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# Fosaprepitant and Aprepitant for Chemotherapy-Induced Nausea and Vomiting in Children

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The Food and Drug Administration (FDA) has recently extended approval for fosaprepitant (Emend® for injection) to include children 6 months of age and older for prevention of chemotherapy-induced nausea and vomiting (CINV) associated with highly or moderately emetogenic chemotherapy (HEC or MEC).[1] Fosaprepitant is a prodrug of aprepitant that can be given intravenously; it was introduced in the US in 2008. Aprepitant was first approved by the FDA in 2003, with the oral capsule and suspension formulations of the drug approved for use in children in 2015. A review of aprepitant use in children was published in *Pediatric Pharmacotherapy* (volume 21, issue 5) later that year.

The safety and efficacy of aprepitant has continued to be demonstrated in controlled trials to reduce nausea and emesis in children receiving HEC or MEC.[2-6] In a recent systematic review and meta-analyses published by Okumura and colleagues in the *British Journal of Clinical Pharmacology*, the authors found a 52% relative risk reduction of CINV with the combination of aprepitant, ondansetron, and dexamethasone.[6] Based on these studies, the 2016 update of the Multinational Association for Supportive Care in Cancer (MASCC) consensus statement on prevention of acute CINV recommended that aprepitant be included as a standard component in prophylactic antiemetic regimens for HEC and for MEC in children unable to receive dexamethasone.[5] The 2017 update of the Pediatric Oncology Group of Ontario guidelines for prevention of CINV also recommends aprepitant for all children 6 months of age and older receiving MEC or HEC.[6] As the use of aprepitant has become more widespread, fosaprepitant has become a valuable alternative for children who are unable to take the oral medications.

## Mechanism of Action

Fosaprepitant dimeglumine is a prodrug of aprepitant, a high-affinity substance P/neurolinin-1 ($NK_1$) receptor antagonist.[1] Aprepitant has little or no affinity for dopamine, serotonin ($5\text{-}HT_3$), or corticosteroid receptors, giving it a unique mechanism of action compared to other currently available antiemetics. Occupancy of $NK_1$ receptors in the corpus striatum is associated with an antiemetic effect that augments the effects of $5\text{-}HT_3$ antagonists and corticosteroids. Studies conducted using positron emission tomography have shown that at plasma concentrations of 10 ng/mL, aprepitant occupies approximately 50% of brain $NK_1$ receptors and at 100 ng/mL, occupies approximately 90%. The exact percentage of $NK_1$ receptor blockade and its relationship to antiemetic efficacy has not been established.

## Pharmacokinetics

Fosaprepitant is converted to aprepitant via enzymatic conversion in the lungs, ileum, liver, and kidney.[1] Following administration of a single 150 mg fosaprepitant dose infused over 20 minutes, the mean maximum plasma concentration ($C_{max}$) of aprepitant was $4.2 \pm 1.2$ mcg/mL, with a mean area under the concentration time curve (AUC) of $37.4 \pm 14.8$ mcg•hr/mL. Plasma concentrations of fosaprepitant were undetectable within 30 minutes of completion of the infusion. Aprepitant is more than 95% protein bound, with an average volume of distribution of 70 L. Aprepitant undergoes extensive hepatic metabolism, primarily via CYP3A4 and with minor metabolism by CYP1A2 and CYP2C19. Seven metabolites have been identified in human plasma, with little or no pharmacologic activity. The half-life of aprepitant ranges from 9 to 13 hours in adults.

The pharmacokinetic profile of fosaprepitant was investigated by the manufacturer using both study results of patients 6 months to 17 years of age and a simulated model of single and 3-day treatment regimens.[1] Following a 5 mg/kg IV dose in the younger age group, the aprepitant $C_{max}$ was 3.3 mcg/mL with an AUC of 32.7 mcg•hr/mL. In the 2 to 6 years group and the 6 to 12 years group given a dose of 4 mg/kg, the aprepitant $C_{max}$ values were 3.1 mcg/mL and 3.6 mcg/mL, respectively, with AUC values of 28.2 mcg•hr/mL and 35.2 mcg•hr/mL. Patients 12-17 years of age who received a 150 mg dose had similar values, with an aprepitant $C_{max}$ of 3.4 mcg/mL and AUC of 29.4 mcg•hr/mL. After a 3-day regimen of an IV dose and two oral 2 mg/kg or 80 mg doses, AUC values for the same groups were 16.6 mcg•hr/mL, 20.2 mcg•hr/mL, 25.7 mcg•hr/mL, and 18 mcg•hr/mL. All values were similar to those reported in adults.

Clinical Experience

In 2014, Shillingburg and Biondo published the first retrospective study to include use of fosaprepitant as well as aprepitant in children and adolescents.[9] The authors reviewed the cases of 26 patients who received a total of 287 doses over 114 chemotherapy cycles. The patients ranged in age from 11 months to 17 years of age (mean 10.1 years). Fosaprepitant was used in seven of the patients, ranging in age from 13 to 17 years of age, accounting for 18 of the doses given (6%). All doses were either 115 mg or 150 mg. Only eight patients (38%) required rescue antiemetic doses. No adverse reactions were reported.

