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Case Report

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Valproate Induced Behavioral Dysregulation in an Adolescent with Intellectual Disability: A Case Report

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Abstract

A 14-year-old with mild intellectual disability and autism spectrum disorder was admitted to a long-term psychiatric hospital with complaints of treatment resistant aggressive behavior. Her psychopharmacologic regime was Depakote 1500mg, Intuniv XR 2mg twice daily, and Inderal 10 mg thrice daily, for her mood and behavior symptoms, and prn Ativan and Benadryl for acute episodes of agitation. Despite multiple medication trials, she was continued on Depakote for seven months prior to her admission to long term care. During the first month in long term care, she had over 20 emergency interventions due to physical aggression. She was also witnessed to exhibit abnormal behavior and self-harm during this time. There were concerns that Depakote may be contributing to her dysregulated behavior, thus the medication was slowly down-titrated while her other scheduled medications and dosages remained the same. The patient started to require fewer emergency interventions with noted improvement in her behavior. After the complete termination of Depakote, clinical observations were remarkable for mitigation of aggressive and abnormal behavior as evidenced by the patient going six weeks without any emergency intervention. Behavioral dysregulation is a possible adverse effect of valproate. Individuals with intellectual disabilities are most vulnerable to polypharmacy for management of aggression, behavioral problems, and other psychiatric comorbidities. There is a need for pharmacovigilance on the negative behavioral effects in patients receiving valproate.

Introduction

Valproate (VPA) is commonly used in the treatment of epilepsy, migraines and mood stabilization, particularly bipolar disorder, and has also been used off-label for impulsivity and aggression. Valproate products include: valproate sodium (Depacon), divalproex sodium (Depakote, Depakote CP, and Depakote ER), valproic acid (Depakene and Stavzor), and their generics. Common side effects include gastrointestinal upset, sedation/somnolence, low blood platelet levels, hair loss, weight gain, dizziness, nausea, sedation, and more adversely, liver damage, pseudodementia, inflammation of the pancreas, and encephalopathy [1]. Depakote medication package inserts from Abbott Laboratories comment on possible side effects including depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration [2]. Valproate has been occasionally reported to paradoxically cause agitation or irritability, and can uncommonly exacerbate suicidal thoughts and depressed mood. Behavioral dysregulation as an adverse effect of valproate is rarely reported, however, if noted, this effect can be reversed upon discontinuation of the drug [3]. Moreover, these incidences have been identified primarily among adults.

Long term use of VPA has signified promising treatment for individuals with cognitive limitations and behavioral symptoms. Of note, individuals with intellectual disabilities (ID) are reported to have more idiosyncratic responses to drugs and are more sensitive to adverse effects compared to the general population [4]. Literature has shown that individuals with intellectual disabilities who receive anticonvulsants experience more behavioral side effects, impaired cognition, and volatile behavior compared to matched controls without disabilities [5].

The State of Connecticut Department of Children and Families defines an Emergency Safety Intervention (ESI) as "the use of physical restraint, locked seclusion, mechanical restraint, and/or psychopharmacological agent used as a restraint with a child/youth". An ESI is utilized when there is a situation of imminent or immediate risk of physical injury/harm to the child/youth or others. These events are carefully monitored, documented, and used judiciously as they carry a risk of trauma and/or physical injury to both youth and staff [6]. The ESI's are supported by the Modified Overt Aggression Scale (MOAS) which is a four-part behavior rating scale used to evaluate and document the "frequency and severity" of verbally and physically aggressive episodes, and can provide reliable support for evaluating the effectiveness of interventions aimed at reducing challenging aggressive behavior in the intellectually disabled community [7, 8]. A

common problem in the ID population, particularly the youth, can be behavioral cycling with aggression, self-harm, and other behavior that precludes prosocial engagement with their environment [9]. This case report explores the remittance of behavioral dysregulation of an adolescent with intellectual disability possibly secondary to the withdrawal and discontinuation of valproate.

