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JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Original Article

J Oncol Pharm Practice
0(0) 1–5
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DOI: 10.1177/1078155219895312
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Evaluation of fosaprepitant-associated hypersensitivity reactions at a National Cancer Center

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Abstract

Introduction: At our institution, an increased incidence of hypersensitivity reactions was reported following standardization of fosaprepitant as the preferred agent for the prophylaxis of chemotherapy induced nausea and vomiting (CINV) caused by highly emetogenic therapies. The purpose of this evaluation was to assess the incidence of systemic hypersensitivity reactions (HSRs) to fosaprepitant infusions compared to available literature.

Methods: This evaluation is a retrospective review of electronic health records of adult patients who received their first dose of fosaprepitant for CINV prophylaxis beginning January 1, 2017 through June 30, 2017 at the University of Colorado Cancer Center outpatient infusion center. Subjects were identified using medication administration reports. Individual chart reviews were performed for all patients who received fosaprepitant during the specified timeframe and had a reaction reported on the same date.

Results: A total of 868 patients received fosaprepitant in the outpatient infusion center during the study time period. Four patients (0.461%) had a systemic HSR attributed to fosaprepitant. Two of the reactions were reported as HSRs in the adverse reaction reporting system and two were found in provider notes during chart review. Due to the small sample size, risk factors for HSRs to fosaprepitant were not able to be determined.

Conclusion: The incidence of HSRs to fosaprepitant at our institution was found to be consistent with the $<1\%$ incidence currently noted in literature. Based on these findings, opportunities have been identified for education on fosaprepitant-associated HSRs, proper documentation and patient-specific precautions.

Keywords

Anaphylaxis, fosaprepitant, hypersensitivity, infusion reaction

Date received: 16 August 2019; accepted: 25 November 2019

Introduction

Nausea and vomiting are well-known adverse effects associated with chemotherapy administration.[1] Fosaprepitant dimeglumine (Emend® IV) is an intravenous (IV) antiemetic indicated for prevention of acute or delayed chemotherapy-induced nausea and vomiting (CINV) due to moderate or high risk emetogenic agents.[2] Without adequate antiemetic prophylaxis, 30–90% of patients experience CINV when given moderately emetogenic chemotherapy, and >90% of patients experience CINV when given highly emetogenic chemotherapy.[3] With the use of fosaprepitant, the percentage of patients who experience CINV while receiving highly emetogenic chemotherapy can be reduced to 30–38%.[4] Fosaprepitant is administered over 30 min prior to the infusion of chemotherapy on day one in conjunction with other antiemetic

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premedications, such as dexamethasone, serotonin antagonists and olanzapine. Aprepitant (Emend) is the alternative oral formulation that is administered for three consecutive days starting one hour prior to chemotherapy infusion on the first day of a regimen.[5]

Fosaprepitant and aprepitant are neurokinin-1 (NK_1) receptor antagonists that exert their effect by blocking the binding of substance P to NK_1 receptors which is the primary mediator of the delayed nausea and vomiting phase.[6] The use of oral aprepitant is limited in the outpatient setting due to patient cost, access and concerns for compliance. Considering these factors, University of Colorado Hospital (UCH) added IV fosaprepitant as its formulary NK_1 antagonist for all patients receiving a moderate or highly emetogenic chemotherapy regimen in the outpatient infusion center. The rationale for this change was that administering the medication in the infusion center would benefit patients by improving compliance with recommended guidelines,[7] as well as improve adherence, which could ultimately lead to better patient outcomes.

After the addition of fosaprepitant to the formulary, there was a reported increase in HSRs by infusion center staff. Currently, fosaprepitant is noted to have a <1% incidence of HSRs.[6] The purpose of this study was to assess the incidence of fosaprepitant-associated HSRs at UCH compared to the tertiary literature.

Methods

This retrospective cohort study included adult patients aged 18 to 89 years of age whose first dose of fosaprepitant for the prevention of CINV was administered between January 1, 2017 through June 30, 2017 at one of three UCH ambulatory infusion centers. This chart review excluded patients enrolled in clinical trials and incarcerated or pregnant patients. The study was approved by the Colorado Multiple Institutional Review Board (COMIRB).