Last year, Kusick and colleagues provided a preliminary report of safety data on fosaprepitant use in 20 children between 9 months and 16 years of age who received 87 doses for CINV prophylaxis.[10] Patients weighing less than 30 kg received weight-based dosing, while 14 others received the adult dose of 150 mg. One patient experienced an infusion-related reaction, but their symptoms resolved after discontinuation of the infusion. No other adverse reactions were noted.

Another single-center retrospective study was recently published on-line ahead of print in the *Journal of Pediatric Hematology and Oncology* that describes the use of fosaprepitant in 35 children.[11] The median age of the patients was 10 years, with a range of 10 months to 18 years. The majority (57%) had central nervous system tumors, followed by 20% with sarcomas and 14% with neuroblastoma. All but one patient was receiving HEC. Fifteen patients (60%) had a prior history of CINV with earlier chemotherapy cycles. Over half of the patients weighed less than 40 kg and were given doses of 4 mg/kg. The remaining patients received the standard adult dose of 150 mg. The median number of doses given was 4 (range 1-21). All patients received ondansetron. In addition, 24 (69%) were given dexamethasone, three received scopolamine, two received dronabinol, and one each received diphenhydramine and lorazepam. Forty percent of the patients had nausea and/or emesis, but only 20% had nausea and 11% had emesis during the acute phase (the first 24 hours after chemotherapy). Twenty-six patients (74%) required rescue therapy, with 43% of patients needing treatment during the acute phase and 69% during the delayed phase (hours 25-120).

Patients younger than 6 years of age were more likely to experience emesis, while the adolescents were more likely to report nausea. The median number of rescue doses needed was highest in the adolescents, with a median of 4 doses compared to 2 doses in the infants to 6-year-olds and 1 in the 7 to 12-year-olds. Adverse reactions possibly related to fosaprepitant were noted in sixteen patients (43%). Twelve patients had elevated serum transaminases; however, eight had received high-dose methotrexate which may have contributed to the rise in levels. All cases resolved without intervention. Three patients had headaches, but were also receiving ondansetron, another possible cause, and one patient had intractable hiccups which resolved with baclofen. Two additional patients who were identified as meeting the study criteria were not included in the analysis after they developed anaphylactoid reactions with their first dose.

Contraindications and Warnings

Fosaprepitant and aprepitant are contraindicated in patients with a known hypersensitivity to the active drug or drug product excipients.[1] Hypersensitivity reactions, including anaphylaxis, dyspnea, hypotension, flushing, erythema, and syncope have been reported after their administration. Use of these drugs is also contraindicated in patients taking pimozide. Aprepitant inhibits CYP3A4 and may impair the metabolism of pimozide, resulting in QTc prolongation and the risk for arrhythmias.

Severe infusion site reactions, including thrombophlebitis and vasculitis, have been reported following the use of fosaprepitant. In the majority of these cases, the patient had also received anthracycline-based chemotherapy and had a possible extravasation. The infusion site should be closely monitored during and after fosaprepitant, and the infusion immediately discontinued if symptoms are noted. Most infusion site reactions have been reported within the first three exposures to the drug, with some cases lasting more than 2 weeks. Necrosis may

occur as a result of these reactions, resulting in the need for surgical intervention.

Adverse Reactions

In a controlled trial comparing triple-therapy with fosaprepitant, ondansetron, and dexamethasone versus ondansetron and dexamethasone alone conducted in 1,001 adults, there were no significant differences in any of the adverse reactions reported.[1] The most commonly reported reactions included fatigue (in 15% of patients), diarrhea (13%), neutropenia (8%), asthenia (4%), anemia or peripheral neuropathy (3%), and leukopenia, dyspepsia, urinary tract infection, and pain in an extremity (2%). Infusion site reactions were reported in 2.2% of the triple-therapy patients versus 0.6% in the control group. These reactions included pain at the infusion site (1.2% in the triple-therapy versus 0.4% in the controls), irritation (0.2% versus 0), initial vessel puncture pain (0.2% versus 0), and thrombophlebitis (0.6% versus 0).

In a safety analysis of 69 infants, children, and adolescents receiving a single dose of fosaprepitant in addition to ondansetron and dexamethasone for prevention of CINV with HEC or MEC, the results were similar to those reported in adults.[1] The most common adverse reactions (all occurring in > 15% of patients) were anemia, neutropenia, thrombocytopenia, and febrile neutropenia. The results were also similar in a study of 3-day administration (1 day of fosaprepitant followed by 2 days of oral aprepitant).

Additional safety data comes from a recent single center observational study of aprepitant use in children published in the *Journal of Oncology Pharmacy Practice*. The authors evaluated the cases of 85 children treated with a total of 192 chemotherapy cycles.[12] Twenty-two patients had osteosarcomas and seven had Ewing's sarcoma; the most common treatments were cisplatin-based regimens or high-dose methotrexate. Aprepitant was given in combination with palonosetron and dexamethasone in 95% of the cycles. Seventy-three cycles (38%) were without adverse events. Fifty percent of cycles had at least one adverse reaction, with the most common being anorexia, febrile neutropenia, cough, and headache, all occurring in approximately 50% of patients. The authors call attention to the higher rate of adverse effects in their study suggesting that these results may better reflect routine clinical practice, and that while many of these adverse effects could be attributed to the chemotherapy, they may also reflect the impact of adding an $NK_1$ antagonist.

