

Valproate Induced Hypoactive Delirium in a Bipolar Disorder Patient with Psychotic Features

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Abstract

Delirium may present with hyperactive, hypoactive or mixed clinical pictures. The signs of hypoactive delirium are lethargy, confusion, apathy, hypersomnia, muttering, difficulty in maintaining attention, and difficulty in understanding and performing commands. Valproate is commonly used for the treatment of epilepsy and bipolar disorders. It is also used for the management of alcohol withdrawal delirium and agitative-aggressive deliriums. However, few reports are available about the valproate-induced delirium. In this report, we present a 46 years-old woman with bipolar disorder for 14 years. During her last two hospital admissions, she had been diagnosed with manic episode with psychotic features and she had received valproate. She experienced three hypoactive delirium episodes lasting 2-3 days throughout the treatment period of first week. The patient predominantly had the following signs; vomiting, hypersalivation, confusion, drowsiness, dysphasia, and hypoactivity. At the first day of delirium episode, serum valproate level was found to be within the therapeutic range (98.4, 117.1, and 65.6 µg/ml; respectively). In addition, she had normal results of cranial MRI, complete blood count, urine analysis, electrocardiogram, ALT, AST, albumin, bilirubin, BUN, creatinine and electrolytes. The serum ammonia level of the patient could not be measured due to limitations of laboratory facilities. The patient's consciousness improved dramatically 2-3 days after cessation of valproate.

In conclusion, valproate can induce delirium at therapeutic blood levels in some patients via various mechanisms and this side effect has to be considered during valproate use.

Key Words: Bipolar disorder, valproate, hypoactive delirium

INTRODUCTION

Delirium develops secondary to organic causes and is a pervasive functional disorder of the brain, which primarily presents with fluctuations in consciousness and may completely resolve with timely and appropriate treatment. It is hard to communicate with such patients due to fluctuating consciousness and hallucinations, if present. They are usually anxious patients and may have impulsive and inappropriate behavior. Impaired orientation, attentional focusing, perception, speech, and sleep may be observed in such patients, and their affects can change rapidly. In delirium, motor retardation, astonishment, apathy, somnolence, retarded speech, inattention, and inability to perceive and perform orders may be prominent clinical features, and

such presentations are referred to as hypoactive delirium (American Psychiatric Association 1994; Askin 2008).

Common etiologies of delirium include multiple drug use, intoxication or drug withdrawal, cerebrovascular accidents, severe head trauma, generalized bodily trauma, infections, neoplastic diseases, metabolic abnormalities, electrolyte and acid-base imbalance, renal insufficiency, liver insufficiency, cardiac and pulmonary disorders, endocrine disorders, hypo- or hyperglycemia, nutritional disorders, major operations, epilepsy, hypoxia, and hypovolemia. Children and the elderly, and people with severe organ insufficiency, and neurological or psychiatric problems are at increased risk for delirium (Aldemir et al. 2001; Askin 2008; Voyer et al. 2009).

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Bipolar disorder is a psychiatric disorder with various clinical presentations and a wide spectrum of symptoms, from mild euphoria to severe psychotic states, which include delusions and hallucinations. Bipolar disorder can present with exacerbations and may have a tendency towards chronicity. Currently, lithium salts, valproate, and atypical antipsychotics are commonly used for the treatment of bipolar disorder. After valproate was determined to be as effective as lithium in the treatment of bipolar disorder, it became one of the drugs of first choice in these patients (Buckley 2008; Wilting et al. 2008). When evaluating bipolar patients, valproate is recommended as a drug of first choice if multiple mood episodes, irritability, aggressiveness, impulsivity, or hyperactivity are detected in the psychiatric history (Swann et al. 2002). A few studies have suggested valproate for controlling agitation and delirium in inpatients with severe physical diseases that do not benefit from antipsychotics or short-acting benzodiazepines (Kahn et al. 1988; Bourgeois et al. 2005).

For the treatment of manic episodes, valproate is effective at serum levels of 50-125 µg/mL. Some patients may require a serum level of 150-200 µg/mL for an effective response; however, the likelihood of adverse events increases at serum levels above 100 µg/mL. The side effects of valproate include gastrointestinal irritation, nausea, vomiting, dyspepsia, diarrhea, sedation, drowsiness, somnolence, confusion, aspiration, blurred vision, akathisia, dysarthria, tremor, hypotension, tachycardia, hair loss, decreased libido, and weight gain, which usually occur at very high doses (McElroy et al. 2000; Vijayan and Spillane 1995). In acute intoxication, serum valproate levels above 450 µg/mL can lead to moderate-to-severe side effects, whereas levels above 850 µg/mL can cause coma, respiratory depression, aspiration, and metabolic acidosis (Spiller et al. 2000). Current data on delirium as a side effect of valproate at doses within therapeutic limits is limited to only a few case reports (Puryear et al. 1995; Weng et al. 2004; Shulman et al. 2005).

