Two Cases of Valproate-induced Hyperammonemic Encephalopathy Without Hepatic Failure

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Abstract

We report two children with localization related epilepsies, who presented with somnolence, seizure exacerbation, behavioral alteration, decline in speech and cognitive abilities, and ataxia while being treated with a combination of valproate and topiramate, but had previously tolerated valproate with other antiepileptic drugs. These children had elevated serum ammonia, normal transaminase levels, and generalized slowing of EEG background activity during encephalopathy, which promptly reverted back to normal along with clinical improvement following withdrawal of valproate. To our knowledge, this is the first documentation of valproate-induced hyperammonemic encephalopathy enhanced by topiramate from India. We intend to alert internists, pediatricians, psychiatrists and neurologists about this underrecognized adverse effect of antiepileptic drug polytherapy. ©

INTRODUCTION

Valproate, a widely used broad-spectrum antiepileptic drug (AED), is also being increasingly used in the treatment of psychiatric disorders and as an antimigraine prophylactic agent.¹ Hyperammonemic encephalopathy (HE), with or without hepatic failure, is a rare but serious adverse effect of valproate therapy.¹ Children younger than two years, those with urea cycle defects or carnitine deficiency, and those on multiple AEDs are predisposed to valproate-induced HE with hepatic failure.¹² However, hepatic dysfunction is notably absent in majority of patients with valproate-induced HE.³⁻⁵

Topiramate is a new AED with a broad spectrum of antiepileptic activity used for indications similar to that of valproate.⁶ There are few recent reports of patients with epilepsy who developed HE during combined treatment with valproate and topiramate, although they have tolerated prior therapy with valproate alone.⁷⁻⁹

We encountered two children during the last three years, who developed HE while on treatment with a combination of valproate and topiramate. Through this report, which appears to be the first documentation of valproate-induced HE in the Indian literature, we intend to alert internists, pediatricians, psychiatrists and neurologists about this rare and often unsuspected drug adverse effect.

CASE REPORTS

Patient 1

A 5 years girl, with normal birth and developmental milestones, had a generalized tonic clonic seizure during sleep at the age of 4 years. After initiation of carbamazepine, the child remained seizure-free for six months. The semiology of subsequent seizures consisted of behavioral arrest with frequent eye blinks. The treating pediatrician added sodium valproate and lamotrigine to carbamazepine. Subsequently, topiramate was added and carbamazepine was tapered off. Two weeks after the institution of topiramate, the child started having sudden flexion or extension of the head and falls several times daily. Her language and scholastic performance declined. When referred to us, the child (body weight of 20 kg) was receiving 400 mg valproate, 100 mg lamotrigine and 50 mg topiramate daily.

On examination, the child had asterixis, gait ataxia and nonfluent speech. Video-EEG monitoring showed a markedly slow background activity, multifocal and generalized spike and wave discharges, and several extratemporal complex partial seizures. Brain MRI, blood counts, liver and renal function tests and urine aminoacidogram were normal. Serum ammonia was 104 µg/dl (normal 17-80 µg/dl). Within a week following withdrawal of valproate, the child became seizure-free, asterixis and ataxia disappeared, and speech became fluent. A repeat EEG revealed near-normal background and infrequent bilateral centro-temporal spike discharges.

When the seizures recurred after one month, the treating pediatrician maximized the doses of lamotrigine and topiramate and restarted valproate. Within four days, the child developed...
head drops, ataxia and language deterioration. Repeat liver and renal function tests were normal. Serum ammonia was 294 µg/dl. We stopped valproate and tapered off topiramate. Within a week, the seizures stopped, serum ammonia level normalized, and language improved to the pre-existing level. During the last six months, the child has remained seizure-free on lamotrigine monotherapy.

**Patient 2**

A 12 years boy, with normal birth and developmental milestones, had simple febrile seizures between the age of 1.5 and 4.5 years. He received valproate monotherapy and remained seizure-free till seven years of age, when valproate was tapered off. A few months later, he had a febrile illness with status epilepticus, which was diagnosed as encephalitis. After recovery, patient started having complex partial seizures characterized by visual hallucinations, behavioral arrest and clonic movements of both upper limbs. The EEG and brain MRI were normal. After failure to control the seizures with carbamazepine, diphenyl hydantoin, vigabatrin, lamotrigine and clonazepam, valproate was restarted and topiramate was later added. Six months after initiation of topiramate, the child (body weight 43 Kg) was hospitalized for poor scholastic performance, decline in speech and impaired attention span, while receiving 1200 mg valproate, 100 mg topiramate, and 4 mg clonazepam. Blood counts, liver and renal function tests were normal. Serum ammonia was 147 µg/dl. The EEG showed generalized slowing of background activity. With discontinuation of valproate, his attention, speech, reading and writing abilities markedly improved, and the hand tremor disappeared. EEG showed normalization of the background activity with bilateral central spike and wave discharges. While on treatment with 200 mg topiramate and 5 mg clonazepam, he had occasional partial seizures during sleep, but the scholastic performance had remarkably improved.