Subjects were first identified using reports documenting fosaprepitant medication administration. This list was then cross referenced with patients who had an International Classification of Diseases (ICD) 10 code for an adverse drug event. Reviews of individual electronic health records were performed for all patients who received fosaprepitant during the study period and had an ICD code for an adverse drug event related to chemotherapeutic agents. All administrations of fosaprepitant for each patient during this period were reviewed in detail. Reactions were confirmed by reviewing adverse event reports and provider notes in patient records. Demographic data collected on patients with a documented reaction included age, gender, cancer diagnosis, chemotherapy regimen and allergies. Further information was collected on those who had a confirmed reaction including a description of the reaction (including severity), time to onset of the reaction and how the reaction was managed. Reaction severity grading was based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0).[8] All patient information was collected from electronic health records and stored securely in REDCap.[9]

The primary outcome was to determine the incidence of fosaprepitant-associated HSRs at UCH in the outpatient infusion centers. Identification of risk factors for fosaprepitant HSRs was the secondary outcome. Risk factors assessed included, but was not limited to, concurrent medications, cancer diagnosis and chemotherapy regimen administered. Descriptive statistics were used to assess the primary and secondary outcomes. The sample size was determined by the number of patients who met the inclusion criteria. Chi-squared tests for categorical data and *t*-tests for continuous data were planned for formal hypothesis testing of between-group differences.

Results

A total of 868 patients received fosaprepitant in the outpatient infusion center during the study period and 245 patients also had a reaction reported on the same day. Demographic information for all patients who received fosaprepitant as CINV prophylaxis and who had a same day associated adverse event is listed in Table 1. The study population was diverse and included patients diagnosed with a variety of malignancies who were prescribed different chemotherapy regimens. All patients were prescribed fosaprepitant 150 mg IV over 30 min. Four patients (0.461%) experienced a systemic HSR attributed to fosaprepitant. Two of the patients had grade 2 reactions, and the other two patients had grade 3 reactions.

Patient one was a 44-year-old female who experienced a grade 3 reaction to her first dose of fosaprepitant prior to cycle one, day one of doxorubicin and cyclophosphamide chemotherapy for breast cancer treatment. For anti-emetic prophylaxis, she received palonosetron and dexamethasone prior to the fosaprepitant infusion. Ten minutes into the fosaprepitant infusion, the patient reported burning in her chest and stomach and feeling anxious. She became flushed on her neck, chest and face. She was diaphoretic and experienced trouble breathing and chest tightness. The patient also reported feeling very hot, especially in her lower back area. The infusion was immediately stopped, and she received 50 mg IV diphenhydramine and was placed on 1 liter of oxygen via nasal cannula. She began to feel better within approximately 5 min.

Table 1. Demographics.

Parameter	$n = 245$
Mean age, years (range)	55 (18–89)
Sex, *n* (%)	
• Female	156 (63.7)
Cancer Diagnosis, *n* (%)	
• Breast	35 (14.2)
• Cervical	8 (3.3)
• Cholangiocarcinoma	7 (2.9)
• Colorectal	9 (3.7)
• Endometrial	8 (3.3)
• Genitourinary	12 (4.9)
• Gastrointestinal	5 (2.0)
• Head and neck	23 (9.4)
• Leiomyosarcoma	6 (2.4)
• Lung	29 (11.8)
• Lymphoma	23 (9.4)
• Ovarian	22 (9.0)
• Pancreatic	6 (2.4)
• Peritoneal	8 (3.3)
• Other	44 (18.0)
Chemotherapy, *n* (%)	
• ABVD	4 (1.6)
• AVD	4 (1.6)
• BEP	1 (0.4)
• Carboplatin	7 (2.9)
• Cisplatin	37 (15.1)
• Dacarbazine, cisplatin	2 (0.8)
• Docetaxel, carboplatin	3 (1.2)
• Doxorubicin, cyclophosphamide	28 (11.4)
• Doxorubicin, carboplatin	3 (1.2)
• Etoposide, cisplatin/carboplatin	15 (6.1)
• FOLFOX	10 (4.1)
• Gemcitabine, cisplatin/carboplatin	16 (6.5)
• Gemcitabine, dacarbazine	4 (1.6)
• Gemcitabine, paclitaxel	2 (0.8)
• MVAC	5 (2.0)
• MVC	1 (0.4)
• Olaratumab, doxorubicin	4 (1.6)
• Olaratumab, doxorubicin, dexrazoxane	4 (1.6)
• Paclitaxel, cisplatin/carboplatin	27 (11.0)
• Pemetrexed, cisplatin/carboplatin	13 (5.3)
• R-CHOP	7 (2.8)
• Romidepsin	2 (0.8)
• THCP	2 (0.8)
• THP	1 (0.4)
• Trabectedin	2 (0.8)
• VAC	2 (0.8)
• Vincristine, cyclophosphamide	1 (0.4)
• Other	38 (16.0)
Allergies, *n* (%)	
• Adhesives	9 (3.7)
• Antibiotics	33 (13.5)
• Antiemetics	7 (2.9)
• Chemotherapy	9 (3.7)
• Iodine	3 (1.2)
• Latex	7 (2.9)
• NSAIDs	7 (2.9)
• Opioids	30 (12.2)
• Silicone	3 (1.2)
• Other	6 (2.4)

