

High-Flux Haemodialysis Treatment as Treatment for Carbamazepine Intoxication

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Summary

Acute severe intoxication with carbamazepine is associated with seizures, coma and respiratory depression. Traditionally, charcoal haemoperfusion is used to remove the drug. We present a case of carbamazepine intoxication, successfully treated with three hours of high-flux haemodialysis. Thus, haemodialysis using high-flux membranes is a feasible and effective therapeutic option for carbamazepine intoxication.

Key Words: Carbamazepine intoxication, High-flux dialyzer membranes

Introduction

Carbamazepine (5H-dibenzazepine-5-carboxamide) is an iminostilbene derivative with a tricyclic structure. It has a large volume of distribution and peak plasma levels occur between 4-8 hours, and up to 24 hours after ingestion. Because carbamazepine may induce its own metabolism, the half-life is also variable. Initial half-life values range from 18-55 hours, decreasing to 5-26 hours on chronic usage.

Acute carbamazepine intoxication can result in stupor, coma, hyperirritability, convulsions, respiratory depression, hypotension and cardiac arrhythmias. There is no antidote. Because of a high degree of plasma protein binding (75%), forced alkaline diuresis (pKa = 0.82-1.43), peritoneal dialysis and haemodialysis would not be expected to be of great clinical benefit. Conventionally, charcoal haemoperfusion has been used in the treatment but this treatment modality is not widely available and has potential severe side effects. Recently, high-flux haemodialysis and high efficiency haemodialysis have been tried with promising results^{1,2}.

We present a case of carbamazepine intoxication successfully treated with high-flux haemodialysis.

Case Report

The patient was a 19 year-old 47kg lady with post-traumatic epilepsy since the age of 12 years. She also had multiple social problems, was poorly compliant with her medications and has had a previous history of drug overdose. On this occasion, she presented with three minutes generalized tonic-clonic seizure occurring 4 hours prior to admission.

On admission, her Glasgow Coma Scale (GCS) was E2, V1 M1 (4/15). Multiple slash marks were noted on the limbs. Blood pressure was 100/70 mmHg; heart rate 78/min; and respiratory rate 20/min. Pupils reflexes were equal and reactive. No focal neurological deficits were noted. Blood investigations on admission revealed: sodium 137 mmol/L, potassium 4.1 mmol/L, urea 2.2 mmol/L, Hb 12.1 g/dL, TWC 10,000/ μ L, platelets 206,000/ μ L, creatinine 65 μ mol/L, calcium 2.44 mmol/L, magnesium 0.83 mmol/L, AST 18 U/L, ALT 13 U/L and albumin 50 g/L.

The patient was initially thought to have been non-compliant with therapy and to have post-ictal drowsiness. She was managed in the coma position with ECG monitoring. She was loaded with

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intravenous phenytoin, 1gm in 100 ml normal saline over 30 minutes.

Nine hours after admission, her GCS was noted to be E1, V1 and M5 (7/15). Phenytoin 100 mg three times daily (tds) was continued. As she had a spike of fever 39.5°C, i.v. ceftriaxone once daily and oral metronidazole 400 mg tds via naso-gastric tube were initiated for treatment of possible aspiration pneumonia.

Twenty-four hours after admission, her GCS deteriorated to E1V2M3 (6/15). CT brain was normal. Plasma carbamazepine level was measured and noted to be high, 25.23 µg/ml (Therapeutic range 4 – 8 up to 12 µg/ml). High-flux haemodialysis with HF80 Fresenius polysulfone dialyzer (1.8 m²) was urgently performed via femoral catheter for three hours. Blood pump was 200 ml/min and there was no net fluid extraction.

At completion of haemodialysis, the carbamazepine level was 14.99 µg/ml and her GCS improved to E4M6V4 (4/15) after dialysis. Subsequent management include hydration and oral activated charcoal (10 tablets of 200 mg, i.e., 2 gm tds).

Twelve hours after dialysis, the plasma carbamazepine level dropped to 7.53 µg/ml and she recovered full consciousness. She then confessed that she had consumed 30 tablets of 200 mg carbamazepine, i.e., 6,000 mg, 6 hours prior to admission.

Discussion

Total carbamazepine concentrations and toxic manifestations are not directly correlated. With increasing plasma concentrations, a greater percentage of patients are likely to be symptomatic. However, severe toxicity has been reported despite "therapeutic" levels. As gastrointestinal absorption of carbamazepine is slow and unpredictable, peak levels may not be seen for up to 72 hours, serial drug concentration monitoring are important to detect the peak plasma concentration.

Due to its anti-cholinergic properties and poor solubility in aqueous media, carbamazepine in the form of tablets may remain in the gastrointestinal tract for extended periods of time. Thus, gastric lavage should also be considered in patients with significant intake, even hours after ingestion. Carbamazepine is well adsorbed by multiple doses of activated charcoal. This

case demonstrates the need for a high index of suspicion with good history taking and prompt verification of drug overdose by measurement of plasma carbamazepine level for the diagnosis of carbamazepine intoxication.

