Refractory Convulsive Status Epilepticus Provoked by Intoxication with Dalfampridine in a Patient with Multiple Sclerosis and Depression Disorder: A Case Report and Literature Review

Mehdi Maghbooli [1], Zahra Jourahmad [2*], Mehrdad Golizadeh

Abstract

Purpose: Dalfampridine (DFP) is used to improve motor functions in patients with multiple sclerosis (MS). Overdose of DFP can occur for a variety of reasons and can lead to a state of epilepsy.

Case report: A 24-year-old woman with MS was admitted to hospital with severe sweating and delirium after attempting suicide by overdosing on DFP. At the time of hospitalization, she developed a tonic-clonic seizure that did not respond to immediate intravenous (IV) diazepam injection, followed by intravenous sodium valproate. Therefore, according to the hospital protocol of the neurology department, the patient was intubated and IV infusion of midazolam was started, Due to the persistence of seizures, sodium thiopental began and the patient was admitted to the intensive care unit (ICU). In the ICU, she received an infusion of sodium thiopental and intravenous sodium valproate, monitored by a daily electroencephalogram (EEG). The patient was discharged after four days due to her stable medical condition.

Conclusion: Epilepsy in case of overuse of DFP should be considered as a life-threatening side effect and timely treatment should be done to prevent damage to the nervous system.

Keywords: **Status epilepticus; intoxication; dalfampridine; multiple sclerosis**

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BACKGROUND

DFP is a potassium channel blocker used for the improvement of motor function in patients with MS. It performs various functions by blocking the kv1 family channels and exerts its effects through improving conduction along demyelinated axons, increase immunomodulation, and limiting neurodegeneration [(1)]. Although seizure occurrence due to DFP is rare, but it is the most serious adverse effects (AEs) caused by potassium channel blockade which can lead to status epilepticus (SE) [(2)]. Here we reported a case of refractory

From the [1]Associate Professor of Neurology, Neurology Department of Vali-e-Asr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran. [2]Department of Neurology, Zanjan University of Medical Sciences, Zanjan, Iran. Resident of Neurology, Neurology Department of Vali-e-Asr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran.
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Correspondence to: Zahra Jourahmad, MD. Department of Neurology, Vali-e-Asr University Hospital, Zanjan University of Medical Sciences,Zanjan, Iran.
Email: zahra.jourahmad@gmail.com

convulsive Status Epilepticus provoked by suicidal attempt with DFP overdose in a patient with MS and depressive disorder.

CASE PRESENTATION

A 24-year-old woman known case of MS and depressive disorder was brought to the emergency room by her family complaining of severe sweating, and delusions that started exactly after she woke up in the morning.

She claimed to have taken 12 tablets of 10 mg of DFP to commit suicide in the middle of the night.

After admission, she sweated profusely and had delirium. The physical examination including pupils' size, pupillary reflex, the cranial nerves assessment, and the complete neurological evaluation were normal. Her blood pressure was 125/80 mmHg, heart rate was 76 beats per minute, and body temperature was 36.3°C. The basic laboratory tests were within the normal range. Serum and Urine toxicological screening test for opioids, barbiturates, benzodiazepines, tricyclic antidepressant, amphetamines, methamphetamines, and methadone was negative. On her past medical history, she was born through vaginal delivery without any complication. There were no significant findings in her childhood, no history of head trauma, CNS infection, renal insufficiency, seizure, or history of epilepsy in the family. Her development was normal, and she was graduated in college with good marks. She was diagnosed with relapsing remitting MS three years ago and was treating with dimethyl fumarate 240 mg bid and DFP 10 mg bid since a year ago. Also, she was taking valproate sodium 500 mg daily, olanzapine 5 mg daily, and clonazepam 2mg HS for treatment of mood disorder from last month. The brain MRI taken a month ago showed multiple inactive plaques consistent with the chronic MS stage. Brain CT scan taken after admission was normal.

