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Journal of Clinical Toxicology

Case Report

Severe Toxic Myocarditis Following Sodium Valproate Poisoning: A Management Hurdle

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ABSTRACT

Sodium valproate is a commonly reported medication with self-inflicted overdose causing morbidity and mortality with severe toxicity. Myocarditis is not a commonly reported complication in valproate poisoning. There is no consensus guideline for the management up to date. We are reporting a case of severe myocarditis with refractory hypotension which was successfully treated with High-dose Insulin Euglycemic Therapy (HIET). We highlight the importance of anticipating toxic myocarditis as a complication of valproic acid poisoning and the possibility of restoration of "metabolic hunger" by HIET which could have been caused by the depletion of myocytic L-carnitine activity.

Keywords: Sodium valproate poisoning; Toxic myocarditis; High dose insulin euglycemic therapy; Poisoning

INTRODUCTION

Sodium valproate is a valproic acid preparation commonly used as an anti-epileptic medication. It is being used to treat bipolar affective disorder as a mood stabilizer and prescribed as a migraine prophylaxis [1]. It is a branched-chain carboxylic acid with a narrow therapeutic range (50-100 µg/mL). [2] Self-poisoning with valproic acid preparations is reported worldwide with an array of clinical complications including multi-organ dysfunction, severe metabolic acidosis, cytopenia, and hyperammonemia encephalopathy. [2] We are reporting a case of acute severe valproic acid poisoning complicated with myocarditis following a self-inflicted overdose.

CASE PRESENTATION

A 48-year-old lady from central province, Sri Lanka admitted with self-ingestion of 21 tablets of 200 mg sodium valproate with a suicidal intention. She was diagnosed with bipolar affective disorder and was on sodium valproate 400 mg twice daily. She was admitted to the toxicology unit, teaching hospital Peradeniya 5 hours following ingestion. She denied vomiting, nausea, regurgitation, abdominal pain, faintness, increased sleepiness, or fever. On examination, the patient was conscious and rational. Her vital parameters were stable with a blood pressure of 120/86 mmHg regular pulse rate of 80 beats per minute and peripheral saturation of 98% on ambient air. Her systemic examination was normal.

Initial hematological and serum investigations were normal (Table 1). Arterial blood gas analysis revealed a pH of 7.36, pCO_2 of 41 mmHg, HCO_3 of 24.3 mmol/L with an anion gap of 7.7 mmol/L and lactate level of 0.6 mmol/L.

Investigation	Result	
Complete blood count	White blood cells	9.6 × 103/µL
	Neutrophils	7 × 103/µL
	Hemoglobin	11.3 g/dL
	Platelets	455 × 103/µL
Serum albumin	34.5 g/L	
Serum creatinine	46.0 µmol/L	
Serum sodium	135.7 mmol/L	

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Received: 22-Apr-2024, Manuscript No. JCT-24-31558; **Editor assigned:** 25-Apr-2024, PreQC No. JCT-24-31558 (PQ);**Reviewed:** 09-May-2024, QC No. JCT-24-31558; **Revised:**16-May-2024, Manuscript No. JCT-24-31558 (R);**Published:** 23-May-2024, DOI: 10.35248/2161-0495.24.14.568.

Citation: Shantha DWA, Kulasinghe A, Hettiarachchi NM (2024) Severe Toxic Myocarditis Following Sodium Valproate Poisoning: A Management Hurdle. J Clin Toxicol. 14:568.

Serum potassium	3.6 mmol/L
Serum magnesium	0.88 mmol/L
Serum corrected calcium	2.13 mmol/L
Blood urea	1.2 mmol/L
SGOT	41 U/L
SGPT	14 U/L
Creatine phosphokinase	393 U/L
PT/INR	0.92 seconds
Random blood glucose	6.2 mmol/L

Table 1: Initial blood investigations.

