Phenytoin-induced bradycardia and hypotension

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Abstract:
Phenytoin is an anticonvulsant which is also a Class IB antiarrhythmic. Its common adverse drug reactions (ADRs) include gastrointestinal symptoms, psychiatric disorders, gingival hyperplasia, and rash. Bradycardia and hypotension following intravenous (IV) phenytoin are rare ADRs. We report the case of a 62-year-old female with subarachnoid hemorrhage and right bundle branch block, who developed sinus bradycardia and hypotension on administration of IV phenytoin. This case report serves as a note for caution on patient selection for the administration of phenytoin and highlights the need for specific guidelines on the same.

Keywords:
Hypotension, phenytoin sodium, sinus bradycardia

Introduction
Phenytoin is an anticonvulsant drug which can be used as a prophylactic agent in postcraniotomy patients to prevent convulsions. Common adverse drug reactions (ADRs) of the drug include skin and subcutaneous tissue disorders (40.5%) including Stevens–Johnson syndrome (6.4%), toxic epidermal necrolysis (2%), gingival hyperplasia (3%), gastrointestinal disorders (11%), psychiatric disorders (7.7%), and megaloblastic anemia (0.2%).[1] Although acute toxicity is usually characterized by severe central nervous system depression, cerebellar disorders, and vestibular defects, serious cardiac ADRs such as arrhythmias and hypotension can occur on intravenous (IV) administration of phenytoin.[2] Till date, 46,996 ADRs of phenytoin have been reported globally to Uppsala Monitoring Center (UMC), Sweden, through the World Health Organization (WHO) Program for international drug monitoring. This includes 11 cases of sinus bradycardia (frequency = 0.02%) and 378 cases of hypotension (frequency = 0.8%).[1] This is the only case of phenytoin-induced bradycardia and hypotension reported till date by our ADR monitoring center (AMC).

Case Report
A 62-year-old female was brought to the Emergency Department with a history of altered sensorium for 1 day following an episode of syncope. The patient had a history of occipitofrontal headache and vomiting of 2-day duration. Her blood pressure was 180/100 mmHg, and heart rate was 66/min at admission. In the electrocardiogram (ECG) recorded at admission, right bundle branch block was noted [Figure 1]. Computed tomography angiogram of the brain showed ruptured saccular aneurysm at the right internal carotid artery–middle cerebral artery junction, as well as hemorrhage in bilateral Sylvian and interhemispheric fissures. She was admitted under the neurosurgery department and was diagnosed to have ruptured berry aneurysm with subarachnoid hemorrhage.

Six hours after admission, the patient developed generalized tonic–clonic seizures
and was given slow injection of phenytoin sodium 1 g IV. About a minute after administration of the drug, she developed sudden-onset bradycardia, with a heart rate of 40 beats/min. Her blood pressure also dropped simultaneously to 90/60 mmHg. ECG recording showed sinus bradycardia with right bundle branch block [Figure 2]. She was managed with a fast infusion of injection normal saline 1000 mL and cardiopulmonary cerebral resuscitation. Serum electrolytes and prothrombin time- international normalised ratio (PT-INR) were within the normal range. The patient recovered within half an hour after the onset of reaction.

The following day, the patient underwent right pterional craniotomy and clipping of aneurysm, and postoperatively she was prescribed injection phenytoin 100 mg IV 8 hourly as the prophylactic anticonvulsant. She did not develop bradycardia or hypotension at this maintenance dose of phenytoin.

**Discussion**

On evaluation at our AMC, this case of phenytoin-induced bradycardia and hypotension was found to be a rare ADR, with a frequency of occurrence of 0.05%. This was a Type A ADR with seriousness categorized as “life-threatening.” Causality of the ADR was assessed as “probable,” using the WHO-UMC causality assessment scale.

Phenytoin has a narrow therapeutic index (10–20 mcg/ml) and saturable kinetics, which predisposes to the occurrence of toxicity. It is a Class IB antiarrhythmic agent which inhibits phase 0 inward intracellular sodium currents,
resulting in widening of the QRS complex in the extranodal cardiac tissue as well as slowing of conduction. Furthermore, relative refractory period is shortened, and ventricular automaticity is suppressed by phenytoin.[3] It is contraindicated in sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular block, and Adams–Stokes syndrome, where adverse cardiovascular reactions including severe hypotension and cardiac arrhythmias can develop.[4] There is a higher propensity for these ADRs in elderly patients with preexisting cardiovascular abnormalities.[2] Furthermore, the use of prophylactic antiepileptic agents may be unfavorable for patients with subarachnoid hemorrhage.[3] Hence, this patient was not a suitable candidate for receiving IV phenytoin. This seems to be a wrong choice of treatment in this patient.

There is a lacuna in guidelines for the use of anti-epileptics during the perioperative period in tertiary care centers. Caution should be exerted while administering the drug to a patient with preexisting cardiovascular rhythm disorder or structural abnormality, as to prevent phenytoin-induced ADR, for which such patients seem to be predisposed.[3,4] This case asserts the need for close cardiac monitoring while administering IV phenytoin and highlights the essentiality of a well laid-out guidelines for patient selection.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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