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Case Study

Phenytoin-Induced Ataxia and Diplopia in a Patient with Recent Subarachnoid Hemorrhage: A Case Report

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ABSTRACT

This case report presents a 25-year-old male with a complex medical history, including a recent subarachnoid hemorrhage (SAH) and a prescription for phenytoin. The patient exhibited neurological symptoms, such as ataxia, blurring of vision, and diplopia, prompting an intricate diagnostic evaluation. The medical history encompassed a prior road traffic accident resulting in a jaw injury, adding to the complexity of potential aetiologies, including cerebellar dysfunction, sequelae from the accidents, medication-related side effects (particularly phenytoin), or infectious/inflammatory causes.

Given the reported symptoms, there arose a suspicion of phenytoin-induced ataxia and diplopia, common neurological side effects associated with this anticonvulsant. These symptoms, suggestive of cerebellar dysfunction, required a comprehensive examination, including neurological assessments and imaging studies, to elucidate the precise etiology. This case underscores the importance of meticulous medication review, particularly for drugs like phenytoin, and emphasizes the necessity of a multidisciplinary approach involving neurologists to navigate the complexities associated with neurological manifestations in the context of SAH and medication use. The findings contribute to understanding potential complications arising from anticonvulsant therapy in SAH patients and highlight the need for tailored diagnostic and management strategies in such intricate clinical scenarios.

Keywords: Subarachnoid hemorrhage, Phenytoin, Neurological symptoms, Ataxia, Diplopia.

INTRODUCTION

Phenytoin, an antiepileptic medication derived from hydantoin (specifically 5,5-diphenylhydantoin), is often selected for seizure treatment primarily because of its affordability and widespread accessibility [1]. Introduced in 1938, phenytoin serves as a widely utilized medication for addressing various types of tonic-clonic and complex partial seizures, excluding absence seizures [2, 3]. Epilepsy, a prevalent neurological condition, aims to be effectively managed by treatment, with the primary objective being the control of seizures while minimizing adverse effects [4]. The potential for phenytoin intoxication is frequently attributed to its substantial pharmacokinetic variability and a low threshold for toxicity [5-8]. Intoxication typically presents with symptoms such as nausea and central nervous system dysfunction, marked by confusion, nystagmus, and ataxia. In severe cases, a diminished level of consciousness, coma, and seizures may occur. Although cardiac issues like arrhythmias and hypotension are uncommon in cases of oral phenytoin ingestion, they may be observed when phenytoin or Fos phenytoin is administered parenterally [9].

Typical neurological side effects of PHT encompass nystagmus, diplopia, ataxia, lack of coordination, choreoathetosis, orofacial dyskinesias, and drowsiness [10-13].

Phenytoin, a widely used antiepileptic drug, has proven efficacy in the management of various seizure disorders. However, its therapeutic range is narrow, and deviations can lead to phenytoin toxicity. Phenytoin toxicity can manifest with a spectrum of symptoms, ranging from mild to severe, and may have serious consequences if not promptly recognized and addressed.

Phenytoin is primarily metabolized by hepatic enzymes, particularly cytochrome P450 (CYP) enzymes, with genetic and environmental factors influencing individual variations in metabolism. The narrow therapeutic index of phenytoin makes it susceptible to dose-related toxicity, complicating its clinical use.

This comprehensive review aims to explore the pathophysiology, clinical manifestations, risk factors, and management strategies associated with phenytoin toxicity. By synthesizing current research findings and clinical experiences, this review seeks to provide a

valuable resource for healthcare professionals to enhance their understanding of phenytoin toxicity.

Case Report

A 25-year-old male patient presented with a myriad of neurological symptoms, including ataxia, blurring of vision, and diplopia, persisting for the past two weeks. Notably, he reported a throbbing headache that responded to medication, postural instability preventing him from standing, and a history of hallucinations. The patient had a noteworthy medical history, having been involved in a road traffic accident (RTA) six months prior, resulting in a jaw injury. Furthermore, he had a recent hospitalization for subarachnoid hemorrhage (SAH), diagnosed one week ago, for which he was prescribed phenytoin.

During the examination, the patient maintained consciousness and coherence, with stable vital signs, including a blood pressure of 110/70 mmHg, a pulse rate of 86/min, and an oxygen saturation of 98%. Cardiovascular and respiratory assessments yielded normal findings. Neurological examination revealed impaired finger-to-nose coordination, a positive swaging test, and no nystagmus. Additional symptoms included weakness in both lower limbs for one day, myalgias in the lower limbs for one day, and difficulty rising from bed since the previous day. There was also a history of difficulty in squatting and climbing stairs, with a progressive increase in weakness noted since the morning.

Given the intricate medical history, recent SAH diagnosis, and the neurological examination findings, potential etiologies encompass cerebellar dysfunction, sequelae from the previous RTA or SAH, medication-related side effects (particularly phenytoin), or infectious/inflammatory causes. Further examinations, such as a detailed neurological assessment, cranial nerve evaluation, and motor/sensory testing, are recommended to comprehensively evaluate the patient. Imaging studies, including MRI or CT scans, will be instrumental in assessing structural abnormalities or changes in the brain. Additionally, a meticulous review of medications, with a specific focus on reevaluating the phenytoin prescription, is imperative. Collaboration with a neurologist is strongly advised to formulate a comprehensive diagnostic and management strategy tailored to the patient's intricate clinical presentation. This case underscores the importance of a multidisciplinary approach in addressing complex neurological conditions.

