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VALPROIC ACID INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

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Abstract:

Valproic acid (VPA) has been used in clinical practice since 60's, with a relatively favourable safety and efficacy profile. Pancreatitis, hepatotoxicity and teratogenicity are the most significant adverse drug reactions. VPA-induced hyperammonemia include: lethargy, impaired consciousness, focal neurological signs and symptoms and increased seizure frequency. More rare described symptoms are: aggression, ataxia, asterixis, vomiting and coma. We report a patient with migraine who developed hyperammonemic encephalopathy in association with valproic acid. The condition improved with a strike of valproic acid and the treatment with carnitine at a dose of 50mg/kg/day for four days.

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INTRODUCTION:

Valproic acid is a broad-spectrum antiepileptic drug that is approved for the treatment of several types of seizures. It is a branch chained fatty acid and can be also prescribed for the treatment of bipolar disorder, schizoaffective disorder, social phobias, neuropathic pain, and for the prophylaxis and treatment of migraine headaches **[3]**. VPA has numerous drug interactions and toxicities; severe toxicities include hepatic damage, pancreatitis, teratogenicity, thrombocytopenia, and hyperammonemia**[4]**. The normal action of VPA is the combined pharmacological effect of increased GABA levels, inhibition of NMDA receptors and blockade of neuronal sodium channel **[4].** Possible mechanism of VPA in migraine prophylaxis is that valproate increases brain GABA levels and in doing so may suppress migraine related events in the cortex, peri vascular parasympathetics or trigeminal nucleus caudalis**[7]**. Some experimental evidence shows that it suppresses neurogenic inflammation and directly attenuates nociceptive neurotransmission and appears to increase protein in the brain that turn off brain chemical that lead to migraines. In addition to it, may decrease the substances in the brain that are related to migraine symptoms **[7]**. The normal dose of valproic acid for migraine prophylaxis is 250mg oral twice daily. There are three forms of encephalopathy is noted in children and adults who are treated with valproic acid. They are (1) encephalopathy as direct toxic effect of VPA with high toxic effects of VPA with high levels of VPA but normal ammonia, (2) hyperammonenemic encephalopathy and (3) encephalopathy with impaired liver function . Encephalopathy is one of the rare complications of VPA therapy. The typical signs of VPA-induced encephalopathy are impaired consciousness, sometimes marked EEG background slowing, increased seizure frequency, with or without hyperammonemia**[4]**. Here we review a case report on valproic acid induced hyperammonemic encephalopathy.

CASE REPORT:

A 15 year old female patient of 43 kg weight came to hospital with the complaints of nausea, vomiting, headache and syncope. History of similar episodes before 2 weeks and now evaluated as migraine headache. The patient was put on sodium valproate 250 mg od. After 4 days of treatment the patient developed vomiting associated with loss of consciousness, hallucination, diplopia and giddiness. General examination revealed that normal vital signs and the patient showed cerebellar dysfunction in the form of severe degree of ataxia and nystagmus. The motor and sensory examinations were normal but deep tender reflexes were decreased. Laboratory investigations include hematology, liver function test, renal function test, serum electrolytes and blood glucose were normal. However, serum ammonia level was raised to 157µg/dl (normal range 30-80µg/dl). Level of serum valproic acid was found to be in normal range 55µg/ml (normal range 50-100µg/ml). CT scan discloses that brain cervical hypo dense lesion. With this background of clinical observations and laboratory assessment we pharm D students found that valproic acid induced hyperammonemic encephalopathy was confirmed. The primary treatment for VHE is the withdrawal of the offending drug. Then administered carnitine of dose 50mg/kg/day.L-carnitine supplementation has been shown to improve the symptoms of VPA related toxicities. On the second day of the withdrawal of the VPA we found that the serum ammonia level dropped to 121 µg/dl. The serum ammonia level was reduced to 90 µg/dl on the third day and the patient attained 67 µg/dl (within the normal range) on the fourth day. L-carnitine is safe and can be administered orally or intravenously at a dose of 50 to 100mg/kg/day.

