National Board of Examination - Journal of Medical Sciences
Volume 1, Issue 12, Pages 767–774, December 2023
DOI 10.61770/NBEJMS.2023.v01.i12.007

CASE REPORT

Death Due to Phenytoin Poisoning in an Intellectually Disabled Female Child: A Case Report

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Accepted: 03-November-2023 / Published Online: 17-December-2023

Abstract
Phenytoin is a commonly used anticonvulsant, but its narrow therapeutic window can lead to toxicity, often due to medication errors or, in some cases, due to intentional overdose. In this article, we present a case of a 12-year-old intellectually disabled female child, who was on phenytoin treatment for seizure disorder and accidentally ingested about 10-15 pills, resulting in fatal toxicity and death. The child presented with a few episodes of vomiting; seizures, followed by respiratory depression before succumbing to the overdose. This case highlights the importance of drug regulators ensuring safe manufacturing practices for medications used in chronic conditions like seizure disorder to prevent unintentional poisonings. At the same time, it is the responsibility of health care professionals, both clinicians and pharmacists to educate the caregivers of children about the hazards of accidental drug poisoning in children.

Keywords: Phenytoin, Intellectual disability, Paediatric toxicity, Female child.

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Introduction

Phenytoin (5,5 diphenyl-2,4-imidazolidinedione), a derivative of hydantoin is a commonly used anticonvulsant in neurology practice across all age groups since several decades. It is a voltage-gated sodium channel blocker that extends the neural refractory period by maintaining the sodium channel's inactive state. Phenytoin exerts ifs effect by acting on sodium channels of heart and brain [1]. Phenytoin exhibits a narrow therapeutic range of 10 -20 mg/L, which is a matter of concern during its prescription [1]. Phenytoin induces Cytochrome P450 2C (CYP2C), Cytochrome P450 3A (CYP3A), and UDP-glucuronosyltransferase (UGT) enzyme systems in humans [2].

The pharmacokinetics (ADME) of phenytoin is nonlinear or saturable, which implies that a slight rise in plasma concentration may lead to drug-induced toxicity due to its saturable enzyme metabolism [3,4]. During an incident of acute phenytoin overdose, the metabolic enzyme systems may get saturated, and the clearance of the drug may be akin to zero order kinetics. The plasma protein binding of phenytoin ranges from 90-95%. The drug distribution is rapid from blood to the tissues and is almost completely metabolized in the liver. The plasma phenytoin concentration normally reaches the steady-state level within 1-2 weeks of drug initiation. The half-life of phenytoin is less than 20 h in low doses, but is prolonged in high doses, newborn infants, and elderly people.

Based on the 2011 Annual Report of the American Association of Poison Control Centres (AAPCC), National Poison Data System, it was found that there were a total of 1971 instances of single-substance phenytoin exposures. Out of these exposures, there were 46 cases that resulted in serious consequences and only one fatality occurred [5]. Unfortunately, there is no poison incident data reporting system in our country which is very much necessary for policy makers and regulatory authorities in preventing poisoning deaths in general.

As per published literature, phenytoin poisoning may arise as a consequence of medication/dosing errors, deliberate poisonings, drug interactions leading to compromised elimination, or failure to adhere to prescribed dosages (compliance issues), inadvertent consumption by children, increased vulnerability of geriatric population (due to compromised hepatic metabolism and renal elimination), all of which can result in elevated concentrations of the drug within the body and end up in fatal outcomes [1].

Case report

A 12-year-old girl child was brought to our institute by her mother with alleged history of consumption of 10-15 phenytoin pills (later discovered to be 100mg each, the total overdose supposedly ranged between 1g to 1.5g) when the child was alone at home. The patient was a clinically diagnosed case of Global Developmental Delay with seizure disorder. She had been using phenytoin for the past five years and the history of use of other drugs was not available. She was referred to our hospital after initial decontamination and management of seizures at another secondary care facility (However, the data pertaining to use of activated charcoal for initial decontamination was not available). After her accidental overdose, she had 5-6 episodes of vomiting which contained food particles and tablets. The vomiting was nonprojectile and nonbiliary in nature.