Case Report

A 14-year-old fraternal, female twin, weighing 94.8kg, with a diagnosis of autism spectrum disorder, mild intellectual disability, and disruptive mood dysregulation disorder was admitted to a long-term psychiatric hospital for treatment resistant aggression. Her past medical history was remarkable for pre-diabetes, galactorrhea and dystonia secondary to previous neuroleptic medications. Her past treatment course was variable and unsuccessful, encumbered by failed trials of multiple medications including aripiprazole, haloperidal, risperidone and other courses of antidepressants and stimulants with adverse effects and/or poor to fair effect responses. She also had a remote episode of seizure-like behavior that was concluded to be non-epileptic in nature by electroencephalogram.

Despite multiple medication trials, she was consistently on Depakote for 7 months prior to long-term hospitalization. Before the initiation of Depakote, her family reported that she did not exhibit aggressive behavior. The aggressive episode that led to her presentation to acute care involved her hitting her in-home therapist and sister, kicking her mother, and then grabbing a knife, with verbalizations of threats to hurt herself and others. At the time of transfer to the acute hospital, she was taking Thorazine 75mg twice a day, Depakote ER 1000mg daily, Intuniv XR 2mg at night, Zyprexa 5mg as needed up to twice daily for agitation up to 2x/day. Her aggression continued in the acute hospital; Thorazine was increased to 150mg and Depakote increased to 1500mg- Depakote sprinkles 500 mg and Depakote ER 1000 mg. Thorazine was eventually discontinued due to over sedation, and a trial of Geodon was initiated. This was trialed only for a short course as she developed tachycardia. Albeit the medication changes and two months of acute hospitalization, her aggression continued with frequent outbursts towards staff, warranting one-to-one intensive support.

At the time of transfer to the long-term psychiatric hospital, the patient was continued on the same dose of Depakote, Intuniv XR 2mg twice daily, and Inderal 10 mg PO thrice daily, with Ativan and Benadryl as needed daily for agitation. Within the first two weeks of admission, she had 16 Emergency Safety Interventions (ESI) for physically aggressive behavior. Her other observed behaviors included frequent disrobing, throwing objects at staff, spitting, cursing, scratching herself and others, and squeezing and licking her nipples. She received a total of 24 ESI's for physically aggressive and assaultive behavior in the first month of admission, on some occasions having up to three ESI's in a day.

After prolonged use of Depakote for more than seven months, without mitigation of behavior, it was suspected that Depakote could possibly be contributing to her dysregulation. Thus, she was first discontinued from her Depakote sprinkle dose of 500mg. After the discontinuation of Depakote sprinkles, the frequency of her ESI's decreased to occurring every three to four days as opposed to daily or every other day. By six weeks into her admission, the Depakote ER was completely discontinued. After the complete termination of Depakote and maintenance of her scheduled medications of Inderal and Intuniv XR, clinical observations were remarkable for a mitigation in aggressive behavior. The patient went almost six weeks free of ESI's. She was better able to interact with staff and her peers. Additionally, there were no observations of abnormal behavior or self-harm, resulting in her being able to go on community passes with staff and family without any acute interventions needed.

Discussion

Valproate (VPA) has been utilized to reduce behavioral disturbances in aggressive and/or irritable pediatric patients who do not suffer from seizures. This case report highlights VPA associated behavioral dysregulation, particularly aggressive and abnormal behavior, in an adolescent with mild intellectual disability without a seizure disorder history. To date, the WHO international drug monitoring center has received 1,104 reported cases of aggression and 458 reported cases of abnormal behavior, globally in patients who took valproate [10]. The number of child and adolescent cases out of the total cases is not known. A literature search has identified case reports of individuals who experienced increased behavioral symptoms secondary to VPA that developed within two days to two weeks of initiation. Within a few days of discontinuation of the medication, a significant improvement of behavioral symptoms was appreciated and the patients returned to their baseline mental state [11]. Our patient's mitigation of abnormal behavior and aggression with the discontinuation of VPA supports the hypothesis that valproate likely contributed to these symptoms. This is additionally supported by the fact that there were not any other treatment changes except for the changes in valproate dosing. Other explanations include VPA-induced hyperammonemia. The symptoms of such include lethargy, impaired consciousness, focal neurological signs and increased seizures. Rarer symptoms include vomiting, coma, asterixis, ataxia, and aggression [12]. Overall, symptomatic hyperammonemia due to VPA is fairly rare. The clinical observations of our patient were different compared to the symptoms of valproate induced hyperammonemia reported in the literature.

