MANAGEMENT OF MILD VALPROIC ACID TOXICITY WITH HEMODIALYSIS – A CASE REPORT

Chow NK*, Heng LM

Department of Pharmacy, Hospital Kulim, Jalan Mahang, 09000 Kulim, Kedah, Malaysia.

*Author for correspondence

ABSTRACT

The management of Valproic Acid (VPA) toxicity is mainly supportive treatment. Invasive management such as hemodialysis (HD) and hemoperfusion were only used in isolated cases where patient is highly VPA toxic, which results in coma. We described a case of mild VPA toxicity (VPA serum concentration 326.42mcg/mL), where the patient was successfully treated with two hours of low-flux HD with no complication. While the guideline of indication of HD in VPA toxicity has yet to be published, low-flux HD can be an effective treatment in cases of mild VPA toxicity, if other supportive measures failed or not available.

KEYWORDS: Valproic acid toxicity; hemodialysis; therapeutic drug monitoring; pharmacokinetic

INTRODUCTION

Valproic acid (2-propylpentanoic acid; VPA) is widely prescribed for the treatment of epilepsy, bipolar mood disorder (BMD), and for migraine prophylaxis. VPA toxicity is an uncommon problem seen in clinical practice. However, due to its increased usage, accidental and intentional overdose can occur. Serious VPA toxicity may lead to coma, confusion, somnolence, hallucinations, cerebral edema and even death. Currently, the VPA toxicity management recommended include initial stabilization and resuscitation, decontamination, pharmacologic therapy, hemodialysis (HD) or hemoperfusion. There are isolated case reports and systematic review regarding management of VPA toxicity, yet, a consensus guideline or protocol is still not available. Hereby, we report a case of VPA toxicity successfully treated with two hours of low-flux HD, resulting in a marked reduction of VPA serum concentration and toxicity symptoms subsided.

CASE PRESENTATION

A 30-year-old woman presented to the Emergency Department at 4.30am due to vomiting and excessive drowsiness after multiple medications ingestion at around 2.30am. The empty medications strips include missing of eight tablets paracetamol, ten tablets chlorpheniramine maleate, ten tablets sodium valproate (Epilim®), and twenty tablets gabapentin. Patient has no underlying epilepsy or psychiatric related illness, and denied high risk behaviour or history of substance abuse. The medications ingested were taken from her uncle who has BMD. Upon admission, patient was not responding to call and pupils sluggish bilaterally (2mm/2mm). Vital signs were normal with oxygen saturation 100% and blood glucose 5.7mmol/L.

MANAGEMENT AND OUTCOME

Patient was given 50g oral activated charcoal (AC) at 6.45am but could only tolerate 25g. She was then sent for brain computed tomography (CT) scan. The serum VPA concentration taken at 5 hours post ingestion for Therapeutic Drug Monitoring (TDM) measured by fluorescent polarization (Cobas Integra 400 plus analyzer, Roche Diagnostics (M) Sdn. Bhd.) was 326.42mcg/mL (therapeutic range 50-100mcg/mL). Paracetamol, salicylic acid, phenytoin and

carbamazepine toxicity had also been ruled out. After CT scan, patient was noted to be drowsier with Glasgow Coma Score (GCS) of 12/15, laboured breathing and was not respond to pain stimuli. The patient was then intubated, ventilated and sedated and was admitted to the intensive care unit. All the blood investigations were normal. Low-flux HD (via a right femoral venous catheter) was performed for two hours with blood flow rate 150 mL/min and was uneventful. On the next day, the second TDM result (12 hours post HD) showed a marked decrease in VPA level to 37.14mcg/mL (non-toxic). Patient had regained full GCS with normal arterial blood gas (ABG) result. She was then extubated and referred to psychiatrist and allowed to discharge two days later with no complication.

DISCUSSION

The classification of VPA toxicity is dose dependent. Mild: Dose >200mg/kg and having risk of CNS depression; moderate: >400mg/kg and having risk of multi-organ system toxicities; severe: >750mg/kg and is potentially lethal. Maximum therapeutic dose is 60mg/kg/day.¹ Since the exact quantity of VPA ingested by the patient might not be accurate, we can only categorize patient based on the symptoms of CNS depression, which is mild toxicity.