Diagnosis: Genitourinary (bladder, vulvovaginal, testicular), Gastrointestinal (esophageal, stomach), Head and neck (mouth, tongue, nasopharyngeal, laryngeal).
Chemotherapy: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), AVD (doxorubicin, vinblastine, dacarbazine), BEP (bleomycin, etoposide, cisplatin), FOLFOX (fluorouracil, oxaliplatin, leucovorin), MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), MVC (methotrexate, vincristine, cisplatin), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), TCHP (trastuzumab, pertuzumab, carboplatin, docetaxel), THP (trastuzumab, pertuzumab, docetaxel), VAC (vincristine, dactinomycin, cyclophosphamide).
Allergies: NSAIDs (nonsteroidal anti-inflammatory drugs).
Note: Some patients had more than one drug allergy.

It was determined safe to proceed with her chemotherapy infusions, after about 20–30 min following diphenhydramine administration. Fosaprepitant was not re-challenged.

The second patient was a 62-year-old female who experienced a grade 2 reaction to her first dose of fosaprepitant prior to cycle two, day one infusion of carboplatin and pemetrexed for lung cancer treatment. She received palonosetron and dexamethasone prior to her fosaprepitant infusion. Eight minutes into the fosaprepitant infusion, the patient started complaining of severe back pain which increased to the point of not being able to stand upright. Fosaprepitant was stopped and 1 liter of normal saline was administered. She received 25 mg IV diphenhydramine, 40 mg IV methylprednisolone and 20 mg IV famotidine. She reported feeling better and it was determined safe to proceed with her chemotherapy infusions. Time to symptom resolution was not reported and fosaprepitant was not re-challenged in this patient.

The third patient was a 58-year-old female who experienced a grade 3 reaction to her second dose of fosaprepitant prior to cycle two, day one infusion of cisplatin for head and neck cancer. She received palonosetron and dexamethasone prior to her fosaprepitant infusion. Two minutes into the fosaprepitant infusion, the patient complained of flushing, shortness of breath, chest pain and low back and tailbone pain. The fosaprepitant infusion was stopped and one liter of IV normal saline was administered. She also received 25 mg IV diphenhydramine and 20 mg IV famotidine per the UCH infusion center's HSR protocol. Her oxygen saturation was 73% on room air and oxygen per nasal cannula was titrated to 4 L/min. An additional 25 mg IV diphenhydramine and 40 mg IV

methylprednisolone were administered. The patient's vital signs stabilized, and oxygen saturation increased to 93% on room air. She reported symptom resolution and it was determined safe to proceed with her chemotherapy infusions. Time to symptom resolution was not reported and fosaprepitant was not re-challenged in this patient.

The fourth patient was a 66-year-old male who experienced a grade 2 reaction to his first and second dose of fosaprepitant prior to cycle one, day one and day eight of gemcitabine and cisplatin for bile duct cancer. On cycle one, day one the patient was given palonosetron and dexamethasone prior to each fosaprepitant infusion. He reported flushing and palpitations 5 minutes into the fosaprepitant infusion. The infusion was immediately stopped, and he received 25 mg IV diphenhydramine and 20 mg IV famotidine. The patient reported symptom resolution within a few minutes and fosaprepitant was restarted at one-half the ordered rate. After 15 min, the infusion was increased to the original ordered rate and the patient tolerated the remaining infusion without incident. The patient voiced no other complaints and tolerated infusions of gemcitabine and cisplatin without difficulty. His next infusion occurred seven days later, on cycle one day eight and he reported severe back pain and facial flushing six minutes into the fosaprepitant infusion. The infusion was immediately stopped, and he received 25 mg IV diphenhydramine, 20 mg IV famotidine, 40 mg IV methylprednisolone and 0.25 mg IV lorazepam per the infusion center's HSR protocol. Heat was applied for back pain and the patient reported symptom resolution. It was determined safe to proceed with his chemotherapy infusions. Time to symptom resolution was not reported and fosaprepitant was not re-challenged again after the second reaction.

