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CASE REPORT

PHENYTOIN INDUCED SEVERE AGRANULOCYTOSIS AND HEPATITIS

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ABSTRACT

Phenytoin is an anti epileptic drug. It is the cornerstone in the treatment of epilepsy disorders. It causes many adverse drug reactions. Neurological complications are commonly observed. Rarely it may cause idiosyncratic reactions in the form of agranulocytosis, hepatitis. Though rare it may pose a serious problem. The treatment is withdrawal of phenytoin and use of appropriate antibiotic.

Key words: *Agranulocytosis, Hepatitis, Phenytoin.*

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INTRODUCTION

Phenytoin is a highly effective and widely prescribed anticonvulsant agent, but it can be associated with dose-related side effects and hypersensitivity reactions. Neurotoxicity is a well known side effect of phenytoin therapy. Hemoatological complications, some fatal, have occasionally been reported with phenytoin. These include thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblasticanemia have occurred, these conditions usually respond to folic acid therapy. Hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have alsobeen reported. Hepatitis is also rare complication.

Case report

A 50 years old male patient was admitted to the emergency department with generalised tonic, clonic seizures. He was started with phenytoin 300 mg daily. After about 8 days patient started having fever which was high grade associated with rigors. General physicl examination revealed oral thrush and hepatosplenomegaly. Hemogram revealed Hb of 9 gm%, TLC 2000/mm^3, $DLCP_5L_{62}M_{33}E_0$, platelet count 2 lakhs/mm^3. Peripheral blood film was suggestive of neutropenia without any other significant abnormality. Bone marrow aspiration showed M:E ratio of 3:1 and no blast cells. Liver function tests revealed serum bilirubin 1.2 mg% direct 0.4 mg%, SGOT-60 IU/l, SGPT-112 IU/l, alkaline phosphatise 890 KA units. Other serological tests viz. viral markers, blood culture, widal test were within normal limits.

Keeping in view above findings, a diagnosis of phenytoin induced neutropenia was considered. Phenytoin was stopped and patient was started with sodium valproate. He was also put on ceftazidime. He improved both clinically and hematologically. On fifth day he became afebrile with a TLC of 8000/cumm. Also LFTs became normal on 7th day. By this time phenytoin levels were within normal limits.

DISCUSSION

The mechanism can be explained as toxic or immune phenomenon. First, ''toxic'' effectshave remained elusive in physiological or molecular terms.Whether they have represented neutrophil necrosis, apoptosis, autophagy, or other processes has not been docu-mented. Second, immune mechanisms have largely beendescriptive and have

rarely been clarified from a cause-effect perspective; for example, the presence of antibodiesto neutrophils might be en epiphenomenon rather thancausative[1]. Other possible explanation may be the generation of ROS(reactive oxygen species) by the NADPH oxidase and myeloperoxidase of neutrophils, which are important for the oxidationof drugs. This generation of ROS, initiated within secondsafter stimulation of neutrophils and lasting for hours, leadsto the production ofhypochlorous acid, HOCl.This acid represents a major system for oxidizing a susceptible drug to a reactive product. That may be covalentbound to cellular molecules and, subsequently, the complex can serve as a hapten, inducing antibodiesmainly directed against neutrophils andneutrophil precursors in the bone marrow[2,3].

Immune-complex, hapten and autoimmune mechanismsare three main mechanisms for drug-induced immune agranulocytosis leading to cell lysis, formation of leuko agglutinins or reticuloendothelial elimination. T-lymphocyte mediated reactions have also been implicated, some act by perforin and granzyme production by cytotoxic T-cellswhile others may act by induction of large granular lymphocyte(LGL) associated reactions[4,5,6].

The mechanism of hepatotoxicity is not completely understood. An immunological reaction or metabolite acting as a hapten may be the possible explanation. This complication is reversible and asymptomatic.The mechanism responsible for hepatitis is unclear. Phenytoin is metabolized to arene oxide in cytochrome P-450 in the liver, which is normally metabolized by epoxidehydrolyzes. It has been hypothesized that if the patient has a genetic or acquired defect in epoxide hydrolase activity, the metabolism of arene oxides will be impaired, and the resulting accumulation of the oxide can lead to hepatic injury[7,8,9].Phenytoin induced severe agranulocytosis and hepatitis is rare occurance, so present case report is to make physician aware about this entity and keeping possibility of phenytoin toxicity in any patient presenting with agranulocytosis and/or hepatitis.

CONCLUSION

Phenytoin is an commonly used antiepileptics. Though, rarely it may be associated with life threatening complications like agranulocytosis, hepatitis. Mechanism of their development is not completely understood but thought to be probably due to toxic or immune mediated mechsnisms. Treatment is supportive. *Professor ** Post Graduate student;

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