There was no history of pain abdomen, seizure like behaviour, fever, respiratory distress, or any bleeding diatheses in the recent past. The antenatal and postnatal history of child was uneventful, and child was born out of a non-consanguineous marriage. Her childhood immunization was incomplete and complete data of the same was not available.

During the initial evaluation, her weight was of 20 kg, heart rate of 140 beats per minute, respiratory rate of 26/min, afebrile, Spo2 96% with room air, and a blood glucose level of 166 mg/dL; CNS: Deep Tendon Reflexes were brisk in nature, CVS: S1 and S2 were present, RS: Normal vesicular breath sounds were present; GIT: P/A was soft and no organomegaly was noted. Clinical chemistry is as follows, RFT: S. Creatinine 0.8 mg/dL and Blood urea: 36 mg/dL. LFT: Serum bilirubin (total): 0.6 mg%, (direct): 0.2 mg%, (indirect): 0.4%; SGOT: 113 IU/L, SGPT: 21 IU/L, S. Alkaline Phosphatase: 316 IU/L. CBP: Hb: 13 g%, TLC: 16,400 cells/cu mm, Platelets: 4.40 lakh/cu mm, DC: Neutrophils: 80, Lymphocytes: 18, Monocytes: 2, Eosinophils: Nil, Basophils: Nil; PCV: 43%. The patient was admitted in ICU where initial fluid resuscitation was given along with supplemental oxygen, IV antibiotics and IV sedation to control the irritability/seizures. The critical event that led to cardiac arrest was respiratory depression in this case. The child slowly decompensated with decreased respiratory drive which led to a cardiac arrest. The child could not be saved in spite of attempting mechanical ventilation due to failure in achieving return of spontaneous circulation. Serum/Blood phenytoin level was not evaluated. The pharmacogenomics data pertaining to phenytoin metabolism was unavailable in the medical records.

At autopsy, the child appeared ill built and was severely malnourished, and teeth showed a brownish discoloration and gum hypertrophy was noticed. Additionally, all internal organs were intensely congested. The stomach contained about 50 ml of yellow colour fluid, which lacked any distinct odour, and the mucosa appeared congested. Heart, lungs, spleen, kidney, and liver did not show any gross abnormality. Phenytoin was detected in the contents of the stomach, small intestine, blood, liver, and kidney through chemical analysis of the viscera at the Regional Forensic Science Laboratory. The histopathological examination of the liver and kidney (Figures l and 2) revealed no pathological abnormalities. The quantitative analysis of phenytoin was not available. Although liver did not show any pathology at autopsy, a raise of liver enzymes was noticed in clinical chemistry along with a mild elevation of TLC. The cause of death in this case was opined as phenytoin poisoning. The total period of survival after ingestion was about 30-36 hours. However, the child was admitted at our facility about 15 hours prior to death.

