Hyperammonemic encephalopathy secondary to chronic Valproicacid overdose

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ABSTRACT

Hyperammonemic encephalopathy secondary to Valproate therapy is an uncommon adverse affect. We had a 70year old female, known case of epilepsy on sodium Valproate form 3 years presented with drowsiness, slurring of speech. Investigations were done Magnetic resonance imagingBrain and Liver Function Tests were normal, Serum Valproate and Serum Ammonia levels were increased. Valproate was withdrawn and patient was started on L – Carnitine. Serum Ammonia levels decreased and patient symptoms subsided. Hyperammoneic Encephalopathy should be suspected in patients on Valproate presenting with Encephalopathy symptoms.

Keywords: HyperammonemicEncephalopathy, Sodium Valproate, Epilepsy, L- carnitine, Serum Ammonia

INTRODUCTION

Valproate is a commonly used drug in epilepsy, seizures, migrane.Valproic acid requires carnitine to enter the liver mitochondria and go into the ß-oxidation process. Therefore, in cases administrating a high therapeutic dose chronically or an acute over dose of valproicacid, carnitine depletion, can occur which results invalproic acid accumulating outside the mitochondria. This process results in abnormal ammonium elimination in the urea cycle. Additionally, valproicacid toxic metabolites can inhibit carbamoyl phosphate synthetase that catalyses the first step of Urea cycle, which is carbamoyl phosphate formation from ammonia and thus increasing ammonia levels. As ammonia levels increasing in the brain, the extracellular level of glutamate increases as the glutamate uptake is inhibited. Concurrently, glutamine synthesis increases and builds up in the astrocytes which result in swelling of the astrocytes and cerebral adema. Although valproic acid is used, hyperammonemia is a very common adverse effect, it rarely results in encephalopathy. The response to treatment with carnitineand stoppage of Valproate may prevent a fatal outcome[1].

CASE REPORT

A 70 yrold female who is known case of epilepsy andValproate for 3 years was brought to the casualty. She presented drowsinessand slurring of speech Liver Function Testsand Magnetic resonance imaging were done immediately and they were normal. Serum ammonia Valproate done (which were raised).Then Valproate wasstopped andcarnitine was given, she improved and finally herSerum ammonia levels decreased

Investigations : Plasma ammonia levels 120.8 µg/dl (27- 90µg/dl)

Serum Valproate : 104.1 µg/ml (50-100 µg/ml)

DISCUSSION

Valproate induced Encephalopathy is a rare side effect. It is a serious disease that can lead to death. It is characterized by acute or sub acute level of consciousness to lethargy to coma and vomiting. Valproate will undergo mitochondrial oxidation and (Proprionyl Co- A) and (Valpproyl Co- A) are formed which inturn inhibits N – acetyl glutamate synthase inturn decreases N – acetyl glutamate which is responsible for activation of carboamyl phosphatise synthase 1 which is used in the conversion of ammonia to urea. In this way urea production is decreased resulting Iammonia accumulation leading to hyperammoneic encephalopathy. L- carnitine is the active form of carnitine and is essential co factor in beta oxidation of fattyacids in the liver. Long term use of Valproate is associated with depletion of serum carnitine levels, primarily by combing with it to form Valproate carnitine which is excreted in urine and secondarily during treatment with Valproate, renal reabsorption of both free carnitine and acylcarnitine are decreased [2,3].

Carnitine deficiency leads to decreased in energy, because Acyl Co- A is not transported to mitochondria and hence beta -oxidation of fatty acids does not occur resulting in decreased ATP production. Carnitine deficiency leads to accumulation of Acyl Co- A cytosol, in turn blocks urea cycle and Carnitine is also useful for the synthesis of N- Acetyl glutamate present in the mitochondrial matrix.

Because of the above 2 criteria: Hyperammonemia may develop with carnitine deficiency as the production of urea is disrupted in mitochondria. Thus, carnitine deficiency plays an important role in the development of hyperammonemia and Valproate induced Hyperammoneic Encephalopathy [4,5.]

CONCLUSION

Early diagnosis and prompt discontinuation of sodium Valproate is associated with subsidence of clinical manifestation. The altered sensorium after the administration of Valproate and the reversibility of the site of consciousness following its withdrawal and also on treating with carnitine decreased ammonia levels were established the diagnosis of Valproate induced encephalopathy

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