This case also demonstrates that haemodialysis using high-flux membranes is a safe and effective alternative approach to charcoal haemoperfusion in the treatment of severe carbamazepine intoxication. Symptomatic improvement was observed immediately after only one session of haemodialysis treatment. Because of its high protein binding, haemodialysis was initially thought to have limited benefit in removing carbamazepine from plasma. However, several recent case reports showed that high-flux haemodialysis was effective in the treatment of severe carbamazepine poisoning and resulted in rapid clinical improvement¹.

Moreover, most drugs and their metabolites are only active in unbound form. Thus, haemodialysis will be helpful for reducing the unbound substance to reduce the toxic effects as long as a significant proportion of the drug remains in the intra-vascular compartment. Low-molecular-weight solutes (<500 daltons) are readily filtered and diffuse easily through the pores of the membrane. Carbamazepine is 236.27 daltons and thus unbound substance is easily dialyzable in theory.

Our patient weighed 47kg. Based on volume of distribution of 1.4 L/kg, the estimated amount of carbamazepine removed during dialysis would be $(25.23-14.99) \times 1.4 \times 47 = 674 \text{ mg}^3$.

Applying first order elimination kinetics for plasma level falling from 14.99 µg/ml to 7.53 µg/ml in 12 hours, if k represents drug elimination rate constant, A is the drug level at time t after initial drug level sampling, and A₀ is the initial drug level measurement. $\ln A = -kt + \ln A_0$, thus $k_{\text{body}} = 0.0574 \text{ /hour}$
 $t^{1/2} = 0.693/k$, the half-life is 12.1 hours in this patient.

Calculating 25.23 µg/ml dropping to 14.99 µg/ml in 3 hours,

Therefore, $k_{\text{total during dialysis}} = 0.174 \text{ /hour}$

From $k_{\text{total during dialysis}} = k_{\text{dialysis}} + k_{\text{body}}$,

thus $k_{\text{dialysis}} = 0.116 \text{ /hour}$

Actual drug removal by dialysis

$= [k_{\text{dialysis}} / k_{\text{total during dialysis}}] \times \text{observed removed drug} = 451 \text{ mg}$

Therefore, a net of 451 mg carbamazepine was removed by these 3 hours of high-flux dialysis.

Clearance = $k \times V_d$ (where V_d is volume of distribution).

Therefore, dialysis clearance of carbamazepine = 7.64 L/hour, i.e., 127 ml/min.

Body clearance of carbamazepine = 3.78 L/hour, i.e., 62.9 ml/min.

Thus, the calculated dialysis clearance of drug in our patient exceeded that reported by Kielstein et al (59 ml/min)¹.

1.8 m² of dialyzer surface area and 200 ml/min were applied in this patient compared to the 1.2 m² and 300 ml/min in Kielstein et al's report. This demonstrates that a higher effective surface area of dialyzer could improve the efficiency in removal of carbamazepine, superior to that achievable by higher blood flow rates.

The body clearance of carbamazepine was equivalent to 0.08 L/hr/kg or 1.34 ml/min/kg and thus was equivalent to the ranges of previous report³.

Dialysis Clearance of unbound drug
= (1 - proportion of protein binding) x blood flow rate
= (1 - 0.75) x 200 ml/min = 50 ml/min

The high calculated dialysis clearance rate of 127ml/min in our patient exceeded that of the dialysis clearance rate of unbound drug (50ml/min). This suggests a high dissociation rate of protein-bounded carbamazepine as occurs in the countercurrent flows in haemodialysis supplemented by the increased flux across the larger pore sizes of the dialyser membrane.

Other undetermined factors include the ultrafiltration coefficient of dialyzers and trans-membrane pressure may play a role in influencing the clearance rate of carbamazepine.

Finally, our case confirms that haemodialysis with high-flux dialyzers, is effective in the treatment of carbamazepine intoxication. It is easier to perform, more readily available nowadays, of lower cost and has fewer complications than charcoal haemoperfusion. It is a good therapeutic option in the treatment of severe carbamazepine intoxication.

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References

1. Kielstein JT, Schwarz A, Arnavaz A, Sehlberg O, Emrich HM. and Fliser D. High-flux hemodialysis – an effective alternative to haemoperfusion in the treatment of carbamazepine intoxication. *Clin Nephro* 2001; 24: 484-86.
2. Schuerer DJ, Brophy PD, Maxvold NJ, Kudelka T, Bunchmun TE. High efficiency dialysis for carbamazepine overdose. *J Toxicol* 2000; 38: 321-23.
3. Hardman JG, Goodman-Gilman A. The pharmacological basis of therapeutics (Ed. 10). *Pharmacokinetic Data*, pp 1935. McGraw-Hill, New York, 2001.