A PubMed search conducted on 20 April 2009 using the key words delirium and valproate returned 69 publications. In 7 publications delirium as a side effect of valproate, alone or in combination with other drugs, was reported. Despite normal liver functions and valproate serum levels, the development of lethargy and delirium is attributed to elevated serum ammonia levels secondary to the disruption of urea synthesis due to deficiency/depression of carbamoyl phosphate synthetase and ornithine carbamoyl transferase enzymes by valproate use. Carnitine is synthesized from the essential amino

acids methionine and lysine. Valproate inhibits carnitine biosynthesis by decreasing the alpha-ketoglutarate concentration. Carnitine is a co-factor that plays a role in the beta-oxidation of fatty acids and valproate. If degradation of valproate via beta-oxidation in mitochondria fails, then the need for omega-oxidation in hepatic cell cytoplasm and, consequently, production of some toxic substances increase. Additionally, valproate is reported to increase the accumulation of serum ammonia by facilitating glutamine transition in renal mitochondrial membranes. Elevated ammonia in blood leads to increases in glutamine in the brain (especially in astrocytes); consequently, water influx to neurons occurs due to increased intracellular osmolarity. Swelling in astrocytes causes brain edema and, along with increased ammonia in blood, progressively deteriorating encephalopathy occurs (Eze et al. 1998; Segura-Bruna et al. 2006; Eubanks et al. 2008; Lheureux and Hantson 2009).

Herein 3 different episodes of hypoactive delirium (each lasted 2-3 days) observed after valproate use in a patient that was hospitalized with the diagnosis of bipolar disorder and psychotic features according to DSM-IV criteria are presented, along a review of the relevant literature.

Case

The patient is a 46-year-old housewife. She had no history of alcohol or substance use, but has been smoking cigarettes since 13 years of age. During the previous 3 months of hospitalization her smoking increased from 1 pack to 3 packs per day. She first presented in 1995 with thoughts that her husband and his relatives was going to harm her children, fear of strangers, looking at the ground continuously, mutism for days, refusing food, and feeling weak and worthless. Following treatment with chlorpromazine, biperiden, and another unknown drug, her symptoms resolved. She discontinued the treatment after taking it a few months more. During the following 6-7 years she did not have any complaints; however, they resumed almost 7 years ago and various treatments were prescribed by various doctors. Five years ago she was prescribed risperidone 4 mg/day and biperiden treatment; she benefited and occasionally used them. Almost 3 years ago, after one of her manic attacks she was started on lithium, but she did not significantly benefit from it.

First hospitalization: The patient was hospitalized for the first time in December 2007 with the diagnosis of bipolar disorder. At that time she was brought to

our clinic with insomnia, restlessness, hyperactivity, increased speech, anger, and thoughts about others harming her and her children. She was started on quetiapine 600 mg/day and valproate 1000 mg/day. To control her aggression, a mixture of haloperidol and biperiden was injected intramuscularly. Zuclopenthixol 200 mg depot IM, haloperidol 10 mg/day, and biperiden in tablet form bid were added to her treatment after 4 days. At the fifth day of her hospitalization her valproate serum level was 95.3 µg/mL. Mild fever (maximum 37.7 °C), cough, limited communication, somnolence, and confusion occurred at the seventh day of her hospitalization and her serum valproate level was 98.4 µg/mL. Computerized tomography of her brain, abdominal ultrasonography, ECG, urine analysis, thyroid hormones, and routine biochemistry were normal. White blood cell count was 17300/mL (neutrophil 89.2%) and there were weak signs of infection detected with anterior-posterior pulmonary radiography. With the preliminary diagnosis of delirium secondary to respiratory system infection her previous treatment was stopped and intravenous double antibiotics treatment (ceftriaxon disodium 2 g/day and clarithromycin 2 g/day) was started. In the following days there was no other pathology that could better explain the patient's clinical presentation. On the tenth day of her hospitalization her white blood cell count was 8100/mL and fluctuations in her consciousness completely remitted.

After achieving clear consciousness, in addition to antibiotics, lorazepam 3 mg/day was added and monitoring of her vital signs were increased in frequency. She did not have any high fever and her blood pressure was between 90/60 and 110/70 mmHg. On the 15th day of hospitalization zuclopenthixol depot 200 mg IM was repeated while continuing lorazepam, antibiotic, and expectorant treatment. On the 20th day of hospitalization she was in partial remission and was discharged with zuclopenthixol depot per every 15 days and lorazepam 2 mg/day .

