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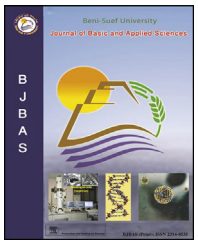

Full Length Article

Effect of antiepileptic drugs on liver enzymes

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ABSTRACT

This study was conducted 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), alkaline phosphatase (ALP) and serum level of antiepileptic drug were determined. No patient developed clinical symptoms of liver disease. 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. The routine screening of hepatic enzymes level during the chronic use of antiepileptic drugs is recommended.

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1. Introduction

Epilepsy is not a disease, but a syndrome of different cerebral disorders of the Central Nervous System (CNS) which is characterized by excessive discharges of large numbers of neurons (Nikalje et al., 2011). It is very disabling condition, rendered especially disturbing because of its unpredictability and its being a common neurological disorder worldwide (Ahmad, 2011).

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 (Arroyo and de la Morena, 2001).

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). Although these enzymes are elevated in liver disease, the elevation can also be secondary to enzyme induction without hepatic pathology (Ahmed and Siddiqi, 2006). In particular, antiepileptic drugs have many serious reactions, as seen with carbamazepine (CBZ), valproic acid (VPA) and phenytoin (PHT). Though relatively rare, 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 (Lee, 2003; Bjornsson, 2008). Such AEDs (CBZ, PHT and VPA) are associated with mild elevations of liver enzymes, which may occur in up to 50% of patients. These elevations are usually transitory or dose-related and do not appear to be associated with hepatocellular injury.

Usually, hepatotoxicity is associated with other clinical manifestations of drug allergy (fever, rash and eosinophilia). This reaction is typical of CBZ and PHT. Another idiosyncratic hepatotoxic reaction comes from hepatotoxic metabolites because of aberrant metabolism. This reaction has been observed with VPA (Arroyo and de la Morena, 2001).

A more than two to threefold increase in liver enzymes during AED therapy should caution the physician of a potential of coexistent liver disease. If subsequent follow-up reveals a progressive increase in the values of the enzymes, investigations for coexistent liver disease are warranted and may require a switch to an alternative AED (Ahmed and Siddiqi, 2006). Therefore the aim of the present work was to study the effect of antiepileptic drugs on liver enzymes.

2. Subjects and methods

2.1. Subjects

This study was conducted on 49 subjects selected from outpatient clinics at Beni-Suef University Hospital. In this cross-sectional study, there were 3 groups of patients: **Group I**: included 16 epileptic patients on carbamazepine medication with daily dose ranging from 200 to 1200 mg. **Group II**: included 16 epileptic patients on sodium valproate medication with daily dose ranging from 200 to 800 mg. **Group III**: included 17 epileptic patients on phenytoin medication with daily dose ranging from 200 to 600 mg.

2.2. Inclusion criteria

The study included epileptic patients receiving one of the following antiepileptic drugs (carbamazepine, sodium valproate or phenytoin) from at least 6 months.

2.3. Exclusion criteria

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

2.4. Through clinical assessment

Subjects included in this study were subjected to careful history taking, general and neurological examination "according to standardized neurological sheet" including the name, age, gender, weight of each epileptic patient, the duration of therapy and the daily dose of antiepileptic drug.

2.5. Laboratory work up

All subjects included in this study were subjected after two hours of the antiepileptic drug's administration to the following laboratory investigations:

1) Serum liver enzymes including:
   a) Alanine aminotransferase (ALT) which has a reference range of 10–55 U.
   b) Aspartate aminotransferase (AST) which has a reference range of 10–40 U/L.
   c) Alkaline phosphatase (ALP) which has a reference range of 45–115 U/L.
2) Serum level of the antiepileptic drug.
   a) Carbamazepine serum level which has a reference range of 4–12 μg/ml.
   b) Sodium valproate serum level which has a reference range of 50–100 μg/ml.
   c) Phenytoin serum level which has a reference range of 10–20 μg/ml.

According to the reference range of either the antiepileptic drug's serum level or the liver enzymes serum level, the epileptic patients in each study group were classified into those with normal and those with abnormal serum level. Finally, the abnormal values of serum liver enzymes of each antiepileptic drug were compared with each other to rank these antiepileptic drugs according to their hepatotoxicity.