Individuals with intellectual disabilities (ID) are more vulnerable to polypharmacy for the management of aggression, behavioral problems, and other psychiatric comorbidities. Frequently, individuals with intellectual disabilities are prescribed medications for off-label uses and at higher doses than commonly administered, which can potentially lead to more adverse effects. Furthermore, it can be more difficult for prescribers to detect these symptoms in patients who may have a limited capacity to communicate. There are also harmful social effects and stigma for individuals with ID. Maladaptive behaviors often hinder their ability to develop social skills and healthy relationships which are imperative for a successful transition to the community. Anticonvulsants' potential paradoxical effects of aggression, self-injurious behavior, hyperactivity, and irritability can very well impede that transition [5].

Broad-spectrum medications increase the likelihood of adverse effects in comparison to narrow-spectrum agents due to the various potential sites of action throughout the body [9]. Anticonvulsants target the cerebral cortex where some areas may have a pathologically increased likelihood of neuronal depolarization and firing leading to seizure activity. VPA is considered a broad-spectrum anticonvulsant given its indication for several seizure types, thus having a potential for greater adverse effects [13]. Individuals with intellectual disabilities have impaired cortical function and can be more susceptible to those side

effects which are only exacerbated by polypharmacy.

The mechanism of VPA is not fully understood. Its anticonvulsant effect has been traditionally attributed to the blockade of voltage-gated sodium channels and increased brain levels of gamma-aminobutyric acid (GABA). Enhancement of GABA with VPA can lead to a paradoxical effect, with dose related agitated delirium, hyperactivity, irritability, and disorganized behavior, rectified reversibly with down titration or discontinuation of valproate [14].

Per the literature search, there were a few notable cases of similar responses to VPA. In one case report, a 12-year-old female in India with a history of complex partial seizures with secondary generalized seizures on 200mg of VPA and 5 mg of clobazam developed abnormal behavior on the 60th day of treatment [15]. The behavior persisted even after the initiation of three antipsychotics to reduce symptoms. After the withdrawal of valproate, the abnormal behavior improved gradually. In another case, a 14-year Asian male with seizure disorder was started on 42 mg/kg (1,600 mg) of Divalproex. After 14 days on the medication, he exhibited disorganized behavior with agitated delirium and hallucinations. His behavior was consequently mitigated when the medication was discontinued [16].

In a side effect study exploring valproate monotherapy within therapeutic lab ranges on 88 pediatric patients, behavioral disturbances including aggressiveness, hyperactivity, and irritability were observed [17]. Eight out of 100 children with seizure disorder treated with valproate monotherapy showed adverse effects evidenced by belligerence and hallucinations [18].

Given concern surrounding an increase in suicidal behavior from individuals taking anticonvulsants, in 2008, the FDA published a meta-analysis including data from 199 placebo-controlled trials of 11 anticonvulsants. It was found consistently among all eleven drugs that patients taking anticonvulsants were at approximately twice the risk of suicidal behavior or ideation compared to placebo. New labeling for all anticonvulsant medications concerning this risk was required [19]. There is no definite time frame where patients are more vulnerable to this risk, as events have been observed as early as one week from treatment initiation until at least 24 weeks.

Behavioral disturbances with VPA is rare, thus reporting such a case can encourage more research on the relation of VPA with behavior exacerbation of patients with and without intellectual disabilities. This case study encourages not only further exploration of the mechanism of action that may contribute to VPA induced behavioral dysregulation, but also encourages drug prescribers to be more pharmacovigilant. If a patient develops new onset or worsening behavioral concerns after starting valproate, a practitioner should consider that this may be a manifestation of an adverse effect of valproate. Additionally, this case report purports prescribers to reduce polypharmacy, as this can potentially increase the quality of life for their patients, particularly those who are intellectually disabled.

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Compliance with Ethical Standards / Ethical Considerations

The Connecticut Department of Children and Families (DCF) Institutional Review Board (IRB) policies and procedures were consulted prior to the development of this case report; after application review, this report was approved to be exempt for further review.

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