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Hepatotoxicity Induced by Prolonged Use of Phenobarbital: A Case Report

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ABSTRACT

Drugs can induce almost all forms of acute and chronic liver disease, with some drugs more than one type of hepatic reaction. Many drugs cause elevate liver enzymes with apparently no clinically significant adverse effect. Drug induced liver injury is a diagnosis of exclusion that rests upon ruling out other common causes of liver disease. Hepatotoxicity has been reported with agents such as anti-tubercular drugs, NSAIDs, hypolipidimics, antiepileptic drugs etc., there are few evidences of hepatotoxicity with Phenobarbital on prolonged use. We here report a case of hepatotoxicity induced by prolonged use of Phenobarbital in a 30 year old female patient of enteric fever, having increased liver enzymes.

Key words: Hepatotoxicity, Phenobarbital, Anti-epileptic drugs, Hepatic reaction, Liver disease.

INTRODUCTION

Hepatotoxicity is a medical term for damage to the liver caused by a medicine, chemical, herbal or dietary supplements. Antiepileptic drugs (AEDs) are no longer restricted to the treatment of epilepsy. These are widely used in a broad spectrum of psychiatric and neurological disorders. Liver plays a major role in the metabolism of a majority of these drugs. [1] Almost all the AEDs with the exception of Gabapentin and Vigabatrin undergo hepatic biotransformation. Phenobarbital is predominantly metabolised by the liver. Long-term administration of phenobarbital has been reported to cause hepatic injury in dogs. [2] Phenobarbital induces hepatic enzymes, and it may be difficult to distinguish the effect of enzyme induction on serum liver enzyme activities from actual hepatic damage. [2] Phenobarbital (PB) is the oldest antiepileptic drug in common use. [3] Some prospective studies suggest that less than 1% of subjects develop elevations in serum aminotransferases levels during long-term Phenobarbital therapy. Because of the variability of manifestations and the lack of specific diagnostic markers for drug induced liver injury, attribution of causality to a specific medication is difficult and depends upon identification of a typical clinical signature and exclusion of other causes of liver disease. Drug induced liver injury is a diagnosis of exclusion that rests upon ruling out other common causes of liver disease, and knowledge of the pattern of injury associated with the specific drug. [4]

Mechanism of injury: The mechanism of Phenobarbital hepatotoxicity is thought to be hypersensitivity or an immunological response to a metabolically generated drug-protein complex.

Outcome and management: Phenobarbital hepatotoxicity is usually rapidly reversible with improvements beginning within 5 to 7 days of stopping the drug and being complete within 1 to 2 months. In cases of severe injury, progression to acute liver failure and death can occur. [4]

CASE PRESENTATION

A 30 year old female patient admitted in female medical ward with complaints of

fever and giddiness since 3 days and vomiting 5 to 6 episodes per day. She was apparently normal 3 days back and developed fever which is associated with intermittent chills, giddiness which increases on walking and sudden onset, vomiting was watery with non-blood stained. She was a known case of epilepsy on T. Phenobarbital 60mg 1-0-1 frequency since from 12 years. She had a last episode of epilepsy 1month back. She was experiencing decreased appetite. She was not having any history of loose stools, abdominal pain or pedal oedema. She was a non alcoholic. The patient was well built and nourished. In PICCLE, icterus was present. Clinical examination including general and systemic was done and were found to be normal except tenderness in abdomen. The routine baseline investigation including CBC, LFT, RFT, electrolytes were done. Elevated lymphocytes (75%) and Decreased neutrophils (25%) and widal test was showing positive results. Based on this, they have done a provisional diagnosis it as enteric fever. Advised IV Fluids 2 pint IV, Inj. Ondansetron 4mg IV 1-0-1, Inj. Pantoprazole 40mg IV 1-0-0, Tab. Paracetamol 500mg PO 1-1-1, Inj. Paracetamol 1g IV SOS, Inj. Ceftriaxone 1g IV 1-0-1. But there was elevated liver enzymes (AST-320 U/L, ALT-280 U/L), and bilirubin levels (total bilirubin-5.5 mg/dL, direct bilirubin-1.6 mg/dL) and USG abdomen showing spleenomegaly. Clinicians ruled out all possible causes (risk factors like pre-existing liver disease, age and sex related problems, polypharmacy, concurrent disease effects etc..,) for these manifestations and suspected as hepatotoxicity induced by prolonged use of Phenobarbital. Hence they withdrawn the offending drug and given treatment for enteric fever. The LFT parameters start to get decrease after withdrawal of Phenobarbital i.e. AST-171 U/L, ALT-196 U/L, total bilirubin-3.5 mg/dL, direct bilirubin-2.6 mg/dL after 4 days. Based on this, causality assessment was made using WHO scale.

DISCUSSION

Epilepsy is a disorder that is best viewed as a symptom of disturbed electrical activity in the brain, which may be caused by a wide variety of aetiologies. [I] Various AED are used to treat epilepsy. Phenobarbital is a sedative and hypnotic and first effective organic antiseizure drug belongs to barbiturate class of drugs which is used to treat insomnia, for sedation and can also be used as an AED. [II,4] drugs can induce almost all forms of acute and chronic kiver disease. [III] Phenobarbital is having ataxia, hyperactivity, headache, unsteadiness, nausea as common side effects. Prospective studies suggest that less than 1% of subjects develop elevations in serum aminotransferases levels during long-term Phenobarbital therapy. In some cases, hepatic involvement is more prominent with marked elevation in serum enzyme levels, jaundice and even signs of hepatic failure. We hereby reported a case of hepatotoxicity induced by prolonged use of Phenobarbital. Enteric fever may also affect liver but only after 7-14days of infection, but in this patient the liver related manifestations were within 3 days of infection.

CONCLUSION

In conclusion, our case report provides additional information about the existence of a relationship between the use of Phenobarbital and the occurrence of hepatotoxicity when used for a long-term as an adverse effect though rarely seen. This adverse effect is very rare and usually harmful if left untreated. It is very important for the clinicians to investigate and rule out other causes of hepatotoxicity and to be aware of this unusual side-effect of Phenobarbital. Stoppage of the drug usually results in the subsidence of hepatotoxicity.

Abbreviations Used: NSAIDs- Non-steroidal anti-inflammatory drugs, AED-Anti-epileptic drugs, PICCLE- Palor, Icterus, Cyanosis, Clubbing, Lymphadenopathy, Edema, CBC-Complete blood count, LFT- Liver function test, AST- Aspartate aminotranferase, ALT- Alanine

aminotransferase, RFT- Renal function test, WHO- World Health Organisation.

INFORMED CONSENT:
Written informed consent was obtained from the patient for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST: None

STATEMENT OF HUMAN AND ANIMAL RIGHTS
All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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