Case Report

A long-term side effect of chronic phenytoin use-cerebellar atrophy

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Abstract

Phenytoin is one of the oldest anti-convulsant being used for many years for generalized tonic-clonic seizures and focal seizures. One of the main reason for its persistent use till date is the economic feasibility that it provides. However, phenytoin is associated with acute and chronic toxic effects due to its narrow range of therapeutic index. Hereby, we present a case of a 31-year-old male who is a known case of generalized tonic-clonic seizures on phenytoin for 11 years and had developed cerebellar symptoms due to the cerebellar toxicity and atrophy caused by prolonged use of phenytoin. Patient's symptoms improved upon gradual withdrawal of the drug. This report therefore, emphasises on the need for regular monitoring of patients on phenytoin and also the need for monitoring levels of phenytoin in the blood.

Key words

Chronic phenytoin use, Cerebellar atrophy, Side effects.

Introduction

Epilepsy is defined by International League Against Epilepsy (ILAE; 1993) as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause [1]. It is estimated that the overall prevalence of epilepsy in India is 5.59-10 per 1000 that is about 10 million Indian population [3].

Phenytoin, first identified to have anti-seizure activity in 1938, is the oldest non-sedating drug

used in the treatment of epilepsy. It is prescribed for the prevention of focal seizures and generalize tonic-clonic seizures and for the acute treatment of status epilepticus.

Phenytoin, sometimes referred to as diphenylhydantoin, is the 5,5-diphenyl-substituted analog of hydantoin. Phenytoin is most commonly prescribed in an extended-release capsule containing phenytoin sodium and other excipients to provide a slow and extended rate of absorption with peak blood concentrations from 4 to 12 hours [2].

Phenytoin is a sodium channel-blocking anti-seizure drug that is thought to protect against seizures by interacting with the voltage-gated sodium channels (Nav1) responsible for the rising phase of neuronal action potentials. Phenytoin binds when the sodium channel is in the inactivated state, causing it to be stabilized in this state. During high-frequency firing, sodium channels cycle rapidly through the inactivated state, allowing the block to accumulate. This leads to a characteristic use- dependent blocking action in which high-frequency trains of action potentials are more effectively inhibited than are either individual action potentials or the firing at low frequencies [2].

Absorption from the gastrointestinal tract is nearly complete in most patients, the time to peak may range from 3 to 12 hours. Phenytoin is extensively (90%) bound to serum albumin and is prone to displacement in response to a variety of factors (e.g.- hyperbilirubinemia or drugs such as warfarin or valproic acid), which can lead to toxicity. At low blood levels, phenytoin metabolism follow first- order kinetics. However, as blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolize the drug is approached (saturation kinetics). Even small increases in dose may be associated with large changes in phenytoin serum concentrations. In such cases, the half-life of the drug increases markedly, steady state is not achieved in routine fashion (since the plasma level continues to rise), and patients quickly develop symptoms of toxicity. The therapeutic plasma level of phenytoin for most patients is between 10 and 20 mcg/mL.

Early signs of phenytoin administration include nystagmus and loss of smooth extraocular pursuit movements; neither is an indication for decreasing the dose. Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment; sedation usually occurs only at considerably higher levels. Gingival hyperplasia and hirsutism occur to some degree in most patients. Long-term use is associated in some patients with coarsening of facial features and with mild peripheral neuropathy, usually manifested by diminished deep tendon reflexes in the lower extremities. Long-term use may also result in abnormalities of vitamin D metabolism, leading to osteomalacia. Low folate levels and megaloblastic anemia have been reported, but the clinical importance of these observations is unknown.

Case report

A 31-year-old male, who was a known case of seizure disorder with generalized tonic-clonic seizures since 15 years was on Tab. Phenytoin 300 mg per day since 11 years. The last episode of seizure was 1 year ago when the patient had skipped medications for 2 days after which he had 3-4 episodes of generalized tonic-clonic seizures. No further seizure episodes since then.

At present, patient came with the complaints of giddiness and difficulty in walking since 3 months. The giddiness was present even in sitting position that was aggravated on standing or walking. It was occasionally accompanied by 2-3 episodes of vomiting that contained food particles and were non-bilious and non-projectile. Due to the giddiness the patient had difficulty in walking that was affecting his daily activities with few episodes of fall. No history of ear pain or ear discharge or tinnitus. No history of hearing disturbances. No history of motor or sensory loss.

On examination, nystagmus was present in both the eyes on lateral gaze (left>right), finger-nose test abnormal on left side, dysdiadechokinesia on left side, knee-heel test abnormal on the left side.

CT brain at the time of admission revealed generalized cerebellar atrophy with normal cerebral parenchyma as depicted in **Figure - 1**.

Keeping in view the use of phenytoin for a long period of time and the cerebellar atrophy in CT scans, a serum phenytoin levels we sent to correlate the cerebellar atrophy with phenytoin use. The level of phenytoin was 55 microgram/ml that is in the toxicity range as shown in **Figure - 2**. The normal therapeutic range of phenytoin is between 10-20 micrograms/ml.

Figure – 1: CT brain showing generalized cerebellar atrophy.

