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Phenytoin overdose treated with hemodialysis using a high cut-off dialyzer

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Abstract

We describe the case of a 52-year-old man who presented after having ingested an unknown quantity of phenytoin. Peak phenytoin concentration was 51.2 mg/L (therapeutic range 10–20 mg/L). Five days after admission, the patient became comatose and was intubated. Because of persistent toxic phenytoin levels and unchanged clinical status for 12 days, hemodialysis (HD) was prescribed to enhance elimination of phenytoin. HD was performed using a Gambro Theralite™ filter (Baxter International Inc., Deerfield, USA), a high cut-off filter that allows the removal of molecules of up to 45 kDa. Phenytoin concentration readily decreased during the 8-hour HD treatment from 38.9 mg/L to 27.8 mg/L (28.5% decrease); during HD, phenytoin half-life was 18.5h (compared to 1109.8h before HD and 56.3h after HD), phentyoin clearance averaged 80.1 mL/min and a total of 1.1 g of phenytoin was removed. Albumin removal from the Theralite filter was most important at the beginning of HD. The high clearance of phenytoin obtained with this filter was likely due to its high surface area rather than its capacity to remove the albumin-phenytoin complex.

Key words: Phenytoin, hemodialysis, intoxication, albumin

INTRODUCTION

Voluntary overdose with phenytoin may cause serious morbidity; although fatalities are rare, overdose may lead to prolonged ataxia, coma, and seizures.[1] The American Association of Poison Control Centers documented 2745 phenytoin exposures in 2014, 527 of which had a clinical outcome defined as moderate or severe.[2] Most cases can be managed with standard supportive care, gastrointestinal decontamination, and multiple-dose activated charcoal.[3] The role of extracorporeal treatments (ECTRs) in phenytoin toxicity remains uncertain. Because of phenytoin's high protein binding (90%), it is hypothesized that hemodialysis (HD) using more porous filters capable of clearing serum protein could accentuate clearance of phenytoin. We describe a case of a phenytoin overdose that was treated with HD using a high cut-off filter.

CASE STUDY

A 54-year-old, 61 kg, man with a history of alcoholism and epilepsy was admitted to the emergency room of a community hospital (Quebec, Canada) after having voluntarily ingested an unknown quantity of phenytoin at an unspecified time. There were no other known co-ingestions. The patient was previously taking phenytoin 100 mg three times daily for a number of years for a seizure disorder. Upon admission, the patient's vital signs were normal, but he was agitated, confused, and ataxic.

Initial investigation showed normal biochemistry, normal ECG, kidney function, liver function, and a normal

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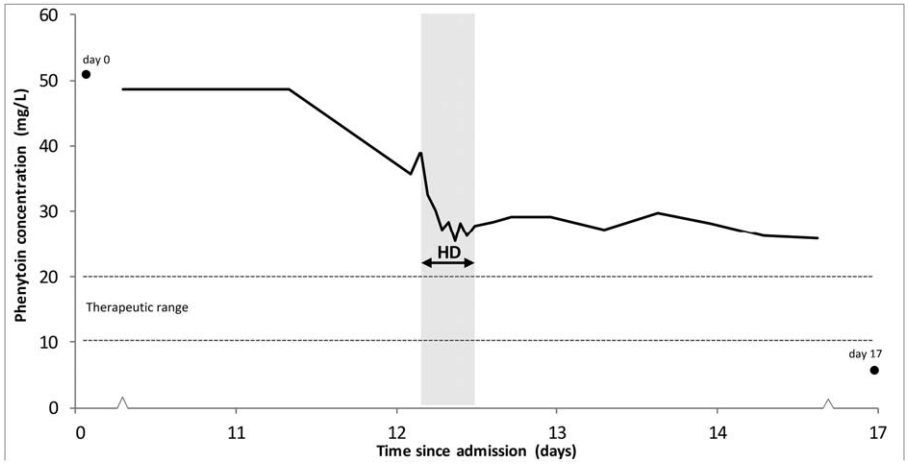

Figure 1 Phenytoin concentration over time.

complete blood count. The total phenytoin level was 51.2 mg/L (therapeutic range 10–20 mg/L); the ethanol concentration was undetectable and urine toxicology screen was negative.

The patient was administered midazolam and thiamine. Activated charcoal was not given because of ileus. The patient was intubated on day 5 to protect the airway. Because of the presence of persistent toxic levels of phenytoin (38.9 mg/L on day 12) and lack of neurological improvement, the patient was transferred to a tertiary care center for hemodialysis.

Upon transfer, the patient had remained dependent of mechanical ventilation but was hemodynamically stable. Laboratory results included a normal kidney function, normal transaminases, and an albumin concentration of 26 g/L. HD was initiated and performed for 8 h via a left jugular 20 cm temporary Quinton catheter and a Gambro Theralite™ filter (Polyarylethersulfone/Polyvinylpyrrolidone membrane, UF coefficient 52 mL/h/mmHg, albumin sieving coefficient = 0.2, surface area 2.1 m^2, Baxter International Inc., Deerfield, USA). Blood flow was prescribed at 400 mL/min, dialysate flow was 750 mL/min, and no ultrafiltration was prescribed. Blood flow was 400 mL/min during the first 6 h, then was lowered to 300 mL/min due to the patient's agitation, and, finally, increased to 350 mL/min during the last hour of HD.