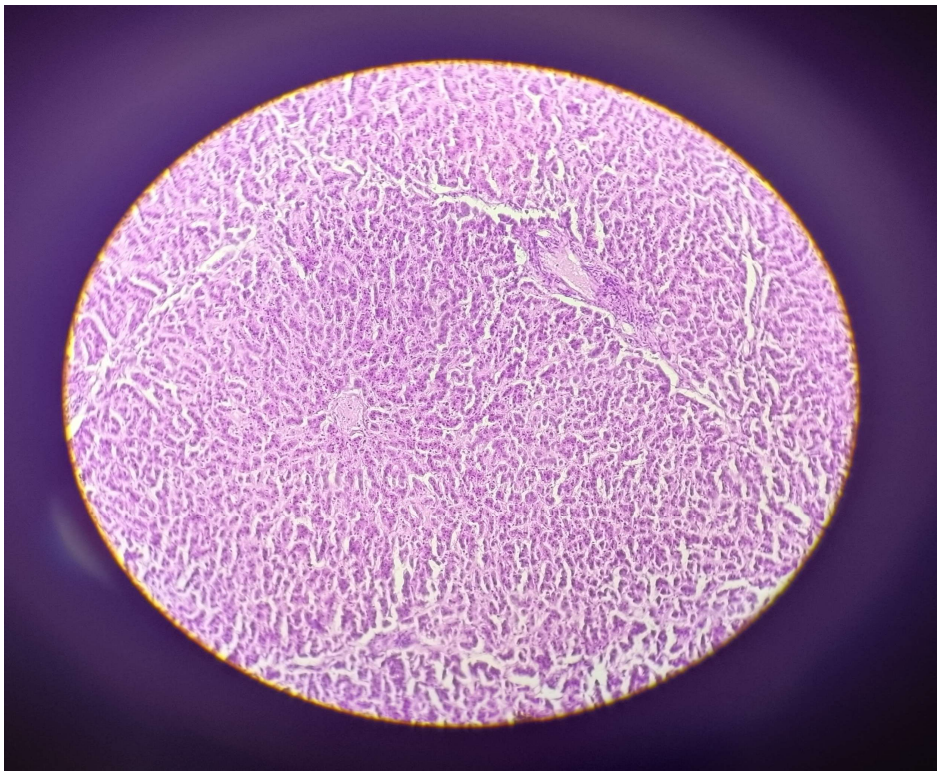

Figure 1. Histopathological examination of liver (Photomicrograph), H & E, Scanner View, within normal limits

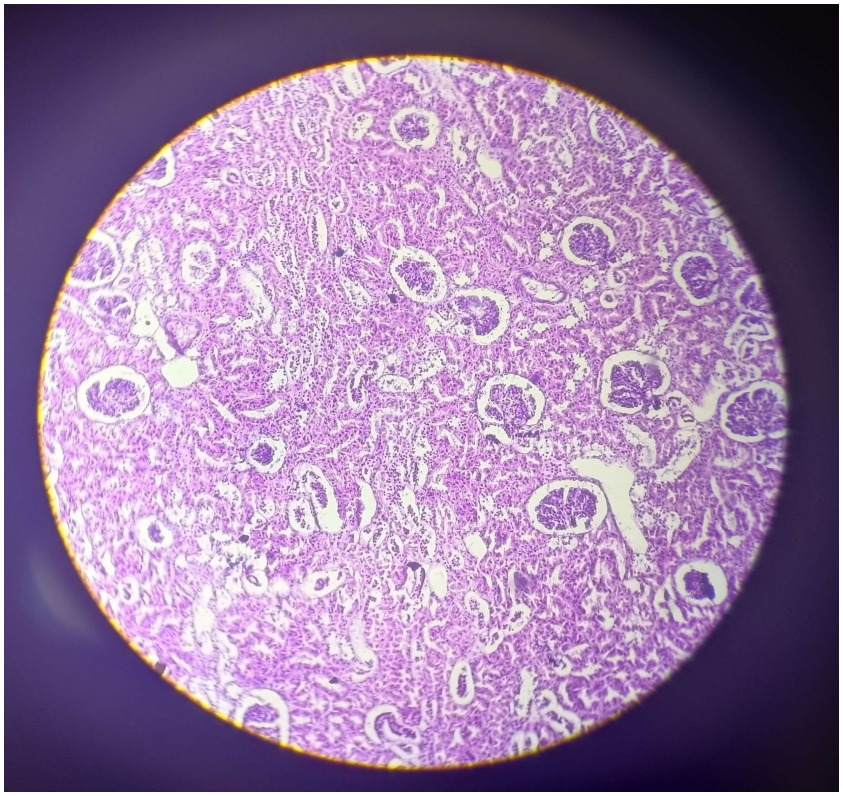

Figure 2. Histopathological examination of Kidney (Photomicrograph), H & E, Scanner View, within normal limits.

Discussion

Phenytoin poisoning can present in many forms, namely acute, subacute, or chronic, and is characterized by a range of clinical manifestations. Neurological manifestations of acute phenytoin toxicity include hyperreflexia or hyporeflexia, aberrant gait, encephalopathy, and rarely seizures. The mental state of an individual can vary along a spectrum, ranging from a state of normal functioning to a state of coma, particularly when there is concurrent ingestion of other CNS depressants. The ophthalmic manifestations of toxicity include nystagmus, ophthalmoplegia, diplopia, and alterations in pupil size. The chronic toxicity of this substance has the potential to result in peripheral neuropathy, priapism, urine incontinence, choreoathetoid movements, dysarthria, dysphagia, and, in rare instances, mortality [4]. The dermal manifestations of toxicity include hirsutism, acne, jaundice, periorbital or facial oedema, erythema multiforme, skin rashes, etc. The overdose of phenytoin has been linked to the development of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, a profound hypersensitivity reaction that typically manifests 2 to 6 weeks following exposure. The symptoms encompass a range of manifestations, such as fever, rash, lymphadenopathy, hepatitis, myocarditis, and various systemic presentations [1].

