study". The aim of this study was to evaluate the safety of statins mainly atorvastatin on liver as estimated by liver aminotransferase assay. Patients with indication of atorvastatin were included in the study. Study was conducted in 250 patients with hypercholesterolemia and cardiac disease in cardiology ward or clinic of Modarres hospital. All the patients with clear indication for HMG-COA reductase took atorvastatin and after three months the level of aminotransferases were measured. Patients with history of alcohol use, known liver diseases, like hepatitis, decompensated heart failure or hemodynamic instability, taking medications with the elevation of liver enzymes as their side effects like valproate, were excluded. Study also excluded patients with prior elevated liver enzymes, but giving another class of lipid lowering agent due to ethical consideration. It was a before and after study that the serum level of transaminases were measured both before and after taking atorvastatin. All statistical analysis were performed by SPSS version sixteen. Student t–test was used for evaluating the relationship among quantitative variables of the study and Chi square of qualitative ones. As a before and after study all the patients underwent serum level measurement of aminotransferases at the beginning and after three month of taking the drug. The incidence of increased aminotransferase level in patients on atorvastatin was 18 percent. Ten patients from all of 250 patients (4%) had more than 3 times increase in liver transferases that the medication was discontinued. Two percent for patients taking less than 80 mg atorvastatin and 5 percent of patients on 80 mg of the drug had more than 3 times elevation in aminotransferase level. Age distribution of the patients was between 40 to 80 years old in 86.6%. Age and sex had no impact on atorvastatin induced elevation of transaminases.

Conclusion

Anti-epileptics are important class of drugs used for epilepsy. Statins are drugs used as lipid lowering agents. Among the different drugs that induces hepatotoxic effects, effect induced by co-medication of anti-epileptics and statins in an epileptic patient is much less studied. This review gives an overview of hepatotoxic effects induced by anti-epileptics and statins as individual drugs. The importance of evaluation of hepatotoxicity in patients taking both antiepileptics and statins can be magnified by carrying out further studies on assessment of serum liver enzymes in epileptic patients.

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