The patient started a multiple-dose activated charcoal protocol where she was given 50 g of activated charcoal 4 hourly three doses. Patient was started on intravenous crystalloid (0.9% NaCl), Omeprazole as a gastric mucosal protector and patient was monitored to identify organ failures. On day two following admission patient developed gradually worsening tachycardia and hypotension. Her blood pressure dropped to 84/54 mmHg with a pulse rate of 120 beats per minute. Initial ECG showed sinus tachycardia with flattening of the T wave in inferolateral leads (Figure 1). The patient denied chest pain but complained of generalized malaise without fever. Repeated ECG revealed widespread T-wave inversions which rose the suspicion of myocarditis (Figure 2). High sensitivity troponin I was significantly positive with a value of 1888 pg/mL (<58 pg/mL) and 2D ECHO cardiogram showed global hypokinesia with globally impaired left ventricular function (Ejection fraction-40%).

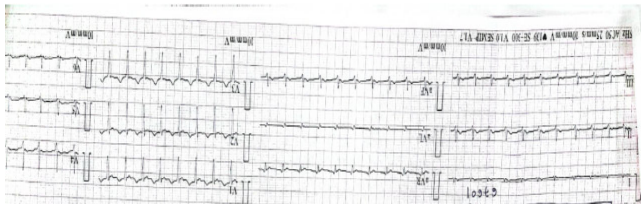

Figure 1: ECG on day 2 shows sinus tachycardia with inferolateral T wave flattening.

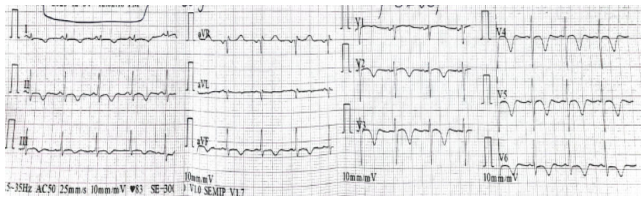

Figure 2: Repeat ECG with wide-spread T wave inversion.

The patient was started on intravenous noradrenalin which was titrated up to 0.6 µg/kg/minute. The patient has developed shortness of breath and clinical examination revealed bilateral fine basal crackles. Point of care ultrasonography showed multiple B-lines and chest X-ray showed features of pulmonary edema (Figure 3).

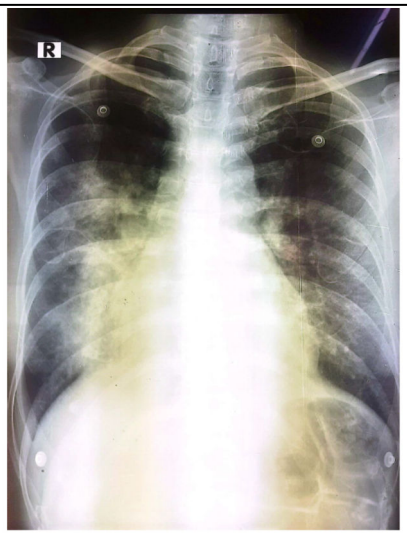

Figure 3: Chest X-ray with features of pulmonary edema.

Intravenous furosemide 5 mg/hour infusion was started and considering poor response to initial inotrope therapy, started on intravenous dobutamine as well. Despite two inotropes patient has had persistently low blood pressure. Therein high-dose insulin euglycemic therapy was initiated with intravenous insulin 0.5 units/kg/hour. Euglycemia and serum potassium levels around 4 mmol/L was maintained with 10% dextrose and intravenous KCL infusions considering the possibility of refractory toxic myocarditis.

The patient was clinically improved with a stable blood pressure of around 110/70 mmHg and a heart rate of around 76 beats per minute. A dropping trend of troponin titer was observed (1880 pg/mL 942 pg/mL 855 pg/mL). Inotropes and oxygen were tailed off while the patient was started on an Angiotensin-converting enzyme inhibitor, cardio-selective beta blocker, and mineralocorticoid receptor inhibitor for heart failure optimization. The patient was discharged after 20 days of inward treatment with cardiology review where repeated 2D-ECHO cardiogram showed improvement in left ventricular function.

