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# Two Cases of Fatal Encephalopathy Related to Ifosfamide: An Adverse Role of Aprepitant?

Alice Séjourné[a, b] Sabine Noal[d] Mathieu Boone[a] Céline Bihan[a]
Marion Sassier[d] Michel Andrejak[c] Bruno Chauffert[a]

Departments of [a]Oncology, [b]Rheumatology and [c]Clinical Pharmacology, University Hospital Amiens, Amiens, and [d]Department of Oncology, F. Baclesse Center for the Fight against Cancer, Caen, France

**Key Words**
Aprepitant · Ifosfamide · Encephalopathy · Drug interaction

**Abstract**
Ifosfamide is used in the treatment of sarcomas and other tumors. It sometimes provokes encephalopathy, which is a serious complication even if it is usually reversible within 48–72 h after drug cessation. Ifosfamide is required to be activated by hepatic cytochrome P450 (CYP), especially the 3A4 subtype, leading to 4-hydroxy-ifosfamide. Ifosfamide is also converted by CYP3A4 to inactive but neurotoxic metabolites. Aprepitant is a neurokinin-1 receptor antagonist that is a potent antiemetic used in combination with 5-$HT_3$ antagonists and corticosteroids. Aprepitant has an inhibitory effect, as well as a possible inductive effect, on CYP3A4. Since ifosfamide and aprepitant are both substrates of CYP3A4, a pharmacokinetic interaction could result in secondary effects such as the potentialization of neurological side effects. In this report, we describe 2 cases of fatal encephalopathy in patients who have received both ifosfamide and aprepitant, and we discuss the mechanisms that could be involved. Our observations draw attention to the fact that aprepitant must be avoided, or at least used with caution, in patients who are receiving ifosfamide due to the risk of severe neurological side effects.


## Introduction

Ifosfamide (IFO) is an alkylating agent used to treat a large range of malignant tumors, including sarcomas. IFO-related toxicity to the central nervous system occurs in 10–40% of

Bruno Chauffert
CHU Amiens, Department of Oncology
Avenue Laënnec
FR–80480 Salouël (France)
E-Mail chauffert.bruno@chu-amiens.fr

patients [1]. Encephalopathy may manifest in various forms ranging from mild confusion to seizures or coma [2]. Aprepitant is a selective antiemetic that antagonizes substance P/neurokinin-1 receptors with high affinity. It is metabolized by cytochrome P450 (CYP) and has been shown to be a moderate dose-dependent inhibitor as well as a possible inducer of CYP3A4 [3, 4]. It is currently recommended for use in patients receiving moderately to highly emetogenic chemotherapy, in association with 5-$HT_3$ antagonists and corticosteroids to prevent chemotherapy-induced nausea and vomiting. Usually, IFO-induced encephalopathy is rapidly and fully reversible after drug cessation [5]. Nevertheless, we report 2 cases of fatal irreversible encephalopathy related to IFO and discuss the potential adverse role of aprepitant.

## Case Description

*Case 1*

A 39-year-old woman had a surgical resection for a uterine leiomyosarcoma in February 2011. A local relapse was treated by resection in March 2012, and the patient was referred for adjuvant chemotherapy in May 2012. Because of the deterioration of her general condition due to an early local relapse, she received first doxorubicin 75 mg/m$^2$ alone. Improvement of her general condition allowed for a combined treatment with doxorubicin (60 mg/m$^2$) and IFO (9 g/m$^2$) for the next 4 cycles. In the 5th and 6th cycles, IFO alone was used because of the cumulative dose of anthracyclines (adjuvant epirubicin had previously been given for a breast cancer). A partial response was obtained, but the tumor remained unresectable and a therapeutic break was decided. In February 2013, CT scan showed progression, and IFO (5 g/m$^2$/day) was started again. Aprepitant (125 mg on day 1 and 80 mg on days 2 and 3) was given with steroids to prevent nausea. Within a few hours after the 2nd cycle, the patient had obnubilation and awareness troubles without any other symptoms. These troubles did not improve with the evacuation of a vesical globe or the cessation of neurodepressing drugs (oxycodone and chlorpromazine). There was no hydroelectrolytic disorder. Encephalic MRI did not show bleeding or a cerebrovascular event. IFO-induced encephalopathy was suspected, and a treatment with methylene blue was started. Improved awareness was transiently observed, but the patient remained disoriented and died 8 days later, without return to normal consciousness.

