

Systemic hypersensitivity to fosaprepitant – A report of two cases

Allison Baxley¹, Zoe Lee² and Patrick Medina²

Abstract

Fosaprepitant is a widely administered antiemetic used mainly for moderately to highly emetogenic chemotherapy. Local injection site reactions are the most common type of infusion reaction reported from fosaprepitant. At our institution, two separate patients have experienced systemic hypersensitivity reactions to their infusions of fosaprepitant. We report a review of the literature and the details of these reactions.

Keywords

Fosaprepitant, infusion reaction, hypersensitivity, anaphylaxis

Introduction

Fosaprepitant, a prodrug of aprepitant, is a neurokinin-1 receptor antagonist (NK₁ RA) FDA-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV). It is used in combination with other antiemetic agents such as 5-hydroxytryptamine type-3 receptor antagonists (5HT-3 RA) and a corticosteroid. Including fosaprepitant as part of the antiemetic regimen may increase patient compliance to chemotherapeutic treatments and the quality of life of patients receiving highly to moderately emetogenic chemotherapy.^{1,2} Fosaprepitant was generally found to be safe and effective with common side effects of infusion site pain, erythema, and thrombophlebitis.³ A literature search was performed on MEDLINE (1948–2016) using the search terms: *fosaprepitant*, *infusion reaction*, *hypersensitivity*, and *anaphylaxis*. To our knowledge, there have previously not been any reported cases of hypersensitivity reactions that have included systemic symptoms, nor are any reported in the FDA-approved package insert. In this paper, we report the cases of two patients who experienced grade 2 and 3 systemic hypersensitivity reactions possibly attributed to fosaprepitant.

Case presentation I

DA was a 53-year-old male diagnosed with head and neck cancer, who developed an anaphylactic-like

reaction after the start of fosaprepitant, which was being administered prior to his third cycle of chemotherapy. He received dexamethasone, followed by palonosetron, then fosaprepitant. Four minutes into the start of the fosaprepitant infusion, the patient appeared bright red and had very labored breathing. O₂ saturation levels were found to be at 83% on room air. The fosaprepitant infusion was discontinued and the institutional hypersensitivity protocol was initiated. The patient was given intravenous (IV) diphenhydramine 50 mg, an intramuscular injection of epinephrine 0.3 mg, IV methylprednisolone 125 mg and placed on 5 L of oxygen. The patient's vital signs following initiation of the hypersensitivity protocol were: blood pressure of 150/71 mmHg, heart rate of 111, and O₂ saturation 89%. The patient was then given intravenous hydrocortisone 100 mg, after which the patient reported feeling better. Vitals were repeated and reported as: blood pressure 143/66, heart rate 97, O₂ saturation 97%, and 20 respirations/min. The administration of the remaining fosaprepitant dose was held, and the patient was not re-challenged. The patient then

¹Stephenson Cancer Center, OK, USA

²College of Pharmacy, University of Oklahoma, OK, USA

Corresponding author:

Allison Baxley, Stephenson Cancer Center, 800 NE, 10th St, Suite 3030, Oklahoma City, OK 73104, USA.

Email: Allison-baxley@ouhsc.edu

continued his chemotherapeutic treatments for the rest of the day.

The patient had previously received two cycles of cisplatin 40 mg/m² weekly with radiation therapy along with three antiemetics – fosaprepitant, dexamethasone, and palonosetron. He tolerated the two previous infusions of fosaprepitant well without any adverse event. After the anaphylactic-like reaction experienced during the third cycle, fosaprepitant was permanently discontinued. He did not receive any other new medications to our knowledge. He tolerated four subsequent cycles of dexamethasone, palonosetron, and cisplatin well, supporting the hypothesis that fosaprepitant was the likely causative agent of the hypersensitivity reaction.

Case presentation 2

A 22-year-old female with an immature teratoma of the ovary received fosaprepitant prior to bleomycin, etoposide, and cisplatin (BEP). Her baseline vital signs were: blood pressure of 107/57, heart rate of 113, O₂ saturation of 98% and 15 respirations/min. On her first day of the five-day treatment, she received dexamethasone, palonosetron, then fosaprepitant. Five minutes into the start of the infusion, the patient appeared flushed and panicky. She complained of a tight, burning chest, and complained of a numb sensation in her lips. The fosaprepitant was stopped and the patient received 50 mg IV diphenhydramine. Shortly after the administration of diphenhydramine, the patient reported that the numbness in her lips had faded, but she still felt a slight burning in her chest. The patient's vitals were repeated and her blood pressure was 113/59, heart rate 87, O₂ saturation 96%, and 16 respirations/min. The fosaprepitant infusion was not initiated again and after resting for 30 min, the patient was able to continue the rest of her chemotherapy.

This was the patient's first cycle of BEP and her first dose of fosaprepitant. The use of fosaprepitant was not re-challenged in this patient in subsequent chemotherapy cycles. She tolerated three subsequent cycles of BEP without adverse effect. Of note, she did switch from palonosetron to ondansetron beginning with cycle 2 for undocumented reasons, though she did receive a second dose of palonosetron on day 4 of her first cycle without complication.

Discussion

Fosaprepitant is the injectable pro-drug formulation of aprepitant and works by inhibiting substance P centrally.⁴ It is a single-dose of 150 mg that helps prevent both the acute and delayed phases of

nausea due to chemotherapy. While a three-day oral regimen of aprepitant was the first approved NK₁ RA, randomized controlled trials have shown that a single IV dose of fosaprepitant is non-inferior to aprepitant and may be more convenient for patients.^{4,5}

According to the National Comprehensive Cancer Network antiemetic guidelines,² the addition of an NK₁ RA to dexamethasone and a 5HT-3 RA is an effective combination for relieving CINV due to highly and some moderately emetogenic chemotherapy. The most common adverse reactions reported for fosaprepitant are fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, and pain in the extremity.⁶ In a study conducted by Lasseter et al.,⁷ it was determined that the tolerability of fosaprepitant was seen at doses of up to 150 mg and that adverse events experienced aside from the common infusion site reactions were headache and dizziness.

Aapro et al.¹ completed a 10-year review that determined the safety and efficacy of NK₁ RA, and there were no reported instances of systemic hypersensitivity reactions. While infusion staff should always be prepared to respond to unexpected infusion reactions to any medication, patients are generally monitored more closely when medications that have a high incidence of hypersensitivity reactions are administered, such as paclitaxel or cetuximab. In general, fosaprepitant would not have been a medication that our infusion staff would perform specific observation for, as systemic reactions have been unreported until now. We report the experience at our institution to alert all practitioners using fosaprepitant that such a reaction is possible and has occurred in more than one patient in our infusion center. Additionally, absence of an infusion reaction to the initial infusion does not preclude subsequent infusion reactions, as evidenced by our patient DA who had previously received two doses of fosaprepitant without issue. Our second patient experienced a reaction with her first dose. Providers administering fosaprepitant should be aware of the risk of systemic hypersensitivity reactions and ensure proper medications and trained personnel are available to respond in the event of such a reaction.

Conclusion

Fosaprepitant is an essential antiemetic that is used in combination with dexamethasone and a 5-HT₃ receptor antagonist for the use of CINV. It is important that monitoring of hypersensitivity reactions outside of local infusion site pain, erythema, or thrombophlebitis be followed not only for the initial dose but for any subsequent doses. These cases demonstrate that rare

adverse reactions may occur at any moment and that clinicians should err on the side of caution due to these possibilities.

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