DISCUSSION

Ataxia refers to a neurological condition characterized by a lack of coordination and control of voluntary muscle movements. Individuals with ataxia may experience difficulties in maintaining balance, walking steadily, and performing precise, coordinated movements. This condition can result from dysfunction in the cerebellum, a region of the brain responsible for coordinating motor activities. Ataxia can manifest in various body parts, affecting fine and gross motor skills.

Diplopia, commonly known as double vision, is a visual phenomenon where a person sees two images of a single object instead of one. This occurrence can be disruptive to vision and may result from misalignments in the eyes or other abnormalities in the visual system. The two images can be horizontally, vertically, or diagonally displaced. Diplopia may be temporary or persistent.

Certain medications, like those used for seizures or to induce sleep, may lead to ataxia as a side effect. Drinking too much alcohol can also impair coordination temporarily. Exposure to toxins or heavy metals, such as lead, can contribute to ataxia, and conditions like diabetic neuropathy, affecting peripheral nerves, may result in similar symptoms. Problems with the inner ear, often due to infections or inflammation, can disrupt the vestibular system and lead to ataxia. Severe visual impairments or eye disorders can contribute to coordination difficulties, and infections affecting the central nervous system may cause ataxia. Head injuries, especially those impacting the cerebellum, can result in coordination problems.

Phenytoin, an anticonvulsant medication commonly used to treat seizures, is associated with several side effects and potential adverse drug reactions. These include drowsiness, dizziness, nausea, and gingival hyperplasia, as well as more severe effects such as diplopia, cognitive impairment, hirsutism, blood disorders, ataxia and liver function abnormalities. Rare but serious hypersensitivity reactions, including skin conditions like Stevens-Johnson syndrome, have been reported. Additionally, long-term use of phenytoin is linked to a potential risk of osteoporosis and decreased bone mineral density[15].

In the context of subarachnoid hemorrhage (SAH), alternative treatments to phenytoin for seizure prophylaxis are considered to avoid potential side effects associated with phenytoin use. Levetiracetam (Keppra) and lacosamide (Vimpat) are among the antiepileptic medications that have been explored as alternatives to phenytoin in SAH patients. These alternatives are chosen for their potential to provide effective seizure prophylaxis with a more favorable side effect profile. A study by Neidich *et al*. (2015) compared levetiracetam and phenytoin for seizure prophylaxis in SAH patients and found that levetiracetam was associated with a lower incidence of adverse effects, making it a viable alternative. Lacosamide, with its different mechanism of action, is another option that may be considered due to its generally well-tolerated profile [16].

Phenytoin, an antiepileptic medication with a narrow therapeutic range of 10–20 mcg/mL, exhibits distinct pharmacokinetic characteristics. The drug follows first-order elimination kinetics at plasma concentrations below 10 mcg/mL, with a variable half-life ranging from 6 to 24 hours. However, within the therapeutic range (10–20 mcg/mL), the metabolic pathway becomes saturated, leading to a shift to zero-order elimination. In zero-order kinetics, a constant amount of the drug is eliminated per unit of time, resulting in a disproportionate increase in plasma concentration even with small dose increments.

The half-life of phenytoin is subject to variation based on concentration, increasing as concentrations rise. This is a critical consideration, as higher concentrations lead to a longer duration for half of the drug to be eliminated. Monitoring plasma concentrations is essential, given that toxicity is generally correlated with increasing levels. Moreover, the transition to zero-order pharmacokinetics can contribute to a prolonged duration of toxic symptoms, emphasizing the need for vigilant monitoring to prevent adverse effects.

In managing patients on phenytoin therapy, healthcare professionals must closely monitor plasma levels, especially during dose adjustments, to balance maintaining therapeutic efficacy and preventing toxicity [14].

Phenytoin-induced ataxia (lack of coordination) and diplopia (double vision) are likely associated with the medication's impact

on the nervous system. Phenytoin works by blocking voltage-gated sodium channels, which play a role in the transmission of signals in nerve cells. This sodium channel blockade may affect the normal functioning of neurons, including those in the cerebellum, a part of the brain responsible for coordinating movements. Consequently, disruptions in motor coordination, leading to ataxia, may occur. Additionally, phenytoin has been reported to influence neuromuscular transmission, potentially contributing to muscle weakness and coordination difficulties associated with ataxia. In terms of diplopia, the drug might impact the control of eye movements, affecting the oculomotor nerves or neuromuscular junctions responsible for coordinating the eyes and leading to double vision. It's important to recognize that individual factors such as genetics, dosage, and treatment duration can influence the likelihood and severity of these side effects. While the exact mechanisms are not fully understood, these insights provide a general understanding of how phenytoin could contribute to ataxia and diplopia. If individuals experience these symptoms, it is crucial to consult with healthcare professionals for appropriate evaluation and management. Adjustments to the medication regimen may be considered based on the individual's response and clinical condition [17].

CONCLUSION

A recent case report highlights the significance of raising awareness among physicians regarding phenytoin toxicity. It underscores the importance of closely monitoring the plasma concentration of phenytoin in patients undergoing chronic drug therapy to prevent toxicity. This monitoring allows for the customization of drug dosage based on the individual pharmacokinetic needs of each patient. Regular follow-up assessments are essential to evaluate patient compliance and response to the prescribed drug dosage regimen. Additionally, it is crucial to educate patients and their caregivers about the clinical manifestations of phenytoin toxicity, enabling early recognition and appropriate intervention.

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CONFLICTS OF INTEREST

None.

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