Second hospitalization: Two months after her discharge she was re-hospitalized. She presented with general somatic pain, insomnia, restlessness, aggression towards her husband, increased speed and quantity of speech, and thoughts about her superior abilities and persecutions from others. Mental state examination showed signs consistent with bipolar disorder with psychotic features. Routine biochemistry, hematology, urine analysis, and ECG were normal.

In her follow up visit 1 week prior to her re-hospitalization,

she was prescribed zuclopenthixol IM and ziprasidone 160 mg/day; therefore, ziprasidone was continued in addition to lorazepam 5 mg/day. As motor restlessness, and accusative and grandiose speech were still present 15 days after her hospitalization, she was put on valproate 1000 mg/day. A few days later valproate was increased to 1500 mg/day. Then, 3 days after this increase the patient was in a state of delirium. She was weak, and had difficulty sitting, confusion, sialorrhea, mumbling, and vomiting, and difficulty eating, drinking and going to the bathroom. Her drugs were stopped due to her confusion. Supportive treatment with intravenous hydration and frequent monitoring of her vital functions was started. Her neurological examination revealed confusion, partially dilated pupils with intact pupillary reflex, 2-3/5 muscle strength in all extremities, hypoactive deep tendon reflexes, and no signs of rigidity, neck stiffness or Babinski. Despite repeated laboratory and brain imaging investigations, and physical examination we were unable to demonstrate any of the frequent etiologies of delirium in the patient. Complete blood count, routine biochemical analysis (ALT, AST, bilirubin, BUN, creatinine, uric acid, lipid profile, blood proteins, and electrolytes), ECG, and serum valproate level (117.1 µg/mL) were within normal range. Serological test (sedimentation rate, ASO, CRP) results were highly elevated. Abdominal ultrasonography and internal medicine consultation due to vomiting did not reveal any pathology. After 2 days, the patient's delirium substantially improved.

After achieving clear consciousness, treatment of her manic episode resumed. Ziprasidone was discontinued because it was considered ineffective despite a sufficient dose for almost 3 weeks and because it might play a role in the development of delirium. As lithium was ineffective for her a few years ago, its use was not considered as an alternative. Immediately after having a clear consciousness the patient's persecutory and grandiose delusions, blaming of her husband and his relatives for harming herself and her children, and her insomnia increased in severity. For this reason the next day she was started on valproate 1000 mg/day. Due to development of impairment in her consciousness, somnolence, significant decrease in speech and motor activity, urinary and fecal incontinence, and inability to sit and swallow in the third day of valproate treatment. She was diagnosed as delirium due to valproate. Thus, it was discontinued and intravenous supportive treatment was initiated, her serum valproate level was 65.6 µg/mL: however, we were unable to analyze her ammonia level due to temporary

problems in our laboratory. Considering the improvement in her delirium after 2 days it was concluded that the delirium was due to valproate use.

Risperidone 4 mg/day and lorazepam 2 mg/day was given to treat her manic episode. After 9-10 days the patient's clinical condition moderately improved and she was discharged with risperidone 4 mg/day and alprazolam 0.5 mg/day. Significant improvement in the general condition of the patient was observed during the follow-up visits that were scheduled every 2-3 weeks.

Discussion

Delirium is seldom encountered in psychiatric clinics, despite its frequency in intensive care units and emergency services (Aldemir et al. 2001). The present case experienced 3 episodes of delirium. The patient's second and third episodes of delirium were definitely due to valproate use, whereas the first was not. Moreover, after the third episode of delirium, while re-evaluating the first episode we suggested that it was most probably also due valproate use. The second and third episodes of delirium were seen while the patient was under observation during the first 10 days of her second hospitalization. The third episode occurred a few days after valproate was initiated and disappeared 2 days after its discontinuation.

As the patient's serum valproate level was within the normal range and despite the lack of prominent signs in posterior-anterior pulmonary radiography, delirium during her first hospitalization was attributed to respiratory tract infection, not an adverse drug event. High white blood cell count, cough, and mild fever also supported that infection was the cause. Antibiotics were used based on the recommendations of the infectious diseases and internal medicine departments. During the episode of delirium all medications were discontinued, and then the level of consciousness in the patient improved. Since in different times the patient was followed by different doctors, we don't know why valproate treatment was not resumed after remission of her first delirium episode. In respiratory tract infections the main cause of delirium is impaired neuronal physiology in the brain due to high fever or hypoxia (Cremer and Kalkman 2007; Calvano et al. 2008). Hypoxia, fever > 37.7 °C, and severe respiratory diseases that decrease the respiration surface, such as pneumonia, were not observed in the patient. In the light of these data the patient's cough may have been due to irritation secondary to smoking or partial aspiration of sputum.

