

Case Report



Should we do early and frequent charcoal hemoperfusion in phenytoin toxicity?

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Abstract

Phenytoin toxicity or adverse drug reaction is common due to its narrow therapeutic window. Mild and moderate toxicity require supportive care and enteral activated charcoal. In severe toxicity, charcoal hemoperfusion (CHP) have been shown to decrease serum phenytoin half-life and early recovery. Here, we report two cases with phenytoin toxicity who showed marked clinical improvement after early and frequent CHP treatment.

Keywords: Charcoal hemoperfusion, hemodialysis, phenytoin toxicity

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.175936

Quick Response Code:



Introduction

Phenytoin toxicity is commonly seen in renal and hepatic compromise patient and with massive ingestion.^[1] Clinical feature of phenytoin toxicity are reversible and mostly correlate with its serum concentration. Common clinical features are nystagmus, diplopia, ataxia, confusion, disorientation, and hyperactivity; while in severe toxicity leads to coma and seizure.^[1,2] In the absence of antidote, clinical observation and supportive care is required in patients with mild to moderate poisoning; while in the case of severe toxicity, there are few case reports where charcoal hemoperfusion (CHP) have been tried, with both successful and unsuccessful reports. Here, we presented two cases of phenytoin toxicity in whom repeated CHP done with a successful outcome.

Case Reports

Case 1

A 58-year-old man with a known case of seizure

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disorder on phenytoin (100 mg BD) and alcoholic liver disease was admitted to the emergency department with a history of altered sensorium and fall. There was an alleged history of intake of phenytoin tablet of unknown amount. On arrival his vital parameter were heart rate (HR)-88/min, blood pressure (BP)-100/60 mm of Hg, relative risk (RR) - 30/min, SpO₂ - 94% and neurological examination revealed Glasgow Coma Score (GCS) - 9 (E2V2M5) and both pupil 2 mm and reacting to light. Computed tomography (CT) brain was normal, and chest X-ray showed infiltrate in right lower lobe suggestive of aspiration pneumonia. Laboratory blood investigation was normal except serum albumin 2.4 g/dl and total serum phenytoin level of 54 µg/ml. Initially, the patient was managed with enteral activated charcoal. As the sensorium worsened patient was intubated and mechanically ventilated. CHP was started for 3 h and after hemoperfusion patient sensorium improved, but again worsen in few hours.

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How to cite this article: Sahoo JN, Gurjar M. Should we do early and frequent charcoal hemoperfusion in phenytoin toxicity?. *Indian J Crit Care Med* 2016;20:123-5.

Post CHP serum total phenytoin level was 44.5 µg/ml. Further two secessions of CHP were done in a gap of 24 h, and the total phenytoin level decreased to 24 µg/ml with no improve in sensorium [Table 1]. As the patient required prolonged mechanical ventilation for aspiration pneumonia, further CHP was not done. After 6 days, patient sensorium improved along with respiratory parameter and was weaned from mechanical ventilation and extubated. On the 6th day, patient total serum phenytoin level was 16 µg/ml and was started on levetiracetam. On the 7th day, patient was transferred to the ward.

Case 2

A 64-year-old man with a known case of seizure disorder on phenytoin (200 mg OD, sustain release tablet) was found in an altered sensorium state by his relative and was brought to the emergency department. History of normal sensorium 8 h prior to altered sensorium and general examination revealed HR-64/min, BP-108/54 mm of Hg, RR-38/min with labored respiration, oxygen saturation of 94% and central nervous system examination showed both pupil of 2 mm in size and reacting to light with a GCS of 8/15 (E2V2M4). Further history revealed probable intake of 40–50, 200 mg phenytoin tablet. The patient was intubated and mechanical ventilated for airway protection. CT scan of the brain was normal. Further investigation showed total serum phenytoin level of 63 µg/ml. Diagnosis of phenytoin poisoning was made and CHP was started (13 h after last found conscious or in a normal state). During the 3 h period of CHP patient gradually regained consciousness and

at the end patient GCS improved from 8 (E1V1M4) to 9 (E3VTM6). Post CHP total serum phenytoin level decreased to 52 µg/ml but the sensorium gradually deteriorated to pre-CHP level within 2 h. The second cycle of CHP was started after 8 h of the first cycle for 3 h. The patient response was same to the first and the total serum phenytoin level decreased to 40 µmg/ml. Hence, we decided to do hemoperfusion every eight hourly till the total phenytoin level comes down to <30 µmg/ml. A total of 4 cycles of hemoperfusion was done, and the last phenytoin level was 19 µg/ml [Table 1]. There was no significant complication apart from thrombocytopenia (1.9 lacks/µml to 32,000/µml) and leukopenia (10,800 cells/cmm to 3300 cells/cmm). The patient was weaned from mechanical ventilation and extubated on the 3rd day after optimization of serum electrolyte. The antiepileptic medication was changed to levetiracetam and patient was discharged from Intensive Care Unit the following day.

