

# Ifosfamide-induced Encephalopathy Precipitated by Aprepitant: A Rarely Manifested Side Effect of Drug Interaction

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## Abstract

Central nervous system (CNS) toxicity has been reported in approximately 10%–30% of patients receiving intravenous infusions of ifosfamide. Encephalopathy is a rare but serious CNS adverse reaction in these patients, and although usually transient and reversible, may cause persistent neurological dysfunction or death. Clinical features range from fatigue and confusion to coma and death. Ifosfamide forms backbone of various treatment regimens including curative treatment and palliative chemotherapy regimen. Precipitation of ifosfamide-induced encephalopathy (IIE) by aprepitant has been reported in the literature rarely. Ifosfamide is moderately emetogenic; hence, aprepitant is used to prevent emesis induced by ifosfamide. We here report a case where a patient of recurrent B-cell Philadelphia-negative acute lymphoblastic lymphoma was given aprepitant to prevent ifosfamide-induced emesis. After 24 h of ifosfamide infusion, the patient developed symptoms of encephalopathy, i.e., headache, vomiting, and one episode of seizure which was followed by disoriented behavior. After doing all routine investigations and neuroimaging, the diagnosis of IIE was kept on clinical grounds, and after looking for the various factors, we came across injection fosaprepitant as the precipitating factor. On the clinical grounds, the patient was treated with hydration and injection methylene blue for above complaints, and the patient recovered without any residual deficit within 48–72 h. Hence, in the presence of causative agent, i.e., ifosfamide and precipitating agent injection fosaprepitant with negative imaging and normal laboratory parameters as well as the early and good response to methylene blue, the diagnosis of IIE precipitated by aprepitant was confirmed.

**Keywords:** Aprepitant, ifosfamide, methylene blue

## INTRODUCTION

Ifosfamide is a bifunctional alkylating agent, an oxazaphosphorine derivative with a structural formula similar to that of cyclophosphamide. It is used as a racemic mixture by intravenous (IV) route in the treatment of various tumors. Incidence of ifosfamide-induced central nervous system (CNS) toxicity occurs in 10%–40% patients and is usually associated with protein malnutrition.<sup>[1]</sup> However, the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant use has been implicated in few case reports.<sup>[2–4]</sup> The manifestation can range from mild confusion to coma. It is metabolized primarily within hepatic enzymes (cytochrome p450) with excretion through the urinary tract. Aprepitant is a novel and selective antiemetic that antagonizes substance P/neurokinin 1 (NK1) receptors with high affinity. Its mechanism of action is distinct from the

common targets used to prevent chemotherapy-induced nausea and vomiting: the serotonin (5-hydroxytryptamine type 3), dopamine, and corticosteroid receptors. It is metabolized by the cytochrome p450 system and is a moderate dose-dependent CYP3A4 inhibitor.

Here, we present one such case of ifosfamide-induced encephalopathy (IIE) occurred with concomitant aprepitant use with normal serum albumin and was successfully treated with drug withdrawal and IV methylene blue.