The days before her first episode of delirium the patient was given quetiapine, zuclopenthixol, haloperidol,

and biperiden, in addition to valproate. Use of multiple drugs and their sedative and anticholinergic effects might have contributed to the development of confusion and delirium (Voyer et al. 2009). Additionally, the doses of antipsychotics and biperiden during that period were not so high as to cause confusion. Neuroleptic malignant syndrome was not considered in the differential diagnosis of the first episode of delirium because there was weakness instead of muscle rigidity, her fever was not very high, muscle enzymes were normal, and the other possible findings suggesting delirium were not sufficient to support the diagnosis of neuroleptic malignant syndrome (Iseri and Selekler 2005). Because the patient's biochemistry, electrolytes, ALT, AST, bilirubin, BUN, creatinine, and fasting blood glucose were within normal limits organ failure was not considered among the causes of her delirium. Her respiration and cardiovascular evaluations were also normal. Based on these data, similarities between the second and third episodes of delirium, and a re-evaluation of her medical records by pulmonologists, we concluded that her first episode of delirium was probably due to valproate use.

Frequent side effects of ziprasidone are reported to be somnolence, vertigo, nausea, and dizziness (van Kammen and Marder 2000). At the time of the patient's second episode of delirium she was taking lorazepam, ziprasidone, and valproate. It is reported that concomitant use of these drugs may increase sedation (www.gipsy.uni-goettingen.de/interactions_calculator.php); however, there was no mention of sialorrhea, vomiting, lethargy, or delirium. Valproate's dose and serum level in our patient were similar to the doses that are frequently used for bipolar patients in psychiatry clinics. Initially, we did not suspect hyperammonemia, as this side effect of valproate had not been previously observed in our clinic, and ALT, AST, bilirubin levels, and abdominal ultrasonography were normal. After achieving clear consciousness, valproate was re-initiated to treat the patient's mania because ziprasidone was ineffective, despite its use for 3 weeks, and its possible contribution to the patient's delirium.

Delirium in the present case was thought to be due to valproate, as it developed within a few days of beginning valproate monotherapy when its serum level was normal (65.6 µg/mL). The drug was immediately discontinued and supportive treatment was initiated. It is a limitation of this case report that during the third episode of delirium we were unable to measure the patient's blood ammonia level due to a laboratory problem; however, during all 3 episodes of delirium symptoms of acute

nausea, vomiting, confusion, somnolence, lethargy, and retardation in mental functions were present, which are observed in cases of acute elevation of blood ammonia levels (Duarte et al. 1993; Segura-Bruna et al. 2006).

There are only a few reported cases of bipolar disorder with clinical and laboratory findings similar to those of our patient. Serum valproate levels were slightly higher than 100 mg/L and BUN, ALT, and AST levels were within normal limits in these previously reported cases. Acute confusion, such as delirium and/or coma, was observed in the first few days of treatment in those patients and high blood ammonia levels were demonstrated as the cause of delirium in those patients. One of those case reports was a 33-year-old woman (Eubanks et al. 2008) with comorbid post-traumatic stress disorder, substance dependency, and borderline personality disorder, in addition to bipolar disorder. The serum valproate level in this patient was 120 mg/L and the ammonia level was 283 µmol/L (normal reference: 2-30 µmol/L). In addition to 1500 mg/day valproate treatment, this patient was also taking venlafaxine, hydroxyzine, mirtazapine, bupropion, and clonazepam. After discontinuation of all drugs she was treated with carnitine 3 g intravenous, and then oral carnitine and lactulose. Her consciousness completely cleared the same day and her clinical symptoms improved within a few days. She continued carnitine and lactulose treatment for almost 1 week.

Another reported case was a 69-year-old woman (Eze et al. 1998) with benzodiazepine dependence and bipolar disorder. Blood valproate and ammonia levels were 107 mg/L and 143 µmol /L, respectively. In addition to 750 mg/day valproate, the patient was also taking 50 mg/day trazodone and 2 mg/day clonazepam. On the fourth day of treatment confusion began and progressed to stupor on the fifth day. Hyperammonemia treatment was immediately initiated, and all previous drugs were discontinued, intravenous hydration was given, her airway was kept open, and she was oxygenated. Additionally, albuterol aerosol, naloxane hydrochloride, and nasogastric lactulose were given. Along with the patient's decrease in ammonia, her confusion remitted gradually over 5 days. In both of these cases, carnitine and lactulose treatment, in addition to supportive treatment, was beneficial in the acute treatment of hyperammonemia associated with valproate use (Eubanks et al. 2008; Lheureux and Hantson 2009).

In some patients valproate may cause delirium, even with serum levels of 50-125 µg/mL; therefore, patients should be carefully followed-up, especially during the first week of valproate treatment. On the other hand, when beginning psychiatric treatment, each patient's previous treatment history and observations should be reviewed in detail in order to plan an effective and low-risk therapy regimen.

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