Two of the reactions were reported as HSRs in the adverse reaction reporting system at UCH and two were found in notes during chart review. Due to the small sample size, risk factors for fosaprepitant-associated HSRs were not able to be determined.

Discussion

In this retrospective cohort study, 0.461% of patients experienced a HSR to fosaprepitant at UCH. This is consistent with the <1% incidence currently noted in tertiary literature.[6] The data on HSRs associated with fosaprepitant is limited to case reports and retrospective chart reviews. Boccia et al. conducted a multicenter retrospective cohort study evaluating HSR and infusion site adverse events associated with fosaprepitant in mostly breast cancer patients receiving anthracycline-containing chemotherapy regimens.[10] Over a two-month period, the incidence rate was 28% (35/127 patients) for the combination of HSRs and infusion site adverse events associated with fosaprepitant.

Baxley et al. reported on two cases of HSRs to fosaprepitant.[11] The HSRs in this case report were like the ones seen in our patients with respect to antiemetics administered, severity of the reactions, supportive care given, and time to symptom resolution. One male patient had a grade 3 reaction to his third dose of fosaprepitant and one female patient had a grade 2 reaction to her first dose of fosaprepitant. The same antiemetics (fosaprepitant, palonosetron, and dexamethasone) were given to the two patients in this case report as given to the patients we identified. Both patients were treated with diphenhydramine, steroids and oxygen resulting in symptom resolution.

There is a possibility that infusion rate plays a role in the incidence of HSRs. The standard infusion rate for fosaprepitant at UCH is 150 mg IV over 30 min. The fourth patient was re-challenged at a slower rate of fosaprepitant 150 mg IV over 60 minutes after experiencing a HSR to his first fosaprepitant infusion and received supportive care (25 mg IV diphenhydramine and 20 mg IV famotidine). At the next infusion appointment, the patient experienced a second fosaprepitant-associated HSR. Fosaprepitant was administered at the original rate, 150 mg IV over 30 min and was not re-challenged again.

The product monograph identified polysorbate-80, a preservative found in numerous medications, as the causative agent of hypersensitivity reactions to fosaprepitant.[2,12] Table 2 contains a list of commonly used medications that contain polysorbate-80.[13] Hypersensitivity to polysorbate-80 is a contraindication to fosaprepitant use.[2] Three of the patients who experienced a HSR in our study also had allergies to medications that contained polysorbate-80 as an ingredient, but it was not determined if the reaction was solely to the polysorbate-80 or the active drug in those incidences.[6] Being aware that the medications listed in Table 2 contain this substance is important to improve identification of potential polysorbate-80 allergies. Allergy testing is also an option for some patients.

Table 2. Medications/vaccinations containing polysorbate 80.[12]

Adalimumab	Infliximab
Amiodarone	Influenza vaccine (Fluarix)
Cyclosporine	Methotrexate
Doxorubicin	Paclitaxel/docetaxel
Etoposide	Pneumococcal conjugate vaccine (Prevnar 13)
Fosaprepitant	Ritonavir
Gardasil	Tdap (Boostrix)
Granisetron	Sirolimus

This analysis is not without limitations, many of which are related to the retrospective nature of the study. Data for two of the patients were not accessible through reaction reporting documentation and were solely collected from provider notes. The lack of reporting of HSRs could have to lead to the exclusion of pertinent information in data collection. Underreporting of adverse events associated with fosaprepitant may have resulted in a lower incidence rate than what is truly occurring. The patient IV access site type was also not available in the chart for data collection. Therefore, risk assessment of IV access type and HSRs was not possible.

Conclusion

The incidence of fosaprepitant-associated HSRs identified at our institution was consistent with what has been previously reported. Not all fosaprepitant-associated HSRs included in this study were reported through the institutional reporting system. Education on the risk of fosaprepitant-associated HSRs and reporting and documentation would be beneficial. Further studies with larger sample sizes, possibly conducted prospectively, need to be completed to assess risk factors for fosaprepitant-associated HSRs.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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