In the emergency room, she received appropriate treatment for overdose of DFP with charcoal and other supportive cares. After one hour of hospitalization, generalized tonic-clonic seizure occurred which lasted for 2 minutes and ended after intravenous injection of 20 mg diazepam. Three hours later, the second generalized tonic-clonic seizure occurred and neurological consultation was performed. Seizures did not respond to immediate injection of 10 mg IV diazepam followed by 2400 mg IV sodium valproate (40 mg/kg). Because of significant reduction of oxygen saturation to 70%, the neurologist decided to intubate the patient and administer IV midazolam as a bolus infusion (0.2 mg/kg with 2 mg/min) and maintenance of 0.2 to 0.5 mg/kg/hour (hr) (Based on the neurocritical society guideline for the evaluation and management of status epilepticus) [3].

Due to the continuation of seizures after 60 minutes from starting of midazolam infusion that revealed no response to used antiepileptic drugs, thiopental sodium with a bolus dose of 3 mg/kg and maintenance infusion with 200 mg/hr was added to 4 mg/hr IV midazolam infusion, which led to the cessation of seizures. She was then admitted to the intensive care unit (ICU) with the diagnosis of convulsive status epilepticus (CSE). At the ICU, an EEG was obtained from the patient and underwent cardiac monitoring, a chart of consciousness and vital signs, and the Thiopental sodium infusion (200 mg/hr) with midazolam 4 mg/hr and IV sodium valproate 1000 mg/twice a day were continued in the ICU.

A 60-minute daily EEG (due to the lack of an EEG monitoring system) was recorded from the patient and did not show any epileptic activity. Thiopental sodium and midazolam infusion were tapered and stopped after 36 hours without recurrence of any seizure or epileptic discharge on the EEG.

After discontinuation of intravenous drugs, the patient was extubated 48 hours after the onset of seizures and transferred to the neurology ward. The administration of valproic acid was continued and she remained seizure free. The patient was discharged in the 4th day, with normal mental status and neurologic exam and referred to a psychiatric facility. During the clinic follow-up visits, she was fine and seizure free along with unremarkable office EEG. Thus, valproic acid was discontinued and DFP stopped permanently.

A written consent form was taken from the patient to publish her case in scientific journals if an anonymous identity is provided. Zanjan University of Medical Sciences Ethics Committee has approved this study with an ethics code (ZUMS.REC.1400.074).

Review of case reports: Dalfampridine associated status epilepticus in MS patients

DFP is known chemically as 4-aminopyridine (4-AP). In clinical trials, DFP resulted in objective improvements in walking in a proportion of patients, or responders, as shown by consistent increases in walking speed while on study drug compared to periods off study drug[4].

Seizure rates are reported to be higher in patients with MS compared with the normal adult population. The pro-convulsant effects of 4-AP have long been recognized and have made it a useful tool for investigations of seizure electrophysiology. In vitro, 4-AP is often applied to brain slices to induce epileptiform discharges, and these effects have been shown to be abrogated by anticonvulsant drugs, suggesting that a 4-AP in vitro model may enhance the search and development of new anticonvulsants[5].

In the few cases where plasma concentrations were measured from people who experienced a seizure that was related to 4-AP exposure, plasma concentrations ranged from 136 to 335 ng/mL. These concentrations are approximately 4-10 times higher than the average maximum plasma concentration of about 34 ng/mL (0.36 μM) achieved with DFP extended-release tablets at the recommended daily dose of 10 mg every 12 h[6].

A summary of cases with DFP-related epilepsy in MS patients is presented in Table 1. The association between

Table 1. Case studies with DFP-related epilepsy status in MS patients

Study	DFP dose	Treatment	Intubation	Outcome
Stork et al (one case)	Unknown	Diazepam, phenytoin, and phenobarbital	yes	Fully recovered and discharged after 5 days
Burton et al (four cases)	90.1 mg to 125.6 mg	Benzodiazepine and phenytoin	yes	Three patients fully recovered and discharged but one died due to long hospital stay and systemic complications
Schwam (one case)	200 mg	Lorazepam and phenytoin	yes	Discharged after long hospital stay with permanent short-term memory loss
Gusmao et al (one case)	Therapeutic dose (10 mg bid)	Bolus IV injection of lorazepam and fosphenytoin, and continuous injection of IV phenytoin then levetiracetam	yes	Fully recovered and discharged after 3 days
Thompson et al (one case)	127 mg	Bolus IV injection of lorazepam and diazepam and continuous injection of IV sodium phenytoin	yes	Fully recovered and discharged after 5 days
Mendez et al (one case)	> 80 mg	Bolus IV injection of lorazepam and midazolam and continuous injection of IV valproic acid and levetiracetam	yes	Discharged after 34 days with partial cognitive impairment
Fil et al (one case)	530ng/mL (therapeutic: 25 to 49 ng/mL)	Bolus IV injection of lorazepam, phenytoin and phenobarbital and continuous injection of IV phenobarbital	yes	Fully recovered and discharged after 12 days
Panicucci et al (three cases)	Therapeutic dose (10 mg bid)	-Bolus IV injection of diazepam and continuous injection of IV phenytoin and levetiracetam - IV diazepam - Bolus IV injection of diazepam and continuous injection of IV phenytoin and phenobarbital	no	Fully recovered and discharged
Ali et al (one case)	Therapeutic dose	IV lorazepam and levetiracetam	yes	Fully recovered and discharged