No complications occurred during HD. Upon termination of the treatment, the patient was awake but remained delirious and unable to make eye contact when sedation was lowered, with a phenytoin concentration of 27.8 mg/L. Two 25mg doses of activated charcoal were administered. The patient was extubated 3 days following HD and later discharged from the ICU. He was transferred to the psychiatric ward 20 days after HD and finally discharged from the hospital 12 days later, with no apparent sequelae.

METHODS

Phenytoin sampling

Total serum phenytoin and albumin samples were simultaneously drawn from the arterial (entering) line of the dialyzer and the effluent line approximately every 60 min from the start of HD. Phenytoin was measured by particle enhanced turbidimetric inhibition immunoassay method (Beckman-Coulter DCX600, Mississauga, Canada).

Calculations

1. Apparent half-life ($T_{1/2}$) of phenytoin before, during and after hemodialysis was calculated as: $T_{1/2} = 0.693/Ke$
2. Total body content of phenytoin (TBC) at the beginning of HD was calculated as: $TBC = [phenytoin]_{serum} \times V_D \times W$

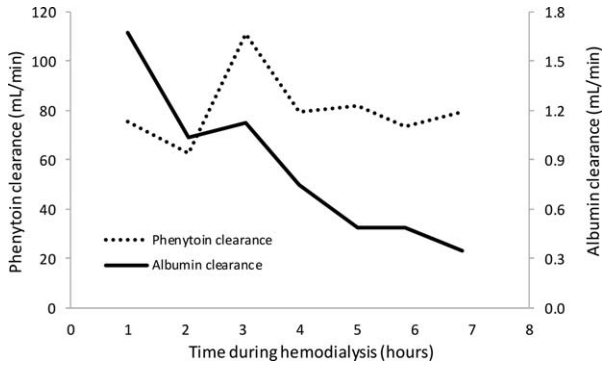

Figure 2 Phenytoin and albumin clearance during hemodialysis.

Table 1 Published reports of HD in phenytoin overdose cases

Authors	Age, Sex, Dose	Peak Phenytoin (mg/L)	ECTR	Dialyzer	ECTR CL (mL/min)[a]	$T_{1/2}$ (HD vs. no HD)
Rubinger, 1979	23 y, M, 10 g	34	Conventional HD	Dialyzer coil, not specified	26	ND
De Schoenmakere, 2004	49 y, F, ND	20.7	HD-HP in series	FX80 (Polysulfone) KUF = 59 mL/h/mmHg Surface area = 1.8 m^2	32[a,b]	ND
Ghannoum, 2010	42 y, F, 3.6 g	50.9	HD	F80a (Polysulfone) KUF = 55.0 mL/h/mmHg Surface area = 1.8 m^2	44[a]	6.8 h vs. 116 h
Gerstman, 2013	23 y, F, ND	193	HD	Rex 25S (Polysulfone) KUF = 102 mL/h/Hg Surface area = 2.5 m2	N/A	Elimination rate=7.75 mg/L/hr vs. 0.66 mg/L/hr[c]
Swartzenburger, 2014	51 y, F, ND	73	HD	ND	N/A	ND
CURRENT CASE	54 y, M, ND	51.2	High cut-off HD	Theralite (PES/PVP) KUF = 85 mL/h/mmHg Surface area = 2.1 m^2	80	18.5 h vs. 53.3 h

[a]Extrapolated from published data.
[b]Assuming a hematocrit of 0.40.
[c]Zero-order kinetics.
CL = clearance; ECTR = extracorporeal therapy; F = female; HD = hemodialysis; HP = hemoperfusion; M = male; ND = no data; $t_{1/2}$ = half-life; y = year old.

3. Recovered phenytoin ($RE_{phenytoin}$) and albumin ($RE_{albumin}$) during dialysis were measured from collected dialysate
4. Instantaneous plasma clearance of phenytoin by HD ($CL_{HD\ INS}$) at various moments was calculated as: $CL_{HD\ INS} = [phenytoin]_{Dialysate} \times Q_D/[phenytoin]_{serum}$
5. Average plasma clearance of phenytoin by HD ($CL_{HD\ AVE}$) was calculated as: $CL_{HD\ AVE} = RE_{phenytoin}/(T \times [phenytoin]_{SERUM\ AVE})$

V_D = Volume of distribution of phenytoin (assumed to be 0.8 L/kg, $[phenytoin]_{serum}$ = serum phenytoin concentration (mg/L), $[phenytoin]_{Dialysate}$ = phenytoin concentration in dialysate (mg/L), Q_D = Dialysate flow rate (mL/min), T = Time (min), W = Patient body weight (kg), Ke = Elimination rate constant (represents the slope from the equation derived by best fit using linear regression log graph).