The intravenous formulation of the medication may lead to cardiovascular adverse effects, including hypotension, bradycardia, and ventricular arrhythmias [1,6]. The occurrence of Purple Glove Syndrome, which is characterized by the presence of limb oedema, discoloration, and pain subsequent to intravenous delivery, has been observed in certain instances.

Gastrointestinal and abdominal manifestations may encompass discomfort localized in the right upper quadrant, as well as symptoms such as nausea and vomiting. Phenytoin is known to cause hepatosplenomegaly and hepatitis. The prolonged exposure to phenytoin can result in chronic toxicity, which has been associated with the development of metabolic disorders such as osteomalacia and hypothyroidism [6]. The adverse effects associated with phenytoin toxicity include cognitive impairment, perceptual disturbances, peripheral nerve damage, increased risk of falls, cerebellar dysfunction, loss of bladder control, abnormal movements, priapism, skin rash, and the development of foetal hydantoin syndrome if the medication is used during pregnancy. This syndrome is characterized by a range of congenital anomalies, including distinctive facial features, ears positioned lower than average, dislocation of the hip joint, and congenital heart problems [4,6].

Fatalities resulting solely from the intake of phenytoin are infrequent. The majority of documented cases entail the consumption of other drugs in conjunction with phenytoin. In instances where individuals have ingested a single dose of phenytoin, fatal outcomes are commonly associated with blood values exceeding 125 mg/L [1]. The treatment in such instances is decided on a case-to-case basis. Patients who need ventilatory support, patients who are hemodynamically unstable, or patients who have abnormal electrocardiograms (ECGs) should be admitted to a monitored setting. Patients presenting with mild to moderate overdoses, exhibiting normal cognitive function, displaying normal

electrocardiograms (ECGs) without any signs of hypotension, bradycardia, or arrhythmias, may be admitted to a hospital bed without the need for continuous cardiac monitoring [1,4,5].

It is recommended to monitor serum phenytoin levels at timely intervals after poisoning for proper management of a case. In order to achieve a precise evaluation of phenytoin concentrations in an instance of over dose scenario, it is important to consider both the bound and unbound forms of the drug present in the bloodstream and factors influencing the availability of free drug like other drug interactions. It is imperative that those who have intentionally overdosed undergo a psychological assessment during their hospitalization to prevent further suicide attempts [1].

Paediatric and adult phenytoin poisoning cases are not much different with respect to clinical manifestations, while the cardiac arrhythmias/manifestations component is an additional consideration in adults. Rapid intravenous injection of phenytoin can cause acute myocardial depression and cardiac arrest due to solvent propylene glycol associated toxicity. In paediatric age group accidental ingestion of pills is the most common cause of poisoning due to pharmaceutical substances. However, since there are a number of *"single pill killers"*, the paediatrician should always be wary about homicidal poisoning in children. The lack of a proper history from the caregivers is one of the important challenges faced in the paediatric ER while dealing with poisoning cases.

A case in literature highlighted the occurrence of encephalopathy in a 7-year-old child due to a medication error involving the double dosing of intravenous phenytoin. Such incidents underscore the high chances of medication errors with drugs like phenytoin [7]. Furthermore, brain-damaged mentally retarded epileptics appear to be unusually susceptible to the side effects of phenytoin [8]. Although death due to phenytoin toxicity alone is less frequent, the factors with can lead death are concomitant ingestion of other drugs (drug interactions), increased genetic susceptibility (viz. cytochrome P450 2C9 poor metabolizer) and preexisting health conditions/co morbidities of the victim [9]. For patients diagnosed with epilepsy, along with intellectual disability, susceptibility to balance disturbances, and cognitive dysfunction, it may be advisable to consider substituting phenytoin with an alternative medication like carbamazepine or oxcarbazepine [8].