DISCUSSION:

The rare complication of VPA is hyperammonenemic encephalopathy. Hyperammonemia is a metabolic condition characterized by elevated levels of ammonia in the blood **[5].** Increased entry of ammonia to the brain is a primary cause of neurologic disorders, such as congenital deficiencies of urea cycle enzymes, hepatic encephalopathy's. Patient was in supratherapeutic VPA levels, but VHE is well documented potential complication of the use of VPA in medical literature and it may occur in people with normal ammonia levels **[8]**. This case report shows the relevance of monitoring side effects appearing in course of treatment with Valproic acid.There are so many probable mechanisms showing the relationship of VPA with carnitine. Ammonia is a by-product of the conversion of amino acids to ketoacids. In the liver, ammonia is converted to urea, which is then excreted in the urine **[8]**. The metabolite of valproate reduces the hepatic N-acetyllutamate concentration, which is an obligatory activator of carbomyl phosphatise synthetaseI, the first enzyme in urea cycle. Decline in carbomyl phosphatise synthetase I activity results in defective ammonia utilization and accumulation of ammonia. Another mechanism explains that VPA plays a role in the reduction of hepatic carnitine levels **[9].** Carnitine is an essential amino acid necessary in beta oxidation of fatty acids and energy production in mitochondria. This reduction in carnitine levels results in the decreased beta-oxidation of fatty acids which in turn results in the reduced levels of Acetyl CoA. This decreased level of acetyl coA disrupts

urea cycle resulting in accumulation of ammonia.it has been hypothesized that valproic VPA may induce a carnitine deficiency in children and in adults and causes non-specific symptoms of hepatotoxicity , hyperammonenemia**[6**]. *Jim Wadzinski et al* in his study pointed out that hyperammonemia stimulates increased glutamine synthetase activity, causing increased production of glutamine in astrocytes. Cerebrospinalfluid and blood levels of glutamine may be elevated in conjunction with hyperammonemia**[8].** *Mark D. Baganz et al* in their study illustrates that astrocytes have been shown to be responsible for brain ammonia de- toxification and initially respond to hyperammonemia by increasing metabolic activity through the proliferation of mitochondria and rough endoplasmic reticulum. Metabolic exhaustion ensues whereby the astrocyte cytoplasm becomes watery and glycogen laden. Disturbance in the composition of the extracellular fluid and osmotic gradients eventually results in cerebral edema. Elevated levels of glutamine have been found in the cerebrospinal fluid of patients with hyperammonemia and may contribute to brain damage, extrapyramidal symptoms and cognitive impairment **[9].**

CONCLUSION:

VHE is a rare complication of VPA. Clinical pharmacist has a key role in this area, in recommending the best treatment and improving the pharmaceutical care. The patient on VPA therapy should monitor the serum ammonia levels and VPA levels. We suggested there is a need of urinary amino acid assay. The primary treatment is the discontinuation of VPA and the treatment with carnitine 50-100mg/kg/day.

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REFERENCES:

1.Carla Souse. valproic acid induced hyperammonemic encephalopathy –a potentially fatal adverse drug reaction. Springer open journal; 2013

2.Carr RB, sherwsburry K. Hyperammonemia due to valproic acid in the psychiatric setting.Am J Psychiatry;2007.Pg.1020-1027

3.Jim Wadzinski, MD, Ronald Franks, MD, David Roane, PhD, and Max Bayard, MD. valproate asso ociated hyperammonemic encephalopathy. JABFM; September-october 2007. Pg.499-502.; Vol.20 No.5.

4.Thorsten Gerstner, Deike Buesing , Elke Longin , Claudia Bendl , Dieter Wenzel , Brigitte Scheid , Gisela Goetze, Alfons Macke, Gerhard Lippert, Wolfgang Klostermann , Geert Mayer , Regine Augspach-Hofmann , Sabine Fitzek, Carl-Albrecht Haensch, Markus Reuland, Stephan A. Koenig. Valproic acid induced encephalopathy 19 new case in Germany from 1994-2003-a side effect associated to VPA –therapy not only in young children. ELSEVIER seizure ;2006.P.443-448;vol.15.

5. VikrantMittal,SunandaMuralee,and RajeshR.Tampi . valproic acid induced hyperammonemia in the elderly; a review of the literature. Hindawi publishing corporation, case reports in medicine;2009

6.Amitav Rath,J.Jaishree Narayanan, G V S Chowdhary.valproate induced hyperammmonemic encephalopathywith normal liver function.Neurology India;2005.p.226-228;vol.53/issue/2

7. Cutrer FM, Limmroth V, Moskowitz MA.Possible mechanisms of valproate in migraine prophylaxis.pubmed; 1997 April.:P.93-100;Vol. 17(2).

8. Jim Wadzinski, Ronald Franks, David Roane, Ma Bayard. Valproate associated hyperammonemic encephalopathy.J Am Board Fam Med 2007;20;499-502
Doi:10.3122/jabfm.2007.05.070062

9.Naresh Kumar, MK Daga, Tarun Kumar, Narendra Singh Choudhary, P Shunmuga Sundaram. Valproate-induced Hyperammonaemia. JIACM 2008; 9(3): 221-3

10. Mark D. Baganz and Peter E. Dross. Valproic Acid-Induced Hyperammonemic Encephalopathy: MR Appearance. AJNR: 15, October 1994:1779-81