Case Report

Valproate induced thrombocytopenia and renal dysfunction: Case report

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ABSTRACT

Valproate acid (2-propylpentanoic acid; VPA) is a branched-chain carboxylic is one of the most common drug used in management of epilepsy. The major side effects known are hepatic dysfunction, thrombocytopenia and renal tubular injury. Although most cases result from overdose and death is rare event.

Keywords: Valproic acid (VPA)

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CASE HISTORY

Two and half year-old child, a known case of mental retardation (full term vaginal delivery, history of birth asphyxia and seizures present)with refractory seizures brought with complaint of fever, cough, cold, decrease oral acceptance since 3 days and respiratory distress and decreased urine output for the last one day. On examination, child was febrile with heart rate of 120/min, respiratory rate of 56/min, oxygen saturation of 90% with intercostal and subcostal retractions. Child was on antiepileptic drugs (valproate 45 mg/kg since 6 month of age). Child was admitted in pediatric intensive care unit with a presumptive diagnosis of pneumonia and severe respiratory distress and put on intravenous fluid, antibiotics (ceftriaxone) and oxygen therapy. Initial investigation revealed hemoglobin of 9 gm/dl, total leucocyte counts 2500/mm^3, polymorphs 80%, lymphocytes 18%, platelet count one lakh/mm^3, blood urea 217 mg/dL and serum creatinine 2 mg/dL. Chest radiography showed features of aspiration pneumonia. On second day of admission child had bleeding from gums and hematuria. Child also developed progressive thrombocytopenia (platelet count 20000/mm^3). Due to worsening of respiratory distress and pulmonary bleed child was put on mechanical ventilation. As the patients was having thrombocytopenia a possibility of valproate induced thrombocytopenia was kept and valproate was stopped and phenytoin was started and serum valproate level were sent. MRI brain revealed sequelae of hypoxic ischemic insult and EEG suggested generalized seizure disorder. Renal function improved (blood urea decreased to 67 mg/dLand later on came to be normal that is 30 mg/dl) with improvement in urine output and platelet count. Respiratory distress also improved with no further episodes of bleeding from ant other site. The biochemical parameters during the hospital stay have been shown in (**Table 1**). Serum valproate level came to be high that is 250 mg/L (therapeutic range 50-100 mg/L). Child improved clinically and was discharged on phenytoin (8 mg/kg/day) and levatiracetam (20 mg/kg/day). He was started on feeds with antireflux measures and advised physiotherapy and stimulation. As patients platelet count and renal functions improved on stoppage of valproate, and valproate levels came to be high the thrombocytopenia and deranged renal functions were attributed to valproate toxicity. Similar findings were observed in another 4 years child with mental retardation and refractory seizure.

Table 1: The biochemical parameters of the patient during the hospital stay.

Timing	Blood Urea (mg/dl)	Serum Creatinine (mg/dl)	Platelet count (lakh/mm^3)	Action taken
Before starting valproate (8 months back)	25	0.5	2.5	
Just prior to admission	NA	NA	NA	
At admission: on valproate (45 mg/kg)	217	2	1	Valproate continued
Day 2	200	1.9	20000	Valproate stopped, phenytoin started
Day 5	127	1.3	50000	Phenytoin 8 mg/kg/day Levetiracetam 20 mg/kg/day
Day 7	67	0.8	1.2	Continue phenytoin and levatiracetam
Day 8	30	0.6	1.5	Continue phenytoin and levatiracetam

DISCUSSION:

Sodium Valproate is commonly used as a major drug for the treatment of various types of epilepsy. Major adverse effects include hepatic and pancreatic dysfunction, thrombocytopenia, hyperammonemia and weight gain. Oxidative stress has been proven to be involved in VPA-induced toxicity. Earlier hyperammonemia was the only renal side effects but now there have been various case reports of renal tubular injury due to valproate toxicity leading to development of Fanconi syndrome [1-5]. Recent evidence suggests that oxidative stress caused by free radicals in kidney cells contributes to the pathogenesis of VPA-induced nephrotoxicity. The levels of oxidative stress markers, lipid peroxidation (LPO), and protein carbonyl (PC) content were significantly elevated. Valproate leads to a significant increase in reduced glutathione (GSH) and non-proteinthiol level (NP-SH). VPA exposure altered the activities of glutathione metabolizing enzymes such as glutathione-S-transferase, glutathione peroxidase, and glutathione reductase and leads to increased secretion of N-acetyl-β-d-glucosaminidase (NAG) in the urine which is a marker of renal tubular injury [6].However there have been no case reports of valproate induced renal dysfunction leading to uremia and increase creatinine levels. There has been only one case of acute overdosing of sodium valproate in a child who presented with coma, seizures and anuria and the progressive renal insufficiency was attributed to rhabdomyolysis and myoglobinuria [7].

In contrast to our case there was one study that demonstrate that VPA has a beneficial effect on the development of proteinuria and the progression of glomerulosclerosis in the experimental Adriamycin nephropathy model [8]. The mechanism explained was that VPA halts glomerulosclerosis through inhibition of podocyte detachment, apoptosis, and proliferation. Hence still the effect on valproate on renal functions is not clear and studies are required to confirm the effects.

CONCLUSION

Valproate therapy can cause deranged blood urea and creatinine levels apart from hyperammonemia and renal tubular injury.

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