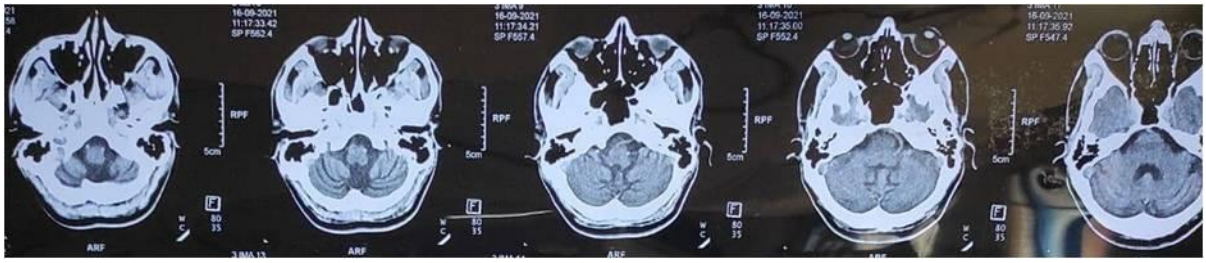

Figure – 2: Phenytoin levels of the patient.

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Name	:	TID/SID	:
Age / Gender	: 31 Years / Male	Registered on	: 29-Sep-2021 / 16:50 PM
Ref.By	: MALLAREDDY INSTITUTE OF MEDICAL SCIENCES	Collected on	: 29-Sep-2021 / 17:01 PM
Req.No	BIL1388044	Reported on	: 01-Oct-2021 / 18:43 PM
	TEST REPORT	Reference	: Mallareddy Institute Of Medical Sciences

DEPARTMENT OF LCMS

Phenytoin, Serum

Investigation	Obeserved Value	Biological Reference Interval
Phenytoin, Serum Method LCMS-MS	55	Therapeutic range : 10-20 µg/mL Toxic range: > 20 µg/mL
Note	Observed values are cross checked twice, Kindly correlate clinically.	

Kindly interpret the result in the light of time of sample collection with regard to drug dosage time.

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--- End Of Report ---

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Discussion

Cerebellar degeneration refers to the chronic and irreversible loss of neuronal structure and function within the cerebellum- the Purkinje cells are most susceptible. The causes of cerebellar degeneration can be broadly divided into two categories: acquired and genetic. Acquired cerebellar degeneration has been attributed to endogenous or exogenous non-genetic causes, such as alcohol abuse and vitamin deficiencies, infections of the central nervous system (CNS),

autoimmune disorders, and primary or metastatic tumors, among others.

Cerebellar degeneration has been associated with epilepsy. Marcian, et al. (2016) [4] postulated a triad of questions; is cerebellar dysfunction a coincidence, consequence, or cause of epilepsy. The authors suggested that cerebellar degeneration can be attributed to cellular damage from seizure activity, the effects of anti-epileptic drugs (AEDs), anoxic-ischemic injury from seizures, or cerebral hemiatrophy of the cerebellum. In many cases, ataxia may be a direct result of seizure mediated cell loss or an adverse effect of certain anti-epileptic medication. The patho-mechanism of observed toxicity associated with chronic phenytoin administration is unclear, but folate deficiency has been implicated due to the fact that low folate levels can impair hepatic drug metabolizing capacity or by impairing neural function directly.

In a case series in 1980, McLain, et al. reported about five patients who were on phenytoin, had developed clinical signs of cerebellar dysfunction and showed diffuse cerebellar degeneration in CT scan. These patients had high plasma phenytoin levels at the time of diagnosis, but the cerebellar symptoms persisted even when phenytoin levels had returned to normal value in follow up [5].

In another study done by Fernando Cendes, et al., among 66 patients, patients with moderate/severe atrophy were those with longer exposure to phenytoin (longer duration of treatment and higher total dosage) showing statistically significant difference when compared to patients with mild atrophy or without atrophy [6].

A higher dosage intake for a longer period of use is associated with more pronounced atrophic changes. Serum phenytoin levels have been observed to be higher in patients with moderate to severe cerebellar changes than those with mild or no cerebellar changes. Also, the neurotoxicity has been found to be more profound with older patients.

The neurotoxic effects of phenytoin are concentration dependent and can range from mild nystagmus to ataxia, slurred speech, vomiting, lethargy and eventually coma and death.

Paradoxically, at very high concentrations, phenytoin can lead to seizures. Symptoms correlate well with the unbound plasma phenytoin concentration. Serum phenytoin level and side effects are as per **Table – 1**.

Table – 1: Serum phenytoin level and side effects.

Serum Phenytoin Level	**Side Effects**
Less than 10 mcg/ml	No side effects
10-20 mcg/ml	Occasional mild horizontal nystagmus on lateral gaze
20-30 mcg/ml	Nystagmus
30-40 mcg/ml	Ataxia, slurred speech, nausea, vomitings
40-50 mcg/ml	Lethargy, confusion
More than 50 mcg/ml	Coma and seizures

Phenytoin has a long half-life and thus has an advantage of lesser daily dosage, however; it follows nonlinear pharmacokinetics, which means a small increment in dose above the required maintenance dose may cause marked side effects. These properties have now led to other newer drugs, such as lamotrigine and topiramate to take over phenytoin in the long-term treatment of epilepsy, especially in young patients where longer treatment duration is expected.

Conclusion

Phenytoin is one of the easily available and economically feasible anti-epileptic that is used for focal as well as generalized tonic-clonic seizures, but it is associated with certain acute and chronic effects. Hence, regular monitoring of patients to look for the side-effects may be

helpful in preventing certain irreversible changes due to phenytoin toxicity.

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