Single Case – General Neurology

Phenytoin Toxicity Treatment with Haemodialysis in Epilepsy due to Glioblastoma Multiforme: Case Report and Review of the Literature

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Keywords

Phenytoin toxicity · Haemodialysis · Drug interactions

Abstract

Phenytoin is one of the most commonly used anticonvulsants in the developing world, but lack of monitoring and concurrent medications can easily lead to toxicity. We report the case of a 35-year-old female on phenytoin for symptomatic epilepsy due to previously treated glioblastoma multiforme, who presented with status epilepticus 1 week after being treated for a urinary tract infection. She was loaded with phenytoin and levetiracetam as per emergency protocol but had a persistently low level of consciousness, and her preloading phenytoin level result came back in the toxic range. She was managed conservatively, but after 4 days with no change she was dialyzed and her level of consciousness improved within 24 h, allowing for safe discharge home shortly after. Our case illustrates the option of haemodialysis in phenytoin-toxic patients who do not improve with conservative measures or who may need urgent reduction due to potentially fatal complications of phenytoin toxicity.

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Introduction

Phenytoin is one of the oldest anticonvulsants available, and due to its availability and cheap price is commonly used for treating epilepsy in the developing world, including Kenya. At therapeutic levels, phenytoin follows first-order kinetics, which changes to non-linear zero-order pharmacokinetics in the upper therapeutic and toxic range [1], with levels >20 mg/L being associated with toxicity. The risk of toxicity with phenytoin is high: it has a narrow therapeutic index, is a hepatic enzyme inducer, and is highly protein bound, all of which make it highly susceptible to saturated metabolism by interacting with other drugs [1]. The first documented case of phenytoin toxicity is from 1948, in a patient with epilepsy for 4 years who took an intentional overdose [2]. The risk factors associated with toxicity are acute overdose, toxicity from dose changes or drug error, altered physiology such as in renal failure/cirrhosis, drug-drug/drug-disease interactions, and unintentional ingestion of phenytoin such as from cocaine adulterated with phenytoin [2]. The treatment of phenytoin toxicity is mainly supportive [2], but there are guidelines that suggest consideration of haemodialysis (HD) in cases of coma and incapacitating ataxia [3]. We describe here a case with phenytoin toxicity who was safely treated with HD, which resulted in a good outcome.

Case Presentation

A 35-year-old female was admitted urgently with status epilepticus to our regional tertiary referral centre. She was known to have epilepsy secondary to glioblastoma multiforme which had been resected 6 years prior, followed by postsurgical chemo- and radiotherapy, and with consequent dysphasia and right-sided weakness requiring home-based nursing with her husband. Her seizures were well controlled on phenytoin 100 mg three times a day until this presentation. Further history revealed that she had been treated for a urinary tract infection with nitrofurantoin for 1 week leading to this admission. On assessment, her Glasgow Coma Scale (GCS) score was 8/15, and she had a tachycardia of 110 bpm, with otherwise normal vital observations. Her blood sugar level was normal at 5.6 mmol/L, and cardiovascular/respiratory and abdominal examinations were unremarkable. As per our emergency department protocol, she was immediately loaded with 1 g of phenytoin intravenously, diazepam 2.5 mg intravenously, then levetiracetam 1 g intravenously, and received some intravenous fluid resuscitation before being transferred to the high dependency unit.

Investigations revealed normal full haemogram, urea, potassium, creatinine, peripheral blood smear for malarial parasites, blood culture, electrocardiogram, and unenhanced computed tomography scan of the head. She had a hyponatremia of 126 mmol/L (normal range: 135–145 mmol/L), and urinalysis was turbid with leukocytes. Her phenytoin levels came back at 24 h and were markedly elevated at 65.6 µg/mL (normal range: 10–20 µg/mL). Phenytoin was therefore withheld and levetiracetam continued as maintenance at 250 mg twice a day intravenously. We added empiric piperacillin-tazobactam for treatment of urinary tract infection. She did not have any further convulsions in the ensuing days, but her GCS score remained depressed at 10/15. Repeat serum sodium revealed a further drop to 122 mmol/L, with a raised urine osmolality of 567 mOsm (normal range: <100 mOsm), confirming syndrome of inappropriate antidiuretic hormone which was managed with 3% hypertonic saline (tolvap-

tan was prescribed but could not be afforded by the spouse). However, despite correction of sodium levels, the patient's GCS score remained depressed and her phenytoin levels remained elevated at 72.9 µg/mL. With no other reversible cause found and after consulting with chemical pathology and nephrology specialists, we proceeded with HD to reduce the phenytoin level more rapidly. The patient was dialysed for 4 h using a low-flux dialyser with no heparin or ultrafiltration, and levetiracetam was administered after the session (as this antiepileptic drug is otherwise dialysed out).