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## CASE REPORT

A 25-year-old male patient diagnosed as a case of Philadelphia chromosome-negative B-cell acute lymphoblastic lymphoma (ALL) and who had relapsed after receiving the Berlin-Frankfurt-Münster 90 acute lymphoblastic leukemia protocol (BFM ALL protocol) was started on MINE protocol (injection ifosfamide 4 g/m<sup>2</sup> was divided over 3 days [day 1–3] and administered IV over a 1 h period, injection mitoxantrone 8 mg/m<sup>2</sup> [day 1] administered as a short IV infusion, injection etoposide 65 mg/m<sup>2</sup>/day [day 1–3] was infused over 1 h, and injection mesna 1330 mg/m<sup>2</sup> [days 1–3]) after the patient had progressed on DHAP regimen (injection cisplatin 100 mg/m<sup>2</sup> [day 1], high-dose cytarabine 2 g/m<sup>2</sup> twice a day [day 2], and tablet prednisolone 40 mg/day [day 2–4]). After 24 h of the 1<sup>st</sup> day of chemotherapy, the patient started developing headache, vomiting which was followed in couple of hours by disoriented behavior, and one episode of seizure. In view of above complaints, patient chemotherapy was withheld as the patient developed headache and vomiting. For the above complaints, patient's all routine investigations such as complete blood count, renal function, and liver function test were performed along with albumin and electrolytes. All the investigations were within normal limits. Electrocardiogram was done which was within normal limits. Magnetic resonance imaging of brain was obtained which did not show any abnormality. Considering the above case scenario and ruling out the possible causes of acute delirious state such as electrolyte abnormalities and intracranial bleed, we entertained the possibility of IIE. The patient was started on hydration therapy with IV fluids and dextrose normal saline infusion at the rate of 100 ml/m<sup>2</sup> followed by which injection methylene blue was procured and started at the dose of 50 mg (1% aqueous solution) IV over 5 min, six times daily, and antiemetics such as ondansetron 4 mg by needle were administered twice a day for initial 3 days and then whenever needed. Within a period of 24 h, the patient started improving in the form of decrease in vomiting and response to oral commands. Later complete recovery occurred within 48–72 h. Till then injection methylene blue and hydration were continued. Furthermore, the patient was given IV 5% albumin.

Hence, the patient who had presented with above-mentioned complaints with normal imaging and blood investigations and who had responded to methylene blue confirmed our diagnosis of the IIE. Furthermore, retrospectively, we looked over the factors that precipitated the IIE. Albumin, renal and liver function, and electrolytes were well within normal limits at the start of infusion of ifosfamide. However, the patient had received injection fosaprepitant before the start of injection ifosfamide.

We then reviewed the literature, and it confirmed that the precipitating factor for IIE was none other than aprepitant.

## DISCUSSION

Ifosfamide (3-[2-chloroethyl]-2-[(2-chloroethyl)-amino] tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide), first synthesized

in the 1960s, is a member of the oxazaphosphorine family of alkylating agents. It was introduced as a chemical modification of cyclophosphamide with a different position of its two chloroethyl groups on the central ring, providing a structure with greater water solubility, antitumor activity and a better toxicity profile. Ifosfamide is a prodrug that requires modification in the liver to an active moiety. Ifosfamide is a moderate to highly emetogenic drug. Aprepitant is a substance P/NK1 receptors antagonist which is used for the prevention of emesis in moderate to highly emetogenic chemotherapeutic agents.

IIE can be precipitated by following factors such as serum albumin level lower than 3.5 g/dl, hyponatremia, elevated serum creatinine level, bulky abdominal disease (and especially bulky pelvic disease), history of nephrectomy, previous treatment with cisplatin, poor performance status and concomitant use of aprepitant.

Ifosfamide is a prodrug that requires hepatic activation to its cytotoxic metabolite, ifosfamide mustard. Ifosfamide is hydroxylated through CYP3A4 to active alkylating agents, ifosfamide mustard, and 4-hydroxy-ifosfamide and also inactive neurotoxic metabolites: the 2- and 3-dechloroethylifosfamide and chloroacetaldehyde (CAA). Competition with 4-hydroxylation is the major oxidative pathway that causes the dechloroethylation and the formation of the neurotoxic metabolite CAA and 2- and 3-dechloroethylifosfamide.

The potential inhibition of CYP3A4 by aprepitant<sup>[5]</sup> may increase the levels of ifosfamide metabolites resulting in accumulation and further risk of encephalopathy and other side effects such as hemorrhagic cystitis or neutropenia.

The exact pathophysiological mechanisms responsible for the development of ifosfamide-induced encephalopathy are not known. The plausible mechanism for neurotoxicity due to ifosfamide is based on findings of increased level of glutaric acid and sarcosine in urine of the patients with encephalopathy precipitated by ifosfamide. According to this hypothesis, glutaric acid increases chloroethylamine levels in the blood which in turn affects the metabolism of respiratory chain in negative manner. The inhibition of respiratory chain leads to accumulation of nicotinamide adenine dinucleotide hydrogen (NADH) which prevents dehydrogenation of aldehyde, i.e., ifosfamide metabolite CAA. Hence, the accumulated CAA crosses the blood brain barrier and leads to IIE.

