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Phenytoin Toxicity Potentially Induced by Addition of Lacosamide in a Long-Term Anticonvulsant Regimen: A Case Report of Rare Drug Interaction

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Abstract
Phenytoin toxicity remains a critical concern when serum levels exceed therapeutic thresholds, with the contribution of drug interactions to this toxicity being well-established. However, the interaction between phenytoin and lacosamide, another anticonvulsant, has seldom been reported. This case report describes a 61-year-old male with a longstanding history of effective seizure control using phenytoin and primidone. Following a recent seizure, lacosamide was added to his regimen. Approximately one-month post-adjustment, the patient exhibited symptoms indicative of phenytoin toxicity, including ataxia, slurred speech, and diminished coordination. This case highlights the necessity for vigilance regarding potential drug interactions in patients with long-term anticonvulsant therapies and underscores the need for cautious regimen modifications. It also prompts further investigation into the mechanisms underlying the interaction between phenytoin and lacosamide to enhance patient safety and treatment efficacy.
Categories: Neurology, Internal Medicine, Medical Education

Keywords: seizure, drug interaction, lacosamide, phenytoin, phenytoin toxicity

Introduction

Phenytoin is a well-established anticonvulsant medication that has been widely used for the prevention and treatment of seizure disorders for several decades [1]. Recognized for its effectiveness in controlling a broad range of seizure types, phenytoin plays a pivotal role in the management of epilepsy. Its mechanism of action primarily involves the modulation of voltage-gated sodium channels, which stabilizes neuronal membranes and prevents the repetitive firing that characterizes epileptic seizures.

Despite its clinical efficacy, the use of phenytoin is often limited by its pharmacokinetic complexity. Phenytoin exhibits nonlinear kinetics, meaning that small increases in dose can lead to disproportionately large increases in drug concentration, potentially leading to toxicity. It is extensively metabolized in the liver primarily by the cytochrome P450 enzyme system and is highly bound to plasma proteins, factors

that contribute to its variable plasma levels and interactions with other medications.

The therapeutic index of phenytoin is notably narrow; maintaining serum levels within the optimal therapeutic range is crucial for maximizing efficacy while minimizing adverse effects. Levels above this range can result in toxicity, characterized by a constellation of neurological symptoms such as nystagmus, ataxia, slurred speech, and decreased coordination [2,3]. Given these challenges, therapeutic drug monitoring is essential to ensure safety and effectiveness, particularly when phenytoin is part of a polytherapy regimen, as interactions with other medications can alter its pharmacokinetics dramatically.

The potential for drug interactions with phenytoin is especially significant due to its enzymatic metabolism and protein binding characteristics. Interactions can occur at various levels including absorption, distribution, metabolism, and excretion, often complicating the clinical management of patients. For instance, other drugs that induce or inhibit the enzymes involved in phenytoin metabolism can decrease its efficacy or increase its toxicity, respectively.

This paper reports a rare case of phenytoin toxicity potentially induced by the addition of lacosamide, a newer anticonvulsant, to a long-standing anticonvulsant regimen [7]. This case highlights the importance of careful consideration of drug interactions in the treatment of epilepsy and underscores the need for vigilant monitoring of drug levels and patient symptoms after adjustments to medication regimens. Through this report, we aim to contribute to the existing knowledge base regarding the complex interplay of drug interactions in epilepsy management, focusing particularly on the interaction between phenytoin and lacosamide.

Case Presentation

A 61-year-old male with a history of epilepsy presented with long-standing seizures managed with phenytoin and primidone for 60 years. After experiencing a recent seizure episode, the patient's neurologist introduced lacosamide as an adjunctive therapy to the existing anticonvulsant regimen after checking the serum phenytoin level, which was within the therapeutic range. No other medications were added during this period. However, approximately one month after the addition of lacosamide, the patient displayed clinical symptoms suggestive of phenytoin toxicity, including ataxia, slurred speech, and decreased coordination. Before that, the patient had never experienced any symptoms or episodes of phenytoin toxicity.