*Case 2*

A 75-year-old woman was diagnosed with a pleiomorphic rhabdomyosarcoma (FNCLCC grade III) of the left thigh. She underwent a tumor resection in April 2010 followed by local irradiation. Bilateral pulmonary metastases were evidenced on CT scan in July 2011. Six cycles of doxorubicin (60 mg/m$^2$ every 3 weeks) were given before the resection of the left metastasis in December 2011 and of the right one in February 2012. Because of tumor invasion of the left pleura, the patient received 3 cycles of IFO (2 g/m$^2$/day for 5 days every 3 weeks) with aprepitant (80 mg/day × 5 days) and steroids. Eight days after the 3rd cycle of IFO, the patient was admitted for sepsis, lung infection, pancytopenia (1,400 leukocytes, 1,200 neutrophils, hemoglobin 8.2 g/dl, and 13,000 platelets) and renal insufficiency (620 μM creatinine). She presented vigilance disorders and confusion (Glasgow score 13). No abnormality or hemorrhage was detected on cerebral CT. MRI was judged nonfeasible. Lumbar puncture showed neither signs of infection nor presence of tumor cells. Methylene blue was ineffective. Despite restoration of normal blood count and normal renal function after one session of hemodialysis, the coma worsened leading to death.

## Discussion

Encephalopathy related to IFO is a serious complication even if it is usually reversible within 48–72 h after drug cessation [5]. IFO is a prodrug that requires activation by hepatic CYP, especially the 3A4 subtype, leading to its active form, 4-hydroxy-ifosfamide [6, 7]. IFO is also converted by CYP3A4 to inactive, but neurotoxic metabolites, 2- (2d-Ifo) and 3-dechloroethyl-ifosfamide (3d-Ifo) [6, 7]. IFO and its metabolites can penetrate through the blood-brain barrier [5]. CYP3A4 is a major metabolic pathway for several drugs and can be both inhibited and induced by some drugs such as aprepitant, leading to complex drug interactions [4]. The mechanisms of IFO-induced neurotoxicity are still poorly understood. Several mechanisms are proposed (fig. 1), the first of which being the accumulation of glutaric acid leading to an increase in chloroethylamine, one of the metabolites of IFO, which could inhibit electron transfer to flavoproteins, thus inhibiting the mitochondrial respiratory chain [2, 5]. Another mechanism may be the accumulation of chloroacetaldehyde, a neurotoxic metabolite, after its penetration through the blood-brain barrier [2, 5]. Since both IFO and aprepitant are substrates of CYP3A4, a pharmacokinetic interaction/competition between them could lead to secondary effects. Indeed, aprepitant may interfere with IFO metabolism as it inhibits CYP3A4, but it can also cause its induction in a dose-dependent manner [3, 4, 6, 8, 9]. Usually, IFO-induced encephalopathy occurs during or in the few hours following IFO administration as in our first case. Imputing IFO is more disputable in our second observation, since it occurred late after IFO cessation, but no other obvious causes of encephalopathy were evidenced. A previous study has shown that the aprepitant-inducing effect on CYP3A4 could extend to up to 2 weeks after drug administration. This, and the renal failure, could explain the delay of the neurotoxic effects encountered in our second case [3]. Previous publications have reported an increased risk of central nervous system toxicity when IFO was associated with aprepitant [8, 10, 11]. An increase of 66.7% in 2d-Ifo and 37.3% in 3d-Ifo was reported when aprepitant was given concomitantly with IFO in one patient [6]. In the thesaurus of drug interactions by the French ANSM (Agence nationale de sécurité du médicament), updated in January 2014, it is now recommended to take into account the augmentation of the IFO-induced neurotoxicity risk when IFO is used in combination with aprepitant [12].

## Conclusions

In conclusion, our two observations must draw attention to the fact that aprepitant must be avoided, or at least given with caution, in patients receiving IFO due to the risk of fatal neurological side effects.

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## Disclosure Statement

The authors have no conflicts of interest to declare.