Drug Interactions

Fosaprepitant is a weak inhibitor of CYP3A4. This effect that lasts for approximately 2 days after administration of a single dose.[1] Once converted to aprepitant, it becomes a moderate inhibitor of the enzyme. As described earlier, aprepitant is contraindicated in patients taking pimozide due to the likelihood for significant drug accumulation leading to QTc prolongation. Aprepitant and fosaprepitant should be used with caution in patients taking any medications that undergo metabolism by CYP3A4, including benzodiazepines, corticosteroids, hormonal contraceptives, and several chemotherapeutic agents.

As a result of their ability to induce CYP2C9, fosaprepitant and aprepitant may increase the metabolism of warfarin, decreasing serum concentrations and leading to a clinically significant reduction in INR values. INR should be monitored after starting fosaprepitant or aprepitant, including an assessment within the first 7-10 days after initial administration. Since aprepitant is also a substrate for CYP3A4, moderate and strong inhibitors, such as clarithromycin, diltiazem, itraconazole, ketoconazole, nefazadone, nelfinavir, troleandomycin, and ritonavir, may increase aprepitant serum concentrations resulting in toxicity. Conversely, strong CYP3A4 inducers, such as carbamazepine, phenytoin, and rifampin, may reduce the efficacy of aprepitant.

The clinical significance of these drug interactions was recently evaluated by Patel and colleagues.[13] The authors reviewed data from 64 publications, 34 of which included information on pharmacokinetic interactions. Thirteen included interactions with aprepitant and chemotherapeutic agents, and one included an interaction with fosaprepitant and ifosfamide. The authors' findings are provided in Tables 1 and 2.

Table 1. Clinically Significant Interactions
Reported with Aprepitant or Fosaprepitant

| |
|---|
| Oral bosutinib |
| IV cabazitaxel |
| IV cyclophosphamide |
| Oral dexamethasone |
| IV methylprednisolone |
| Oral and IV midazolam |
| Oral oxycodone |
| Oral tolbutamide |

Table 2. Possibly Significant Interactions
Reported with Aprepitant or Fosaprepitant

| |
|---|
| Erlotinib (form not specified) |
| IV ifosfamide |
| Oral pazopanib |
| IV thiotepa |

IV dexamethasone
Oral paroxetine
Oral quetiapine
IV tacrolimus

Availability and Cost

Fosaprepitant is available as a lyophilized powder in single-dose vials containing 150 mg.[1] The vials must be refrigerated and diluted with 5 mL of 0.9% sodium chloride prior to administration. The reconstituted vial is stable at room temperature for 24 hours. Prior to administration, the reconstituted solution should be diluted in 145 mL of 0.9% sodium chloride to provide a final concentration of 1 mg/mL. Fosaprepitant is incompatible with solutions containing calcium, magnesium, or other divalent cations, such as Lactated Ringer's solution. The acquisition cost for fosaprepitant is approximately $400 per 150 mg vial.[14]

Dosing Recommendations

Aprepitant or fosaprepitant should be used in conjunction with a serotonin ($5\text{-}HT_3$) antagonist with or without a corticosteroid, typically dexamethasone.[1] For single-day chemotherapy regimens in infants 6 months of age and weighing at least 6 kg to children up to 2 years of age, fosaprepitant should be infused through a central venous catheter at a dose of 5 mg/kg given over 60 minutes. For patients 2 years of age up to 12 years, a dose of 4 mg/kg should be infused over 60 minutes. The maximum dose for both age groups is 150 mg. For adolescents 12 years of age and older, as well as adults, a dose of 150 mg should be infused over 30 minutes.

For multi-day chemotherapy regimens, the manufacturer recommends that fosaprepitant be used on day 1 of chemotherapy, followed by aprepitant solution or capsules on days 2 and 3. In the 6 months to 12 years age group, a dose of 3 mg/kg (maximum dose 115 mg) should be infused over 60 minutes, followed by aprepitant given orally at a dose of 2 mg/kg (maximum dose 80 mg). In patients 12 to 17 years of age, a fosaprepitant dose of 115 mg should be infused over 30 minutes on day 1 of chemotherapy, followed by an oral dose of 80 mg on days 2 and 3. Patients should be monitored for signs of a hypersensitivity and infusion site reactions during and after the infusion.

Summary

The use of aprepitant and fosaprepitant has been a significant step in reducing the nausea and vomiting associated with chemotherapy administration. Over the past two years, several consensus statements and guidelines for the prevention of CINV in pediatric patients have been updated to include their use. New research with fosaprepitant and its approval by the FDA further support its routine use for moderately or highly emetogenic chemotherapy.

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