The patient did not respond to phenobarbital, sodium valproate, and diazepam. Later, she was ventilated and was on thiopentone infusion during which she was seizure free for a period of time.

However, on tapering the dose of thiopentone, she had intermittent seizures during touching, suctioning, and auditory stimulus. Later, the patient was put on tracheostomy and was referred to a higher center for further management including surgery for epilepsy.

**DISCUSSION**

Causality analysis using the World Health Organization scale is categorized as “possible” because the patient is a known case of seizure disorders, and hence, the disease could have an influence on the reaction.

Acute phenytoin intoxication may be due to intentional or accidental consumption of phenytoin. The patient may present with varied symptoms ranging from nausea vomiting to seizures and death. In this case, it was an intentional toxicity, and the patient has progressed to a refractory state of seizures. Plasma concentration of phenytoin has a correlation with the adverse effects.

Phenytoin is a weak acid and has erratic GI absorption. Peak blood levels occur 3-12 hrs. Phenytin metabolism is dose-dependent, and its elimination follows first-order kinetics at the low drug concentrations and zero-order kinetics at higher drug concentrations [2]. This change in kinetics reflects the saturation of metabolic pathways. Thus, very small increments in dosage may result in adverse effects.

The cause was not known for gangrene of her fingers. Gangrene [3] and death [4] have been reported earlier for accidental intraarterial administration of phenytoin but not for oral administration present, MRI reveals cerebral atrophy. Although cerebral atrophy has been reported in chronic phenytoin ingestion [5], we cannot conclusively
prove that this is the reason for cerebral atrophy in this patient as we do not have neurological imaging taken at the initiation of the study. On the other hand, cerebral atrophy could be the reason for non-responsiveness to phenytoin as inactive cells would not respond to the drug.

Such a problem can be prevented in other patients by choosing a different antiepileptic in patients who have indications of cerebral atrophy in neurological imaging at the time of diagnosis of epilepsy.

**Pharmacokinetics**

In very large oral dosage, gastrointestinal absorption can be delayed even to several days [6,7]. We do not have the plasma concentration of phenytoin for this patient. Hence, roughly calculating the plasma concentration with the dose ingested by the patient (1500 mg).

Pt weight - 50 kg

Volume of distribution for phenytoin is 0.7 L/kg

For this patient 0.7*50=35 L

Assuming the drug is available 90% (i.e.,) \( F = 0.9 \).

Known formula for calculating the dose is as follows:

\[
\text{Dose} = \frac{\text{plasma concentration} \times \text{volume of distribution}}{\text{Bioavailability}}
\]

Rearranging

\[
\text{Plasmaconcentration} = \frac{\text{Dose} \times \text{Bioavailability}}{\text{Volume of distribution}}
\]

By substituting,

\[
\text{Plasma concentration} = 1500 \times 0.9/35 = 37.5 \text{ mg/l or 37.5 \mu g/ml}
\]

\( T_{1/2} \) in therapeutic concentration is 12-36 hrs.

At higher concentrations, zero-order elimination occurs as a result of saturation of hydroxylation reaction, and apparent elimination half-life increases to 20-60 hrs [8,9].

From Fig 1, 2, 3, and 4 we infer that it takes 10, 5, 30, and 17 days respectively to reach therapeutic level of 10 micrograms per ml. Hence, from the above figures, we find that for the plasma concentration 37.5 \( \mu \text{g/ml} \) to reduce to the therapeutic level of 10-20 \( \mu \text{g/ml} \) it will take 5-30 days. Added to this as the patient had myoclonic seizures, she was started on valproate which displaces phenytoin, thereby increasing the free phenytoin concentration.

**CONCLUSION**

Seizures are a rare complication of phenytoin. Seizures can be prevented by evaluating therapeutic plasma concentration. In this case, the patient was on chronic treatment, and due to intentional toxicity, the patient progressed to a refractory state of seizures. This could have occurred because of the unique kinetic profile of phenytoin, small therapeutic index, and saturated the sodium channels. Another factor is the inter-patient variability of drug metabolism; certain individuals with a genetic predisposition are disposed to an increased level (slow metabolizers) [10].

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**REFERENCES**