Is Phenytoin and Valproate Combination Therapy Safe? A Case Report and Review of Literature

Pallavi Walunj[1], Nikhil Dongre[2*], Nitin Wadaskar[1]

[1]Department of Internal Medicine, Max Super Speciality Hospital, Nagpur
[2]Department of Neurology, Max Super Speciality Hospital, Nagpur

Correspondence:

Nikhil Dongre

E-mail: nikhilarvinddongre@gmail.com

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Abstract:

Epilepsy, being a chronic neurological disease, requires long-term treatment with antiepileptic drugs. Antiepileptic agents are known for various pharmacological interactions due to their pharmacokinetics. Among antiepileptic agents, valproate is an important one, causing clinically significant drug interactions. We report a case of a young patient with a known history of epilepsy on long-term phenytoin treatment, where the recent introduction of valproate led to an increase in the free fraction of phenytoin and subsequent phenytoin toxicity, manifested as cerebellar ataxia. The concomitant administration of hepatic enzyme inducers significantly alters serum concentrations, resulting in either toxicity or sub-therapeutic effects.

Key words: Phenytoin, Valproate, Antiepileptic, Interaction.

Introduction

Phenytoin is one of the oldest and most trusted antiepileptic drugs used in the treatment of generalised tonic-clonic seizures. The combination of phenytoin with valproate is commonly practised; however, their pharmacokinetics and interaction may lead to increased serum levels of phenytoin, resulting in toxicity and causing neurological symptoms. This can be misdiagnosed as a neurological lesion, hence, requires a thorough review of the medication history, appropriate knowledge of the pharmacokinetics and pharmacodynamics of the drugs, and a high index of suspicion. Here, we report a case of a young male with a known history of epilepsy who presented with recurrent seizures, acute-onset ataxia, and nystagmus localising as a cerebellar lesion, but, upon evaluation, revealed phenytoin toxicity due to combination therapy with sodium valproate.

Case Report

A 28-year-old male, a known case of epilepsy for 20 years, was admitted with recurrent seizures despite being on treatment, along with ataxia and blurred vision over the past 15 days.

His clinical examination revealed gum hypertrophy (Figure 1), positive cerebellar signs, and gaze-evoked nystagmus, with no sensory or motor involvement.

Figure 1: Gum hypertrophy.

The clinical diagnosis suggested cerebellar pathology. His treatment history revealed he had been taking tab phenytoin 300 mg once daily for 20 years, and 6 months ago, tab sodium valproate 500 mg twice daily was added, with a reduction in phenytoin dose to 200 mg once daily (Figure 2).

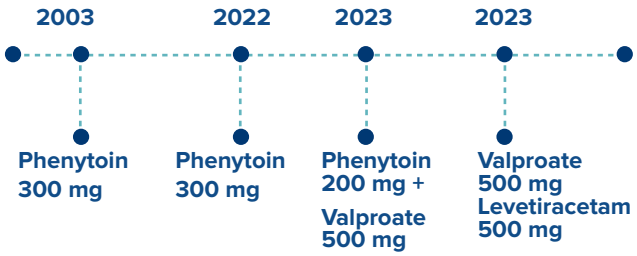

Figure 2: Course of treatment.

Blood investigations were within normal limit. Magnetic resonance imaging (MRI) of the brain did not reveal any new abnormality, except for old findings of mesial temporal sclerosis. His electroencephalogram (EEG) was normal. Serum phenytoin and valproate levels were ordered on suspicion of toxicity. Results are depicted in Table 1.

Drug	Result	Biological reference interval
Phenytoin	38.3 mcg/mL	Therapeutic range: 10-20 Toxic level: >20
Valproate	46.3 mcg/mL	Therapeutic range: 50-100 Toxic level: >100

Table 1: Drug levels.

As serum phenytoin levels were elevated, phenytoin was discontinued and levetiracetam was initiated (Figure 2). Upon follow up two weeks later, his cerebellar ataxia had markedly improved, and he was able to walk independently without assistance. His epilepsy also remained in remission.

Discussion

Phenytoin was discovered in 1908 and was the first non-sedative drug to effectively control seizures. Since then, phenytoin has remained one of the most common and efficacious drugs for the treatment of epilepsy. It is listed as one of the essential medicines in the World Health Organisation (WHO) list of essential medicines. However, regular therapeutic drug monitoring is required due to its narrow therapeutic range (10-20 mcg/mL) for both anticonvulsant and antiarrhythmic effects.[1]

Phenytoin is a cytochrome 450 (CYP) enzyme inducer, hence, has several drug interactions. Medication errors, overdose, and drug interactions are common causes of phenytoin toxicity. Neurotoxicity, as per drug trough levels is depicted in Table 2.

Drug Level (mcg/mL)	Adverse Effects
<10	Rare side effects
10-20	Gaze-evoked nystagmus (occasional)
20-30	Nystagmus
30-40	Ataxia, tremor, nausea, vomiting, slurred speech
40-50	Lethargy, confusion
>50	Convulsions, coma

Table 2: Neurotoxicity according to serum phenytoin level.

Apart from neurotoxicity, phenytoin can cause cardiac toxicity, agranulocytosis, megaloblastic anaemia, purple glove syndrome, Steven-Johnson syndrome (HLA-B*1502), teratogenic effects, foetal hydantoin syndrome, gingival hypertrophy, drug-induced lupus, and osteoporosis.[2] The pharmacokinetics of phenytoin depend on its serum concentration: at lower concentrations, it follows first-order kinetics, whereas at higher concentrations, it follows zero order kinetics. Phenytoin is a CYP3A4 and CYP2C9 inducer, thereby increasing the metabolism of other drugs.

On the other hand, sodium valproate is a newer antiepileptic drug, effective in almost all types of seizures, due to its diverse mechanisms of action. In contrast to phenytoin, it is an inhibitor of CYP enzymes, thereby increasing the plasma concentration of other drugs.

The interaction between phenytoin and valproate is clinically significant and can lead to phenytoin toxicity. This occurs because of two different mechanisms: displacement of phenytoin from plasma protein binding sites and inhibition of CYP enzymes, which reduces the clearance and metabolism.[3]

In our patient, despite a dose reduction of phenytoin, serum drug levels were elevated, and the patient developed neurotoxicity. Both phenytoin and valproate both are highly protein-bound. Valproate initially lowers the total phenytoin concentration by increasing its free fraction, followed by a subsequent rise in phenytoin levels due to metabolic inhibition.[4] As the brain concentration of phenytoin is proportional to its free serum concentration rather than its total concentration, the free concentration of phenytoin may hold greater clinical significance.[5] Hence, the interaction between phenytoin and valproate makes it a less suitable combination therapy for patients with epilepsy.

Conclusion

Phenytoin has potential pharmacological interactions with other antiepileptic drugs, especially valproate. Therefore, it is essential to understand these interactions when designing a safe and effective therapeutic regimen for patients.[6]

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