

CASE REPORT

**PHENYTOIN SODIUM INDUCED CHRONIC LIVER DISEASE - A RARE CASE REPORT****K. Sravani *, P. Venkata Ramana, Y. Parimala, M. Balaji Naik, S. Mohammed Ishak**

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Submitted on: 08.09.18;**Revised on: 27.09.18;****Accepted on: 08.10.18****ABSTRACT:**

Phenytoin is a broad spectrum anti-epileptic drug effective in the management of status epilepticus, Complex partial and generalized tonic clonic seizures. Phenytoin can produce a number of adverse effects on structure and function of hepatocytes. A 39 years female patient was admitted in female medical ward with chief complaints of right quadrant upper abdominal pain which is insidious in onset and gradually progressive, abdominal distension since 2 weeks, yellowish discoloration of eyes associated with fever. Patient had a history of phenytoin use and she got hospital admission due to phenytoin adverse effects on liver. Better vigilance is necessary for implementation of safe and effective treatment for each individual patient.

KEY WORDS: Phenytoin, Chronic liver failure, Causality assessment, Orthotropic liver transplantation (OLT), Vigilance.

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INTRODUCTION:

Phenytoin is a hydantoin derivative through broad spectrum anti-seizure activity effective in the management of status epilepticus, Complex partial and generalized tonic clonic seizures. Phenytoin acts by promoting sodium efflux from neurons located in the motor cortex reducing post-tetanic potentiation at synapses. The reduction of potentiation prevents cortical seizure foci spreading to adjacent areas, stabilizing the threshold against hyper excitability. Phenytoin is completely absorbed from gastro intestinal tract, highly bound to plasma proteins, metabolized by liver, excreted through urine .Phenytoin has a number of effects on hepatic function, it mainly causes elevation of hepatic transaminases in plasma and often occurs asymptotically in the course of the first several months of therapy.^{1,2} It also causes hypertrichosis, ataxia, constipation, mood changes, gingival hyperplasia, psychosis, megaloblastic anemia but a rare and serious complication is Chronic liver failure which is repeatedly fatal. This is a case report of 39 years female patient, was admitted with chronic liver disease with ascites with portal hypertension in female medical ward. More than 100 cases of liver injury due to phenytoin (diphenyl hydantoin) have been published and a characteristic clinical pattern (signature) of injury has been described. The estimated frequency ranges from 1 per 1000 to 1 per 10,000 and probably varies by race and ethnicity. The serum enzyme elevations can be hepatocellular, although mixed patterns are probably. Drugs, toxins, viruses and mixed situations such as metabolic disorders and cardiovascular diseases are the main causes of chronic liver failure. Orthotropic liver transplantation (OLT) is used progressively more

to recover patients with chronic liver failure even though medical supervision has enhanced. Phenytoin is extensively metabolized by the liver and excreted in urine. The risk of injury correlates with the presence of HLA-B*1502. Phenytoin is metabolized by CYP 450 system to arene oxide, which may represent the toxic or immunogenic intermediate & causes serious damage to hepatocytes.^{3,4,5,6}

CASE:

A 39 years female patient weighing 54 kilograms was admitted in female medical ward with chief complaints of right quadrant upper abdominal pain which is insidious in onset and gradually progressive, abdominal distension since 2 weeks, yellowish discolorisation of eyes 1 month back associated with fever, decreased urine output and constipation. Patient past medical history includes patient was a known epileptic since 12 yrs and is on medication with Tab.Phenytoin-100mg. Personal history of patient includes mixed diet, disturbed sleep and Bowel & Bowel habits includes constipation. Patient had family history of epilepsy. On general examination, the patient was conscious & coherent & on physical examination her vitals were found to be HR: 80 bpm, RR: 24 Cpm, BP: 110/70 mm of Hg. On systemic examination P/A: Bilateral edema. Patient laboratory parameters shows as follows
Ultrasound scan abdomen: Liver- hepatomegaly (14.7cm) and severe ascites. Liver function test: SGOT- 119 IU/L, Alkaline phosphatase - 143 IU/L. Based on the subjective and objective Her laboratory investigations shows increased SGOT levels (119 IU/L) and increased ALP levels(123 IU/L) & USG abdomen report shows gross ascites with hepatomegaly. Based on the subjective & objective evaluation the patient was diagnosed with Chronic

