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Case Study

DRUG INTERACTION INDUCED PHENYTOIN TOXICITY: A CASE REPORT

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ABSTRACT

Phenytoin is a narrow therapeutic indexed antiepileptic drug. Many drugs competitively inhibit isoenzymes responsible for its metabolism when concurrently administered and increases the phenytoin plasma concentration leading to serious adverse effects. One such case is being reported with phenytoin toxicity due to concurrent administration of phenytoin and Isoniazid

Keywords: Drug Interaction, Phenytoin toxicity, Isoniazid

INTRODUCTION

Phenytoin is one of the most commonly used antiepileptic medications in clinical practice for generalized seizures.[1] It is known to cause a range of deleterious and erratic side effects, reported previously including nystagmus, ataxia, facial puffiness, urinary incontinence, enlargement of lips, hepatitis, rash and vomiting.[2,3] Drug interactions may alter phenytoin concentrations in plasma and become clinically very significant due to its narrow therapeutic index. The risk of Phenytoin toxicity increases among the patients concurrently receiving Isoniazid, due to impaired phenytoin metabolism by Isoniazid with an increased incidence up to 19%[4]

CASE REPORT

A 21 year old male patient belonging to the middle socio-economic status presented to the neurology outpatient department with complaints of decreased urine output, enlargement of lips, facial puffiness, vomiting, generalized body rashes, blurring of vision and unsteadiness of gait since 2 days.

His past medical history revealed that he was diagnosed with tubercular meningitis and generalized tonic clinics seizures for which he was hospitalized 3 weeks earlier. He had received Tab.Phenytoin 300 mg per day in divided doses and anti tubercular drugs (Isoniazid 300 mg, Rifampicin 450 mg, Pyrazinamide 1500 mg, Ethambutol 800 mg) once daily. After 3 months, the patient presented to the neurology department with complaints of blurring of vision, difficulty in walking, unsteadiness, generalized macular rashes over limbs, chest and back, vomiting, urinary incontinence and decreased urinary output. MRI scan of the brain and spinal cord did not reveal any organic/structural lesions. USG of abdomen including the KUB region was normal. Liver function tests showed a fourfold elevation in amino transferase levels. Other biochemical parameters were normal.

A provisional diagnosis was made of phenytoin toxicity and he was admitted to the hospital. Based on the clinical findings and other evidences, phenytoin and all anti tubercular medications were dechallenged and the patient was started on T. Levetiracetam 500 mg per day for epilepsy, Ondansetron 4 mg for vomiting, Fusidic acid cream for rash, Ursodeoxycholic acid 300 mg for hepatitis. Phenytoin assay showed that his serum Phenytoin levels were found to be > 40 mcg/ml (reference range: 15-20 mcg/ml). Ophthalmological examination revealed gaze included horizontal Nystagmus. After 2 weeks of hospitalization and withdrawal of Phenytoin and ATT, the patient showed a dramatic improvement in symptoms including the visual blurring episode, ataxia, vomiting, enlargement of lips, urinary incontinence and rash. Aminotransferase levels were also found normal in subsequent liver function tests.

DISCUSSION

Phenytoin is one of the most widely-prescribed antiepileptic drugs in clinical practice for the management of generalised tonic clonic seizures and complex partial seizures. It may also be used in the prevention of seizures following head trauma, and in ventricular arrhythmias. The absorption of phenytoin varies with dosage form and in the salt form absorption is rapid and more than 90%. It is highly protein bound and extensively metabolised by hepatic microsomal isoenzymes CYP2C9 and CYP2C19. Phenytoin follows zero order kinetics at therapeutic concentrations, because the rate of metabolism is close to the maximum capacity of the enzyme involved. Clinically effective serum level is usually 10–20 mcg/mL. With recommended dosage, a period of seven to ten days is adequate to achieve steady-state plasma concentration of phenytoin. When phenytoin is co-administered with Isoniazid, the serum concentration levels of phenytoin will significantly increase due to competitive inhibition of CYP2C19 by Isoniazid. A report from previous study suggests that consequences of drug interaction are manifested between 5-22 days.[4] In this patient, phenytoin toxicity was observed after 11 weeks. Investigations were carried out to exclude any structural organic cause for the clinical manifestations and found all negative. The symptoms experienced by the patient in question are understandable in terms of complex pharmacokinetics, narrow therapeutic index and individual variability in metabolism and elimination of phenytoin. This patient developed exaggerated side effects gradually over a period of 3 months after the concomitant use of phenytoin with Isoniazid, which can be explained by gradual elevation of the drug in the plasma over the time as the pharmacokinetic of the phenytoin follows ranging from 1st order kinetic to Zero order kinetic, hence even minor dosage changes can result in variable concentration as the elimination is saturated.

CONCLUSION

This case report serves as an alert to clinicians to remain clinically vigilant for such manifestations in patients when phenytoin and Isoniazid are concomitantly administered. While prescribing Isoniazid and phenytoin, a caution on dosage adjustment of phenytoin is advisable. Since specific guidelines for adjustment of dosage are not established, it is recommended that the required dosage of phenytoin in such situations be guided by the clinical symptoms as well as frequent neurological evaluation serum assay of phenytoin when ever indicated.

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