The treatment protocol in the event of phenytoin over dose as suggested in literature include gastric decontamination with activated charcoal if the victim presents within one hour of ingestion. Multiple dose activated charcoal is also administered every 2-6 hours until passage of charcoal stools, loss of bowel sounds or improved clinical condition [10]. Owing to the albumin binding ability of phenytoin, the results associated with hemoperfusion, and haemodialysis is equivocal [11]. Irrespective of above stated information, adequate hydration, maintaining of airway, breathing and circulation and other supportive care is paramount in management of phenytoin toxicity. It is also documented that phenytoin could induce status epilepticus and managing the same is also a part of the treatment [12].

Preventing accidental poisoning in children with drugs like phenytoin involves a combination of measures aimed at both proper manufacturing of these drugs and

education of stake holders. The use of child-resistant packaging for medications, particularly for drugs with a narrow therapeutic index like phenytoin (which are usually manufactured as bottles of capsules), can significantly reduce the risk of unintentional ingestion. These packages are to be designed in a way that it would be difficult for young children to open but could be easily opened by adults (packaging with force functioning). Clearly printed dosing guidelines on the packaging, including instructions on how to administer the medication safely in the local language apart from English, can help caregivers avoid dosing errors. A thorough review of treatment undergone in the previous healthcare facility should be considered before administering drugs like phenytoin. In the Indian context, there is a pressing requirement for substantial improvements in drug packaging and labelling, bringing them up to the standards observed in Western countries.

Healthcare professionals, both clinicians and pharmacists should educate patients and caregivers about the importance of keeping medications out of the reach of children, storing them securely, and using proper dosing devices (especially in liquid formulations). This education should also emphasize the potential dangers of even small medication overdoses/errors. The manufacturers could make medications less appealing to children by avoiding attractive colours, shapes, or flavours that might tempt them to ingest the medication. There is also a need to promote safe disposal of unused and expired medications to avoid accidental ingestion and environmental contamination. Launching public awareness campaigns to educate parents and caregivers about the risks of unintentional medication poisoning in children and the steps they can take to prevent it is also necessary in this regard.

From the medicolegal standpoint, all clinicians and pharmacists must be aware of the potential dosage and medication errors possible with drugs like phenytoin (because it is also an enzyme inducer) and its ramifications in litigation [13]. Nevertheless, it is worth mentioning that there were some ‘DILANTIN’ related law suits in the USA few years ago about the issue of liability of drug manufacturers pertaining to risk communication about the potential adverse effects of phenytoin like Steven Johnson Syndrome (SJS), Toxic Epidermal Necrosis (TEN), Cerebellar atrophy, birth defects in the offspring etc.

From a forensic pathologist perspective, during autopsy in a case of phenytoin poisoning, it is advisable to look for the presence of any myocardial fibre disarray or/and interstitial fibrosis in the heart. The findings due to toxicological onslaught on the liver and kidney are also of academic interest albeit they are non-specific. Although literature did not hint towards any homicidal phenytoin poisoning incidents, it is necessary to be prepared for such situations which could always be possible in vulnerable groups like elderly and children.

In brief, the manifestation of phenytoin poisoning encompasses a diverse range of clinical presentations that impact several organ systems, underscoring the urgency of timely identification and intervention in instances of toxicity. By the same token, the present case is a classic example emphasising timely tertiary care in poisoning management. This highlights the requirement for the establishment of poison control centres to educate primary care physicians on handling poisoning cases and

facilitate the timely transfer of these cases to tertiary care centres.

Conclusion

In summary, the narrow therapeutic index of phenytoin warrants the significant attention of healthcare professionals regarding the potential for toxicity. This is crucial not only in terms of therapeutic considerations but also in instances of intentional or unintentional overdosing situations, particularly among paediatric patients. The main focus of treatment is primarily centred on providing supportive care, as there is no specific antidote available as of now. In order to improve safety measures to prevent deaths due to drug overdose, it is advisable for regulatory bodies responsible for drug control to contemplate the implementation of rigorous packaging and labelling protocols for pharmaceuticals administered for chronic medical conditions in the paediatric age group.

Acknowledgements

We thank Dr. Anirudh Suseel Nalumaru MS, MCh for his suggestions in improving the quality of the manuscript. We also thank Dr. Pravin Panditrao Kalyankar and Ms Sri Meghana for their support in editing and revision of the manuscript.

Conflict of interest: None to declare.
Financial support: Nil.
Ethical considerations: Addressed by the authors.

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