Accumulated CAA leads to (a) a direct neurotoxic effect, (b) depletion from the CNS of glutathione, and/or (c) the inhibition of mitochondrial oxidative phosphorylation resulting in impaired fatty acid metabolism.

Diagnosis of IIE is based on clinical suspicion. Encephalopathy can occur from 12 to 146 h after the start of infusion.<sup>[6]</sup> No specific electroencephalographic or radiographic changes specific to this condition have been identified. The National Cancer Institute has classified IIE into four grades.

- Grade 1 - Dazed or slightly depressive periods
- Grade 2 - Extensive sleep or agitation

- Grade 3 - Heavy depression, mild hallucinations, or a stuporous condition
- Grade 4 - State of hallucinations or coma.

The treatment of ifosfamide induced encephalopathy involves withholding the infusion of ifosfamide and looking for the precipitating factors and correction of the same. In some patients with supportive treatment, spontaneous resolution of IIE may occur more common in milder grade and sometimes with severe grades within 48–72 h of its onset without the need of any pharmacologic intervention. However, pharmacologic intervention may be required for the control of acute symptoms. The pharmacologic treatment that has been described in literature includes injection methylene blue and thiamine.<sup>[7,8]</sup> K pfer (1994) was the first to describe the use of methylene blue (50 mg [1% aqueous solution] IV over 5 min, six times daily) for the treatment and prophylaxis of IIE.<sup>[8]</sup>

Methylene blue shows various mechanisms in counteracting few of those metabolic pathways mentioned above. Various actions shown by methylene blue are:

- a. Act as an alternative electron acceptor and replaces flavoproteins, thereby acting an alternative electron acceptor in mitochondrial respiratory chain
- b. It may oxidize NADH, thereby curbing the negative effect on dehydrogenation of aldehydes (Hrushesky *et al.*, 1985)<sup>[9]</sup>
- c. Plasma and extrahepatic monoamine oxidases are inhibited by it.

Ifosfamide-induced neurotoxicity resembles Wernicke encephalopathy, which is caused by severe thiamine deficiency due to alcoholism. Hence, the use of IV thiamine as used in Wernicke encephalopathy was experimented first by Buesa *et al.* and published as a case series which showed dramatic improvement in ifosfamide-induced encephalopathy.<sup>[10]</sup> Thiamine is usually given at 100 mg diluted in 100 ml of normal saline as a 10 min infusion every 4 h until resolution or significant improvement of symptoms.

Methylene blue can cause various side effects such as hemolytic anemia and blue-green discoloration of the urine and feces at doses exceeding 4 mg/kg while thiamine causes include local irritation, itching, sweating, and nausea.

Other supportive measures that can be used in the patients with IIE include the use of IV albumin which binds to CAA and prevents it from crossing blood brain barrier. Hemodialysis can also be used as a part of management and has positive results in reversing encephalopathy. Even glucose infusion has been used in treatment.

Pharmacologic intervention that has shown a role includes methylene blue and thiamine which can be well administered with infusion.

## Summary

Prevention is the best treatment as sometimes IIE can be fatal. Hence, while we extend the armamentarium of drugs and

provide cure in various malignancies, avoiding fatal side effects related to the drug may provide a better aspect of treatment in curative as well as palliative setting.

Ifosfamide has been part of various treatment protocols such as Ewing's sarcoma (HR Ewing's protocol), osteosarcoma (MAPIE protocol), and NHL (MINE protocol), proper dosing and look at the preventive factors can avoid disastrous and fatal encephalopathy. Simple measures such as careful assessment of renal function, electrolytes, and albumin and avoiding the aprepitant and other precipitating factors may help in patient care.

## Learning points

1. In patients treated with curative and palliative intent where ifosfamide plays an important role in chemotherapy, regimen morbidity and mortality occurring due to such drug interaction is unwelcomed
2. Furthermore, when ifosfamide acts as a part of salvage regimen which will be followed by transplantation such interaction which can be fatal decreases the cure rate of such malignancies
3. Hence, this case report is to reiterate the fact that aprepitant needs to be avoided in the patient on ifosfamide therapy as a part of antiemetic armamentarium.

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## Conflicts of interest

There are no conflicts of interest.

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