Discussion

Hemodialysis is used to treat selected drugs intoxication. To be removed by hemodialysis the drugs must have certain pharmacokinetics properties such as molecular weight (MW) less than 2000 Dalton, protein binding rate <50%, the volume of distributions <0.75 L/kg and high water solubility.^[3] Serum albumin has an MW of 66,200 Da, so drugs bound to albumin is not cleared by hemodialysis. Phenytoin has an MW of 272 Dalton, the volume of distribution of 0.7 L/kg, extensively bound (90%) to serum albumin and 10% of free drug is responsible for its action.^[1] The plasma half-life ranges from 6 to 24 h at therapeutic

Table 1: Clinical characteristics and outcome of phenytoin toxicity patients using charcoal hemoperfusion

Age/ gender	Serum phenytoin level (pre-CHP) (µg/mL)	Time interval between ingestion and CHP*	CHP				Outcome of patient	Author/year (reference)
			Number of CHP	Time of CHP	Pre-CHP PHT level (µg/mL)	Post-CHP PHT level (µg/mL)		
26/male	75	3 days	1 st	3 rd day	75	62 on 5 th d	Survived	Baehler et al./1980 ^[6]
19/female	~30	18 h	1 st	18 h	~30	16	Survived	Kawasak et al./2000 ^[4]
38/male	87 (347**)	9 days	1 st	9 th	87 (347**)	57 (225**)	Survived	Craig/2004 ^[2]
			2 nd	13 th	88 (350**)	50 (200**)		
35/female	91	91 h	1 st	91 h	91	74	Survived	Eyer et al./2008 ^[5]
			2 nd	108 h	74	45		
			3 rd	133 h	38	28		
4/female	94	9 days	1 st	9 th day	94	56	Survived	Kumar et al./2012 ^[8]
			2 nd	10 th day	56	26		
			3 rd	11 th day	26	23		
			4 th	12 th day	23	12		
58/male	54	13 h	1 st	13 h	54	44.5	Survived	Our 1 st case
			2 nd	40 h	44.5	31		
			3 rd	67 h	31	24		
64/male	63	8 h	1 st	8 h	63	52	Survived	Our 2 nd case
			2 nd	19 h	52	40		
			3 rd	30 h	40	27		
			4 th	41 h	27	19		

*Time since the patient was seen with normal sensorium; **µmol/L. CHP: Charcoal hemoperfusion; PHT: Phenytoin

plasma concentration (10–20 µg/ml) but increases disproportionately as the plasma concentration increase.^[1,4] Phenytoin is metabolized by hepatic enzyme and excreted via the kidney, but the hepatic enzyme is readily saturated at high level (changing from first order kinetics to zero order at high serum concentration).^[4]

The advantage of repeated and frequent CHP is to enhance early drug removal from serum. The plasma phenytoin half-life in overdose patient increase considerably from 24 h to more than 230 h, but during CHP the total and free phenytoin half-life decrease to 3.9 h and 3.2 h, respectively.^[4] The decrease half-life is seen only during CHP and returning to high-level post CHP. This rebound effect is due to the elevation of plasma phenytoin level as a result of redistribution from the deeper compartment.^[2] More than 90% of phenytoin is bound to albumin; this binding has a small binding constant ($k-6 \times 10^6/\text{mol/l}$) with large number (n-6) of binding site.^[4,5] During CHP, the charcoal not only adsorb the free drug but also compete with the albumin for phenytoin and help in dissociation of phenytoin from albumin (low binding constant of phenytoin to albumin).^[4,6] This explain the low half-life of bound and free phenytoin during CHP. Inside the charcoal dialyzed two equilibriums exist, one between the phenytoin and albumin and another between phenytoin and activated charcoal. This explain the high extraction efficiency (up to 45%) of phenytoin in CHP.^[6] In a recent systematic review by the extracorporeal treatments in poisoning workgroup, it has been recommended that use of extracorporeal treatment (ECTR), i.e., intermittent hemodialysis preferably or intermittent hemoperfusion as an alternative, is suggested if prolong coma and/or ataxia is present or expected; and discontinuation of ECTR should be considered when clinical improvement is apparent.^[7] They also recommended that ECTR should

not solely based on dose of phenytoin ingested or serum phenytoin concentration.^[7]

Conclusion

CHP can be an effective way to treat phenytoin toxicity when started early and repeated at frequent interval due to its small binding constant and large number of binding site. However, this was observed only in one patient, and it needs further study to evaluate the high extraction efficiency of CHP in phenytoin toxicity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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