**DISCUSSION**

The patients in this report were children with localization related epilepsies in whom overzealous therapies lead to simultaneous usage of multiple AEDs. They developed encephalopathic features on a combination of valproate and topiramate, but had previously tolerated valproate (without topiramate) well. They had elevated serum ammonia and pronounced generalized slowing of EEG background activity, which promptly reverted back to normal with clinical improvement when valproate was withdrawn. There were no clinical or laboratory evidence of hepatic failure. In Patient 1, inadvertent reintroduction of valproate to topiramate and lamotrigine combination resulted in recurrence of HE.

Although rarely occurs when valproate is used alone,1 HE more often occurs when this drug is used in combination with other AEDs.3,4 HE is seen in children5 and adults6 This complication is not dose dependent, develops within days or weeks after initiation of valproate therapy or introduction of another AED to valproate, and disappears when valproate is withdrawn.1,3,4 Phenobarbitone and phenytoin are well known to facilitate valproate-induced HE.3,4

In recent years, enhancing effect of topiramate on valproate-induced HE is being increasingly noticed.7,9 Hamer et al7 reported two adult patients with focal epilepsy who tolerated valproate in different combinations with other AEDs, but developed HE when combined with topiramate. Login et al9 documented three children with medically refractory focal epilepsy who had tolerated valproate with other AEDs, but manifested HE in combination with topiramate.

The early symptoms of valproate-induced HE without hepatic failure are subtle with somnolence, vomiting, behavioral disturbances, cognitive decline, seizure exacerbation and ataxia.8,9 These can progress on to stupor and coma. The EEG shows diffuse slowing of the background activity.8,9 Serum ammonia levels are elevated with normal serum bilirubin, alkaline phosphatase and transaminases levels.3,4,10 Blood ammonia levels do not correlate with valproate-induced encephalopathy. Hyperammonemia can occur in asymptomatic patients on treatment with this drug,5 and encephalopathy can rarely occur with blood ammonia levels within the normal range.10

A high index of suspicion is required to diagnose valproate-induced HE. Behavioral changes may be ascribed to post-ictal state or nonconvulsive status epilepticus. Seizure exacerbation may prompt the clinician either to increase the dose of existing AEDs or to add more AEDs. Considerable overlap exists in the EEG findings between HE and nonconvulsive status epilepticus.10 Since serum ammonia level may at times be normal, amelioration of encephalopathic features on withdrawal of valproate may be the only way to clinch the diagnosis. Because of these reasons, valproate-induced HE may be a grossly underdiagnosed entity.

Valproate increases ammonia levels through both hepatic (due to decreased hepatic urea production through valproate-induced inhibition of liver carbamoyl phosphate synthetase I) and renal (due to stimulation by valproate of glutaminase activity in the renal cortex) mechanisms.10 Topiramate facilitates hyperammonemia probably through inhibition of carbonic anhydrase (which increases ammonia due to decrease in the mitochondrial urea synthesis in liver) and cerebral glutamate synthetase (which detoxifies cerebral ammonia).7,9

Our experience with these two patients with valproate-induced HE without hepatic failure tell us the following: 1) valproate-induced HE may not be uncommon, 2) in addition to standard AEDs, new AEDs like topiramate may enhance the occurrence of HE, 3) even subtle clinical features such as excessive somnolence, seizure exacerbation, and behavioral disturbance in a patient receiving valproate, especially in combination with other AEDs, should alert the clinician about HE, 4) normal or marginally elevated serum ammonia levels do not exclude HE, and 5) since this complication more often occurs when valproate is used along with other AEDs, unnecessary AED polytherapy should be avoided.

**REFERENCES**

1. Dean JC. Valproate. In: Wyllie E. The Treatment of Epilepsy;

**Announcement**

2nd World Congress of Interventional Cardiology will be held from 24-27th Feb. 2005, at Hotel Taj Mahal, Mumbai. First 400 registrations will get complimentary accommodation.

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**Announcement**

*Second National Asthma Update*

Conference on Asthma, COPD and Other Airway Diseases, 8-9 January, 2005, SP Medical College, Bikaner, Rajasthan. Satellite Symposium at Jaisalmer

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