liver disease with portal hypertension with Ascites. The treatment was given as follows: On day1: Inj. pantop in a dose of 40mg was given twice a day, Inj. Lasix in a dose of 40mg was given twice a day, Syp. Lactulose in a dose of 10ml was given thrice in a day, Inj. Tramadol in a dose of 50mg was given twice in a day, Tab. Hepamerz in a dose of 150mg was given twice a day. On day2: Same medication was continued & Tab. Spiranolactone in a dose of 50mg was added once in a day. On day 3: Same medication was continued & was advised to take high protein diet. On day 4: Same medication was continued. On day 5: Same medication was continued & ascitic fluid was tapped. On day6: Same medication was continued & Inj. Cefotaxim in a dose of 1gm was given twice a day & it is newly added. On day7: Same medication was continued & syp. Astymin forte contains Vit. A, Vit B1, B2, B6 & B12 calcium pantothenate, folic acid, Nicotinamide, vit. C, vit. E, Leucine, L-isoleucine, L-lysine, L-Phenyl alanine, L-threonine) in a dose of 10ml was given twice a day and it is newly added. On day8: Same medication was continued. On day 9: Same

medication was continued & Tab. B. Complex in a dose of 67mg and Tab. Vit. C in a dose of 500mg was given once in a day and these are newly added. On day 10 11 12 & 13: Same medication was continued. On day 14: The patient was discharged with the following medication: - Syp. Lactulose in dose of 10ml was given twice in a day, Tab. Lasix in dose of 40mg was given twice in day, and Tab. Spironolactone in dose of 50mg was given twice in a day, Syp. Astymin forte in dose of 10ml was given twice a day & Tab. Pantoprazole in a dose of 40mg was given once in a day. Based on the above information here we have suspected that this is an ADR of Tab. Phenytoin and also the reason for hospital stay.

Causality assessment:

To evaluate the relationship between the drug and reaction, we have performed causality assessment by using scales like WHO causality assessment scale, naranjo's scale and karch lasagna scale and analysis of observed ADR (Table 1) & (Table 2).

Table1: Causality assessment of suspected ADR

ADR SCALE	WHO-UMC	NARANJO'S	KARSCH&LASAGNA
ASSESSMENT	Probable	Probable	Probable

Table 2: Analysis of observed ADR

SEVERITY ASSESSMENT	Moderate Level-4
PREVENTABILITY	Definite Preventable
PREDICTABILITY	Unpredictable

RESULTS & DISCUSSION:

Epilepsy is a collective chronic neurological condition characterized by continuing seizure activity (recurrent attack of seizures). These seizures are brief signs and symptoms of irregular, excessive or synchronous neurological activity of brain. If seizures happens repeatedly, neurons can be injured, which may leads to change in memory and cognitive functions. Epilepsy additional likely to occur in children or people over the age of 65yrs, however it can occurs at any time. Epilepsy is generally organized, but not healed with medication, even though surgery may also effect in different cases.⁷ These seizures are temporary signs and symptoms of irregular, too much or synchronous neurological activity. Phenytoin is highly effective in status epilepticus and also effective against complex partial and generalized tonic clonic seizures. In our case Phenytoin was given in status epilepticus for reducing hyper excitability. Generally it will cause common adverse drug reactions like Steven Johnson Syndrome, encephalopathy, ataxia, teratogenicity, and rare but serious complication is Chronic liver failure.^{8,9} In our case, patient had a history of usage of Phenytoin since 12 years and had developed chronic liver failure; this is the reason for hospital admission. After hospital admission as a clinical pharmacist we have identified adverse drug reactions as follows, the

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patient was under the medication with phenytoin, based upon the literature reviews and based on laboratory investigations we have concluded that this condition is due to the drug phenytoin and performed causality assessment, severity, preventability, predictability. After the identification we have immediately withdrawn the drug phenytoin and provided appropriate treatment. So, monitoring of liver function tests is necessary during treatment with phenytoin.

CONCLUSION:

Better vigilance is necessary for implementation of safe and effective treatment for each individual patient. In-order to prevent serious adverse drug reactions of this drug, dosage adjustment according to the bodyweight and frequency, close monitoring during treatment course, creating awareness, recognition of the problem and careful management of all patients who receive this medication are essential. If close monitoring is not provided during treatment course, which may lead to permanent disability, morbidity, mortality. This case differs from other cases reported in the literature that describe phenytoin-induced hepatic injury. The majority of these cases are accompanied by immune-allergic features. To our knowledge, there have been no reported cases in the literature resulting in phenytoin-induced chronic liver disease.

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