RESULTS

Phenytoin concentration decreased readily during the 8-h HD treatment (Figure 1) from 38.9 mg/L to 27.8 mg/L (28.5% decrease). A total of 1.1 g of phenytoin was removed during HD, which represents 57.4% of total body burden of phenytoin at the onset of HD. During HD, measured apparent half-life was 18.5 h as compared to 1109.8 h before HD and 56.3 h after HD. Instantaneous phenytoin clearance during HD remained constant during HD and averaged 80.1 mL/min. Albumin loss during dialysis was estimated at 11.0 g, but this removal was highest at the beginning of treatment and steadily decreased as the dialysis went on (Figure 2). A small rebound in phenytoin concentration was observed (5%) approximately 4 h after the end of HD.

DISCUSSION

Phenytoin is a first-line treatment used to treat seizure disorder.[4,5] Toxicity can be observed when phenytoin's total concentration surpasses the therapeutic range (10–20 mg/L). The patient presented here had significant neurological toxicity, which was still manifest 12 days after admission. The mechanism for the extended toxic

concentrations in this case is unclear, but we hypothesize that concretions in the small intestine may have prolonged the absorption phase[6,7] and that reduced clearance may have been present due to saturation of liver enzyme system at supratherapeutic concentration.[8]

The use of ECTR for elimination enhancement of phenytoin in patients with overt toxicity have traditionally been restricted to hemoperfusion[9,10] and therapeutic plasma exchange[11] because of phenytoin's high protein binding (≅90%). Recent reports, however, have shown promise with hemodialysis using high-efficiency dialyzers,[12–17] because of phenytoin's low binding constant to albumin ($K = 6 \times 10^3$/mol/L),[12,18] which provides a constant pool of unbound freely diffusible phenytoin. In 2015, the EXTRIP Workgroup published a neutral recommendation for the use of ECTR in cases of severe phenytoin toxicity, with intermittent HD as the ECTR of choice.[3]

This report is the first description of phenytoin removal using a Theralite™ filter. The treatment was well tolerated and there was marked improvement of phenytoin's toxicokinetics during the procedure: phenytoin's apparent half-life was considerably shortened and over 1 g of phenytoin was recovered. Clearance obtained during HD (80.1 mL/min) was superior to those obtained with prior reports (Table 1).

High cut-off filters are characterized by their large pore size which permit passage of plasma components up to 45 kDa. They have been developed and used for the removal of free light chains in multiple myeloma. Theralite™ membranes have a pore size of 0.008–0.01 μm, up to threefold that of other high-flux membranes. Although albumin has a molecular mass (66.5 kDa) over the theoretical cutoff of Theralite™ filters, the heterogeneity in pore size permits removal of large molecules, especially during convection, as suggested by the sieving coefficient of 0.2 for albumin, 1.0 for β2-microglobulin and 0.9 for myoglobin.[19] In studies, patients treated with Theralite filters have noticeable decrease in albumin concentration and may require supplementation.[20] An in vitro model quantified albumin loss with a Theralite 2100 up to 18 g during an 8-h HD session.[21] In line with the manufacturer's reported albumin loss, it averaged 21 g in patients undergoing a 6-h HD treatment and could reach 60 g per session with convective therapies.[22] This case shows that albumin removal is most prominent at the beginning of HD and decreases rapidly thereafter, which suggests either adsorption of albumin or albumin deposition on the filter (a "protein cake" effect). The albumin loss in this report (11.0 g) was half of what is usually reported, but could simply reflect the lower albumin concentration at the onset of HD.

Compared to a previous report using a modern dialyzer,[12] we obtained a higher phenytoin clearance (80 mL/min vs. 44 mL/min). We hypothesize that this was more due to a higher achievable blood flow (381 mL/min vs. 241 mL/min), a higher dialysate flow (750 mL/min vs. 500 mL/min), and especially a larger surface area of the Theralite filter (2.1 m^2 vs. 1.8 m^2), rather than the dialyzer's ability to remove bound phenytoin. This is suggested by the following observation: At the beginning of HD, the patient's phenytoin concentration was 38.9 mg/L, 90% of which is bound, and the albumin concentration in serum was 26 g/L. The phenytoin content bound per albumin in serum represents $0.9 \times 38.9/26$ or 1.3 mg phenytoin/g albumin. Dialysis removed 11.0 g of albumin (or 14.7 mg of phenytoin bound to albumin), which represents only 1.4% of all phenytoin removed. Additionally, while albumin clearance decreased steadily, phenytoin clearance remained stable throughout the treatment, which further strengthens the hypothesis that phenytoin's clearance during HD was independent of albumin removal. Finally, it is unlikely that the enhanced clearance of phenytoin confirmed in this study is explained by removal of other serum proteins as phenytoin's binding to α-globulins and β-lipoproteins is negligible.[23,24] Further studies are needed to evaluate if filters with similar surface areas and permeability would provide comparable phenytoin clearance, without the unwanted removal of albumin or the elevated cost ($800) of such filters.

CONCLUSION

This is the first case of a phenytoin overdose treated with hemodialysis using a high cut-off dialyzer which greatly accelerated clearance of phenytoin.

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