RESULTS AND DISCUSSION

Toxic myocarditis is a known entity following exposure to different medications and toxins. Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hematine, interleukin inhibitors, clozapine, heavy metals, scorpion, bee and wasp stings, snake, and spider bites, carbon monoxide, inhalants, phosphorus, arsenic, and sodium azide are some of the established agents [3].

Valproic acid overdose is usually associated with central nervous system complications including coma, hyperammonemia encephalopathy, and severe hepatic failure, but it is not commonly associated with myocarditis though there were cases of arrhythmias and hypotension [4]. There is a case-control study

in Australia using 105 cases which showed that co-ingestion of clozapine and sodium valproate increases the risk of clozapine-induced myocarditis [5]. Our patient did not have established coronary artery disease. However, she developed persistent hypotension following a sodium valproate overdose (105 mg/kg) fulfilling the criteria for myocarditis. She has had new onset cardiac failure with electro cardio-graphic, ECHO cardio-graphic, and myocardiocytolysis markers which confirm the diagnosis of myocarditis according to the European Society of Cardiology (ESC) task force criteria for myocarditis [3]. We have not measured the serum valproic acid levels due to the unavailability of the laboratory facility but with the fact that there were no other established risk factors and offending agents, we started treating the patient as toxic myocarditis secondary to sodium valproate overdose.

Valproic acid is a highly protein-bound molecule with a low volume of distribution (0.1 to 0.4 L/kg) and its elimination half-life varies between 10-16 hours [6]. It is mainly metabolized by the liver and only 3% will be excreted by the kidneys [6]. Considering the toxicokinetic, hemodialysis was used in several instances in severe poisoning where it showed rapid clearance of valproic acid and successful recovery from Central Nervous System (CNS) complications [7,8]. Due to hemodynamic instability and preserved CNS and liver functions hemodialysis was not taken as an option of treatment. Instead, we have optimized the inotropic support and cardiac failure management to stabilize the vital organ perfusion to support the natural elimination process.

Most of the CNS effects due to valproic acid toxicity can be attributed to L-carnitine-based pathophysiological mechanisms. It is an essential co-factor that improves the transportation of fatty acid to mitochondria and acts as the rate-limiting step in ketogenesis in astrocytes [9]. Intravenous L-carnitine is used in severe poisoning where it exhibits satisfactory outcomes [1]. L-carnitine has an important role in myocytes since it is a pivotal factor in fatty acid oxidation in mitochondria which improves the myocardial contractility and calcium homeostasis [10]. Considering the above concept, we have postulated that there can be a state of "metabolic hunger" in myocytes due to hindrance of the carnitine activity which manifests as hypotension refractory to multiple inotrope therapy in our patient.

HIET therapy is a standard mean of treatment in calcium channel blocker and beta-blocker poisoning which enhances cardiac contractility by improving glucose and lactate uptake by the myocytes, accelerating lactate metabolism, stimulating calcium-dependent ATPase activity in the sarcoplasmic reticulum and increasing calcium influx in mitochondria [11,12]. Intravenous L-carnitine was not available in the hospital setting and then the patient was started on High-dose Insulin Euglycemic Therapy (HIET) as a measure to support the "metabolic hunger" of the myocytes. The patient got improved and we were able to gradually wean off the inotropes. Standard management for cardiac failure was initiated when blood pressure was stable including Angiotensin-converting enzyme inhibitor, cardio-selective beta blocker, and mineralocorticoid receptor inhibitor.

CONCLUSION

This is one of the rare cases of toxic myocarditis following sodium valproate. Overdose presented with refractory hypotension which was successfully treated with high-dose insulin euglycemic therapy. And other supportive measures in a resource-limited setting. It is important to monitor the patients with valproic acid overdose, anticipating myocarditis as one of the life-threatening complications.

AUTHOR CONTRIBUTIONS

All authors examined, assessed, and involved in the management of the patient. All authors collected and analyzed data. All authors read and approved the final manuscript.

FUNDING

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Written informed consent was obtained from the patient.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

Authors acknowledge the patient who consented to publish the data and the health care team and para medical team who involved in the management.

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