Overdose of gabapentin and chlorpheniramine maleate can cause subtle mental status changes and drowsiness too. However, only mild clinical effects have been documented following significant overdose of gabapentin and chlorpheniramine due to their benign side-effect profile. VPA has neither significant interaction nor synergism effect with both gabapentin and chlorpheniramine.

The time for the enteric-coated sodium valproate tablet to reach maximum concentration (T_{max}) normally occurs within 3-7 hours. In this case, deterioration of patient condition happened at around 5 hours post ingestion might be due to the high serum VPA concentration at T_{max} . Decontamination with activated charcoal is best to be administered within 0.5-1 hour of VPA ingestion for maximum effect. AC may still be indicated after one hour post ingestion for enteric coated preparation due to the potentially delayed absorption. As this patient was admitted two hours post ingestion and could not tolerate AC, other modes of treatment are required.

Some literatures had documented naloxone for the reversal of sedation and coma at VPA level of 487.8mcg/mL and in cases of opioid co-ingestion.² Since this patient's condition was manageable after intubation, naloxone was not given. On the other hand, L-carnitine is also suggested for hyperammonemia associated with carnitine deficiency caused by long-term or high-dose VPA use. L-carnitine is not available in our setting and this patient had normal liver function tests with no hyperammonemia.

Therefore, the modes of treatment left to enhance elimination of VPA from the body available in our setting were HD and hemoperfusion. Despite the benefit of extracorporeal elimination techniques is undeniable, the clear indication and method of the techniques in VPA toxicity is still undefined. Charcoal hemoperfusion is proved to be more superior in clearing protein-bound and lipid soluble drugs, with equal effectiveness in clearing water soluble and small molecule drugs if compared to HD.³ Since VPA is poorly water soluble (solubility in water 1.3mg/mL at room temperature), charcoal hemoperfusion seems to be more eligible treatment option. However, it has limitation in terms of complications, such as thrombocytopenia, electrolyte imbalance, disturbances in coagulation and technically and logistically more complicated.^{3,4}

On the other hand, VPA is a small molecule (MW 144.2) with about 90% plasma protein binding. At supratherapeutic level, the binding sites may become saturated, causing the amount of free drug to increase rapidly.⁴ Low molecular weight and decreased protein binding during toxicity make it ideal for removal through HD. With 2 hours of low-flux HD conducted, the VPA serum concentration was able to reduce by 88.6%.

Rebound phenomenon was reported by a few studies, where a slight increase in VPA levels noted after termination of HD.^{4, 5} This suggests that VPA may not follow single compartment kinetics at toxic concentration and redistribution from other body compartments may occur. In order to avoid rebound concentration of VPA after HD, repeated TDM level of VPA was scheduled at 12 hours post HD.

CONCLUSION

We have shown in our patient that HD is effective to eliminate excess VPA concentration in acute poisoning case when supportive measures failed or not available. More studies are required to identify the recommended indication for HD based on VPA serum concentration and also weighing the risk and benefit of HD or hemoperfusion in different clinical situation. More evidences are also needed regarding the TDM sampling time of VPA serum concentration in acute toxicity cases, including the initial post ingestion sampling time and also post dialysis sampling time, by taking the rebound phenomenon into consideration.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia for his permission to publish this article.

CONFLICT OF INTEREST

The authors affirm that this case report is original and have no conflict of interest to disclose.

REFERENCES

1. Truven Health Analytics. Micromedex Drug Information. Michigan: Truven Holding Corp; 2017.
2. Thanacoody HKR. Chronic valproic acid intoxication: reversal by naloxone. *Emerg Med J* 2007; 24: 677–678.
3. Winchester JF. Hemoperfusion. In: Drukker W, Parsons FM, Maher JF, editors. Replacement of renal function by dialysis: a textbook of dialysis. Netherlands: Springer; 1983: 305-322.
4. Meek MF, Broekroelofs J, Yska JP, Egbers PHM, Boerma EC, van der Voort PHJ. Valproic acid intoxication: sense and non-sense of haemodialysis. *The Journal of Medicine*, Netherlands, October 2004; 62 (9): 333-336.
5. Van der Wouden EA, Dekkers A, Kruis HME, van Geijlswijk IM, Tjan DHT, Feith GW. Extracorporeal elimination in acute valproate intoxication. *BMJ Case Reports* 2009.