Upon hospital admission, the patient underwent a comprehensive evaluation, including magnetic resonance imaging (MRI) and electroencephalography (EEG), both of which showed normal results. The phenytoin level on the first day of hospitalization was 39.1, double the therapeutic level. Consequently, all antiepileptic medications including phenytoin, lacosamide, and primidone were discontinued. On the next day, the phenytoin level decreased to 32.3, and on the third day, it further decreased to 26.9. By this time, the patient's speech had improved. The patient started walking without ataxia or incoordination.

On the fourth day, the neurologist resumed phenytoin and primidone administration, and permanently discontinued lacosamide. He remained in a hospital under observation for a day and was subsequently discharged the next day with a phenytoin level decreasing to 21.6. As part of his follow-up care, the patient was advised to have his phenytoin levels checked after a week, which was found to be downward trending (Table *1*). Further monitoring was recommended, with monthly phenytoin level assessments for at least a year.

	A Year before	A Month Before	1st day in hospital	2nd day in the hospital	3rd day in the hospital	4th day in the hospital	Week after discharge
Phenytoin level (microgram/ml)	17.2	15.7	39.1	32.3	26.9	21.6	18.5

Discussion

Phenytoin, a widely used anticonvulsant with a narrow therapeutic index, has been a cornerstone in the management of seizure disorders for decades. Its clinical utility, however, is complicated by its pharmacokinetic properties, including extensive hepatic metabolism primarily via the cytochrome P450 enzyme system and high plasma protein binding. These properties render phenytoin particularly susceptible to drug-drug interactions, which can significantly alter its plasma concentration, thereby impacting its efficacy and safety [4-6].

The case presented involves a patient with a long-standing history of seizure control, managed effectively on a regimen of phenytoin and primidone. The introduction of lacosamide, a relatively new anticonvulsant, was followed by the emergence of signs indicative of phenytoin toxicity. This clinical scenario underscores the complexity of managing drug interactions in a real-world setting and highlights several critical points for consideration.

Firstly, the interaction between phenytoin and lacosamide demonstrated in this case is not commonly reported in the literature, suggesting a gap in our understanding of the interaction profiles of newer anticonvulsants with established drugs. The observed interaction could potentially be mediated through inhibition of phenytoin's metabolic pathways by lacosamide, although lacosamide is generally considered to have a minimal interaction profile [8]. The precise mechanism, possibly involving competitive inhibition or alteration of enzyme kinetics, warrants further investigation. Additionally, genetic factors such as polymorphisms in the genes encoding for metabolizing enzymes could play a significant role in such interactions, emphasizing the need for personalized approaches in pharmacotherapy.

Secondly, this case illustrates the critical importance of vigilant therapeutic drug monitoring when changes are made to medication regimens, especially in patients with stable, long-term treatment histories. The symptoms of phenytoin toxicity appeared despite the fact that initial phenytoin levels post-lacosamide addition were within therapeutic limits, suggesting that drug interactions can dynamically evolve. This points to the necessity of not only initial but also sequential monitoring following any modification in drug therapy.

Moreover, the case provides a poignant reminder of the clinical implications of drug interactions. The symptoms of toxicity—ataxia, slurred speech, and decreased coordination—although reversible, posed significant risks to the patient's safety and quality of life. This event could have led to severe complications, including increased risk of falls, injuries, or further uncontrolled seizures, had it not been promptly recognized and managed.

Conclusions

This case strongly indicates the potential for phenytoin toxicity upon the addition of lacosamide to a long-term anticonvulsant regimen. It emphasizes the importance of careful monitoring of phenytoin serum levels when introducing new medications such as lacosamide. Further studies are warranted to elucidate the specific mechanisms of interaction between these drugs to optimize safety and efficacy in epilepsy

management.

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