## References

1 Sweiss KI, Beri R, Shord SS: Encephalopathy after high-dose Ifosfamide: a retrospective cohort study and review of the literature. Drug Saf 2008;31:989–996.
2 Ajithkumar T, Parkinson C, Shamshad F, Murray P: Ifosfamide encephalopathy. Clin Oncol 2007;19:108–114.
3 Shadle CR, Lee Y, Majumdar AK, Petty KJ, Gargano C, Bradstreet TE, Evans JK, Blum RA: Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. J Clin Pharmacol 2004;44:215–223.
4 Aapro MS, Walko CM: Aprepitant: drug-drug interactions in perspective. Ann Oncol 2010;21:2316–2323.
5 Shin YJ, Kim JY, Moon JW, You RM, Park JY, Nam JH: Fatal ifosfamide-induced metabolic encephalopathy in patients with recurrent epithelial ovarian cancer: report of two cases. Cancer Res Treat 2011;43:260–263.
6 Durand JP, Gourmel B, Mir O, Goldwasser F: Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. Ann Oncol 2007;18:808–809.
7 Kerbusch T, Mathot RA, Keizer HJ, Kaijser GP, Schellens JH, Beijnen JH: Influence of dose and infusion duration on pharmacokinetics of ifosfamide and metabolites. Drug Metab Dispos 2001;29:967–975.
8 Ho H, Yuen C: Aprepitant-associated ifosfamide neurotoxicity. J Oncol Pharm Pract 2010;16:137–138.
9 Product information: Emend®, aprepitant, 2006. Merck & Co., Inc., Whitehouse Station, N.J., USA.
10 Howell JE, Szabatura AH, Hatfield Seung A, Nesbit SA: Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant. J Oncol Pharm Pract 2008;14:157–162.
11 Jarkowski A: Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. Am J Health Syst Pharm 2008;65:2229–2231.
12 Agence nationale de sécurité du médicament et des produits de santé: Thesaurus: référentiel national des interactions médicamenteuses [Web resource]. France, ANSM, 2014. http://ansm.sante.fr/var/ansm_site/storage/original/application/2a67d62293cf0d02cf55a51330ce74b9.pdf (cited January 10, 2014).

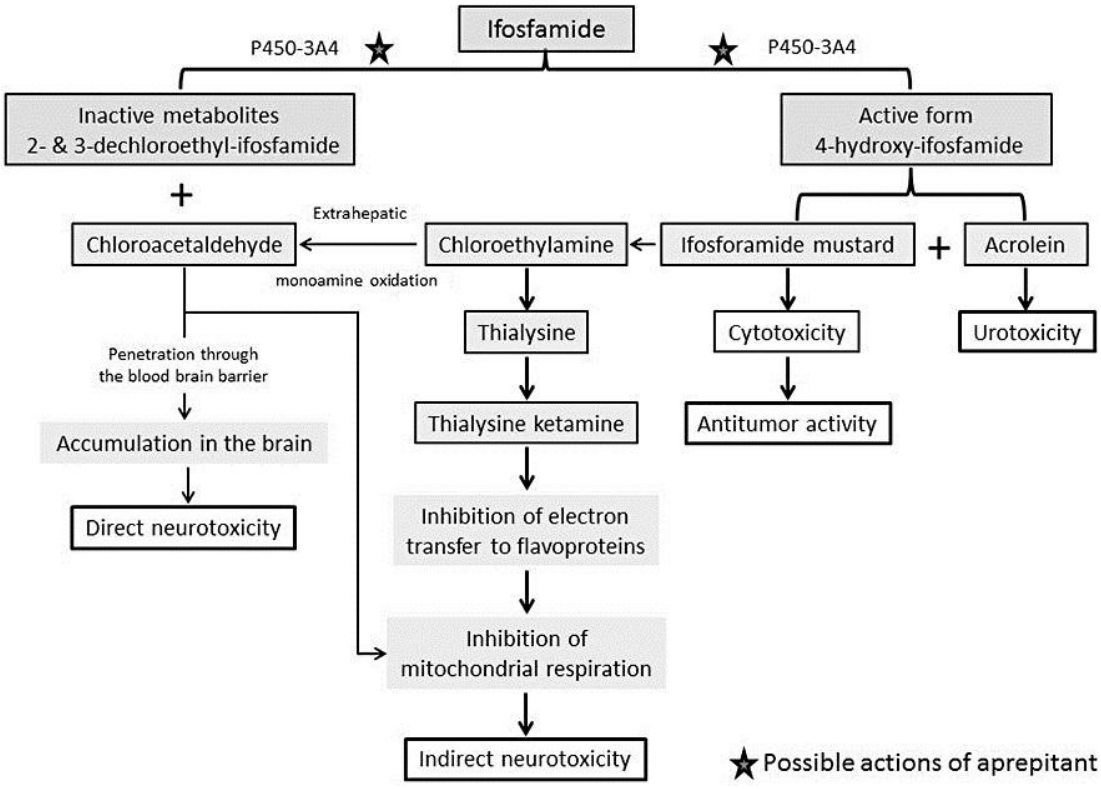


**Fig. 1.** Metabolism of IFO and proposed pathogenesis in IFO-induced encephalopathy.