Phenytoin induced chorea in a pediatric patient: An interaction between phenytoin, phenobarbital and clobazam

Manish Barvaliya, Jayesh Sanmukhani, Tejas K. Patel, C.B. Tripathi

ABSTRACT

A 3-year-old female patient developed chorea possibly due to an interaction between phenytoin, phenobarbital and clobazam used for generalized tonic clonic seizures. Phenytoin withdrawal resulted in recovery within 24 hours. Post reaction computerized tomography (CT)-scan of brain was normal. Combined use of anti-seizure drugs and interactions between them may be responsible for the reaction. Therapeutic drug monitoring is important while prescribing two or more anti-seizure drugs.

KEY WORDS: Adverse drug reaction, anti-seizure drugs, chorea, drug interactions, phenytoin

Introduction

Chorea is the ceaseless occurrence of rapid, jerky, dyskinetic, involuntary flicking movement of hands, face, and other parts of body. Huntington’s disease (HD) and drugs account for more than 50% of such patients.[1] Basic pathology involved in chorea and other hyperkinetic movements is damage to various parts of basal ganglia that ultimately leads to disturbances in neurotransmission.[2] In chorea, there is degeneration of gamma aminobutyric acid (GABA) secreting neurons in the caudate nucleus and putamen of basal ganglia. The normal inhibition by GABA neurons is lost in globus pallidus, and substantia nigra resulting in over activity of excitatory transmitters causing the distortional movements.[3] Phenytoin sodium is an anti-seizure drug widely used for generalized tonic clonic seizures. Hyperkinetic movements are the rare adverse drug reactions of anti-seizure drugs. Few cases have been reported to cause hyperkinetic movements by various anti-seizure drugs.[1,3,4] Here, we report a case of phenytoin induced chorea in a child possibly due to interaction between anti-seizure drugs.

Case Report

A 3-year-old female patient weighing 10.5 kg was admitted in pediatric ward of Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat, with complaint of low grade fever for three days and convulsions with frothing, involuntary micturition, and altered sensorium for one hour. Patient was unconscious at the time of admission with normal pulse and respiratory rate. Blood pressure was 100/60 mmHg. Patient had a history of convulsions two days back. On admission, patient was treated with injection lorazepam (0.04 mg/kg) followed by injection phenytoin (5 mg/kg) intravenously to control the seizures. All investigations like total leukocyte count, differential leukocyte count, liver function tests, renal function tests, random blood sugar, and cerebrospinal fluid (CSF) examination were normal except hemoglobin (9.0 g/dl; reference value: 12.0 to 18.0 g/dl), positive C-reactive protein (CRP), and ionized calcium (1.01 mmol/l; reference value: 1.16 to 1.32 mmol/l). Injection phenytoin (5 mg/kg/day) and injection phenobarbital (5 mg/kg/day) intravenously were given for five days and tablet clobazam (0.75 mg/kg/day) was given for three days to control seizures. Seizures were controlled, but there was no improvement in patient’s sensorium. Provisional diagnosis of viral encephalitis was made. Injection acyclovir (40 mg/kg/day) and injection methyl prednisolone (2 mg/kg/day) were started as empirical therapy on 5th day. From 6th day, syrup phenytoin (30 mg/5 ml), 4 ml, 12 hourly, and syrup phenobarbital (20 mg/5 ml), 6 ml, 12 hourly, were started after stopping injectable anti-seizure drugs. On the 8th day, patient developed involuntary, continuous, uncontrolled, jerky movements of head and upper limbs, which was diagnosed as chorea. There was no family history of HD and diagnosis of viral encephalitis was not confirmed so it was suspected as drug induced chorea with phenytoin being an offending agent. Phenytoin was stopped and other medications were continued. After 22 hours of stopping
phenytoin, involuntary movements disappeared. Post reaction computerized tomography (CT)-scan of brain was normal. Patient was having an attack of convulsions two days after stopping phenytoin; hence, sodium valproate (15 mg/kg/day) was added to treatment. Patient became fully conscious on 10th day and discharged on 13th day.

Naranjo’s scale showed that the relationship between phenytoin and chorea was probable. According to Modified Schumock and Thornton’s criteria, this reaction was probably preventable and Modified Hartwig and Siegel’s scale showed that the reaction was moderately severe (level 3).

Discussion

Phenytoin is widely used for seizure disorders in adults as well as children. Chorea and hyperkinetic movements are the rare side effects of phenytoin. In this case, recovery on de-challenging the phenytoin therapy and normal laboratory investigations are in favor of diagnosis of the phenytoin induced chorea. Normal CT-scan report after emergence of reaction has ruled out any structural damage to basal ganglia. Involuntary movements caused by phenytoin are mainly related to its high plasma concentration (40-50 mg/l). Mechanism of chorea due to phenytoin is still not clear. Prolonged phenytoin therapy or its high plasma concentration is related with increased dopaminergic and serotonergic activity in basal ganglia that may be considered as a cause of chorea. Early identification and withdrawal of phenytoin may prevent the permanent damage to basal ganglia.

Phenytoin toxicity depends on the route of administration, duration, exposure, drug interaction, and dosage. Oral exposures are associated predominantly with CNS symptoms. Individuals with impaired metabolic or excretory pathways may exhibit early signs of toxicity. Phenytoin is predominantly metabolized by CYP2C9 and to a lesser extent by CYP2C19. Drugs that alter the functions of these enzymes can place the patient at risk of toxicity. Clobazam interferes with hepatic degradation of phenytoin. Addition of clobazam to the patients who had been taking maximum tolerable dose of phenytoin is reported to result in its intoxication. Phenobarbital also demonstrates a variable interaction with phenytoin.

Though, both are enzyme inducers, they may increase plasma concentration of each other by competitive inhibition of their metabolism. Acyclovir decreases plasma concentration of phenytoin due to interference in absorption. In our case, acyclovir was started parenterally on 5th day and is less likely to affect the plasma level of phenytoin. Use of phenytoin along with clobazam and phenobarbital may have resulted in increased plasma concentration of phenytoin due to an interaction between them which may have caused the reaction. Combined use of phenytoin and lamotrigine has been reported to cause the hyperkinetic movement disorder.A possible interaction between phenytoin, phenobarbital and clobazam may have resulted in chorea in this case. It is important that therapeutic drug monitoring should be done and drug interactions should be kept in mind especially when two or more anti-seizure drugs are prescribed. Early detection and withdrawal of suspected drug in such cases can help to prevent further harm to the patient.

Acknowledgement

We are very thankful to Dr. Monil Shah, Resident Doctor and Dr. Jayendra Gohil, Professor and Head, Department of Pediatrics, Sir Takhtsinhji General Hospital and Government Medical College, Bhavnagar, Gujarat for reporting this adverse drug reaction to the Pharmacovigilance Cell, Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat.

References


Cite this article as: Barvaliya M, Sanmukhani J, Patel TK, Tripathi CB. Phenytoin induced chorea in a pediatric patient: An interaction between phenytoin, phenobarbital and clobazam. Indian J Pharmacol 2011;43:731-2.

Source of Support: Nil. Conflict of Interest: None declared.