After one session of HD the phenytoin levels dropped to 47.3 µg/mL; assuming a linear reduction in levels [3], the predicted level would have been 59.5 µg/mL, which suggests the dialysis offered a further 16.7% reduction in levels (Fig. 1). Before dialysis, the patient's GCS score was improving by 1 point every 2 days, but after dialysis this rate of improvement was doubled at 4 points in 4 days. The patient was back to her normal neurological status on day 13, with a GCS score of 15/15, and was discharged home on levetiracetam.

Discussion

Our patient had been on phenytoin for control of her seizures for many years, but then decompensated after being treated for a urinary tract infection. Nitrofurantoin is known to interact with phenytoin but by reducing levels of the drug [4]. It is possible that there may have been confusion with the capsules leading to an inadvertent overdose, or concomitant use of other over-the-counter medicines that led to the toxicity. The increased epileptogenesis may have been a combination of both the significant hyponatraemia as well as the paradoxical toxic effects of phenytoin, especially if the level is >50 mg/L [5], and intravenous phenytoin is one of the more common causes of in-hospital hyponatraemia [6].

In addition to standard resuscitative measures, activated charcoal can be used if the patient presents early without a depressed mental state [2], but the timing of overdose in our patient was not known and in deliberate overdose cases has been demonstrated to have occurred a few days prior to reaching a comatose state [7, 8]. Reducing the dose of, or altogether replacing, phenytoin can result in improvement of the toxicity symptoms relatively quickly, especially where there is polypharmacy and therefore more drug-drug interactions, e.g., in an elderly person [9]. However, extracorporeal removal of toxins can become necessary to reduce the risk of potentially fatal toxicity complications such as organ failure [8].

The commonest technique reported is HD, and it is sometimes instituted almost immediately [10]. Other techniques that have been used in phenytoin toxicity include continuous veno-venous haemofiltration [11], charcoal haemoperfusion [12], and the molecular adsorbent recirculating system [13]. Although theoretically plasma exchange and haemoperfusion would more efficiently remove phenytoin from the circulation, intermittent HD is the preferred extracorporeal treatment in phenytoin poisoning, with haemoperfusion being an acceptable alternative if HD is not available and where the molecular adsorbent recirculating system is not accessible [10]. There have been case reports with modifications to HD to try and increase the efficiency of toxin removal by using a high-cut-off dialysers which have been effective [7]. Sometimes the treatments can be combined: since phenytoin has a low volume of distribution and a well-adsorbent property to activated charcoal, HD can be combined with charcoal haemoperfusion [14]. HD may lead to a potentially toxic rebound phenomenon in

highly protein-bound antiepileptic drugs such as valproic acid and phenytoin, although this did not occur in our patient; sustained low-efficiency daily dialysis has been demonstrated to prevent this rebound phenomenon in valproic acid toxicity [15]. A comparison of the advantages and disadvantages of various techniques used for extracorporeal drug removal is summarised in Table 1.

Conclusion

Phenytoin remains one of the most commonly used antiepileptic medications worldwide, and its pharmacokinetic properties can lead to unpredictable phenytoin levels leading to toxicity. For people with epilepsy on phenytoin who experience toxicity and who do not respond to conservative measures or are facing potentially life-threatening complications, our case adds to the evidence base that HD should be considered as an adjunct to lower phenytoin levels safely and efficaciously.

Statement of Ethics

Written informed consent was obtained from the patient's spouse.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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None.

Author Contributions

K. Sharma was involved in writing the abstract, introduction, and discussion and in obtaining patient consent. A. Vakil was responsible for drafting the case summary and investigation results. A. Sokwala and D. Sokhi were responsible for conception of the work, critical revisions, and approving the final draft.

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Fig. 1. The phenytoin, sodium, and Glasgow Coma Scale (GCS) score trends for our patient while in hospital.

Table 1. Comparison of extracorporeal drug removal methods

Method	Advantages	Disadvantages
Charcoal haemoperfusion	high adsorption of toxins; not affected by molecular weight, protein binding, or lipid solubility	limited availability; expensive; short half-life
Molecular adsorbent recirculating system	effective for toxins with high albumin binding	limited availability; expensive; slower clearance rate
Continuous veno-venous haemofiltration	can be used in haemodynamically unstable patients; effective for slow continuous removal of toxins that have large volume of distribution or extensive tissue binding; useful even in case of delayed initiation; avoids rebound toxicity	expensive; has to be undertaken in critical care (added cost); less rapid elimination
Intermittent haemodialysis	readily available; no need to transfer to critical care; effective for drugs with low molecular weight, protein binding, volume of distribution, and lipid solubility	may require repeated sessions; risk of rebound toxicity after cessation of treatment
Sustained low-efficiency daily dialysis	shorter sessions; cheaper than continuous veno-venous haemofiltration	less efficient than intermittent haemodialysis; not suitable if haemodynamically unstable; repeated sessions required