consumption of DFP and development of status epilepticus is reported in limited cases. In a review of 9 case reports describing epilepsy due to overuse of DFP or therapeutic doses in 14 MS patients, only one patient died[7], one patient with permanent short-term memory loss[8], one patient had a minor cognitive dysfunction[9], and 11 other patients fully recovered[10-15].

DISCUSSION

The toxicity with DFP is reported infrequently and manifests as diaphoresis, neurologic excitability, gastrointestinal effect, and cardiac toxicity. Most of these reports describe toxicity with DFP overdose and only few with therapeutic dose[16]. Given the DFP mechanism of action which augments the interneuronal transmission seizure and subsequently status epilepticus can emerge[2]. Also risk factors including earlier MS onset, higher EDSS score, and presence of cortical and cortico-juxtacortical lesions on brain MRI can increase the risk of seizure development in MS patients[17]. The patient presented in this case report did not have any risk factor for seizure development and showed the signs and symptoms of drug toxicity with 120 mg of DFP. Also, patient showed other manifestations of toxicity including diaphoresis and delirium.

The treatment of drug induced seizures is benzodiazepines as first line and barbiturates as second line anticonvulsive therapies[18]. Regarding the convulsive tonic-clonic seizure the condition in which seizures continue beyond five minutes is called generalized convulsive status epilepticus (GCSE)[19]. The first line treatment of GCSE is commonly a sufficient dose of IV benzodiazepine such as lorazepam followed by a long-acting anti-seizure drug including phenytoin, fosphenytoin, phenobarbital, valproate, lacosamide, or levetiracetam. If the first line therapy fails to stop seizure many neurologists prefer to administer IV midazolam[3]. Status epilepticus unresponsive to adequate dose of first- and second-line anticonvulsant treatment is defined as refractory status epilepticus (RSE)[20,21]. Based on the opinion of most experts the RSE is treated by continuous infusion of midazolam, phenobarbital, thiopental, or propofol inducing the therapeutic coma [22-24].

In a review of 9 case reports, including 14 MS patients describing DFP-induced epilepsy, 11 patients underwent aggressive treatment and were placed in an induction coma [7-13,15].

In the present case, the seizure persisted despite adequate use of IV diazepam, midazolam, and valproic acid. Therefore, according to the diagnosis of Refractory SE, administration of IV sodium thiopental was considered to induce coma in the patient. The patient fully recovered after 36 hours and was discharged after four days.

As a weakness of our case report, Long-term video EEG monitoring was inaccessible for us; therefore, we replaced a 60-minute daily EEG recording as a non-standard management in refractory status epilepticus.

CONCLUSIONS

This case report shows the development of epilepsy in an MS patient with an overdose of DFP. Although rare, epilepsy should be considered as an important side effect during DFP treatment, especially during drug overdose. There was no difference in the tendency for DFP-related seizures to occur in patients with or without any risk factors for seizures. In comparison to the previous case reports, this patient had shorter duration of hospitalization and she could be discharged in a sooner time. Also in current patient, contrary to other reports in most of them phenytoin has been used as an anticonvulsant, we used sodium valproate as an antiepileptic drug. Contrary to other reports, under general anesthesia, we used sodium thiopental with a low dose of midazolam, which was a different treatment regimen than other reports.

Also, rapid intubation at the beginning of the seizure (before severe hypoxia) to prevent hypoxic injury and maintain adequate oxygen levels helped to control the seizure and prevent further neurological damage.

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