



Use of Aprepitant to Prevent Nausea and Vomiting in Children

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In spite of a number of treatment options, including serotonin 5-hydroxytryptamine (5-HT₃) antagonists, phenothiazines, and corticosteroids, many pediatric patients continue to experience nausea and vomiting with chemotherapy or after surgery. A recently published phase 3 study demonstrated significant benefit from the addition of aprepitant to standard therapy in children receiving emetogenic chemotherapy.¹ Aprepitant (Emend®, Merck), a substance P/neurokinin-1 (NK₁) receptor antagonist, was initially approved by the Food and Drug Administration on March 27, 2003 and is currently indicated for prevention of both chemotherapy-induced and postoperative nausea and vomiting (CINV and PONV).^{2,3} Merck plans to submit a request for a pediatric indication based on the results of this study and several currently underway, as well as a New Drug Application for an oral suspension.

Mechanism of Action

Occupancy of NK₁ receptors in the corpus striatum is associated with an antiemetic effect that augments the effects of 5-HT₃ antagonists and corticosteroids. Based on studies conducted using positron emission tomography, at plasma concentrations of 10 ng/mL, aprepitant occupies approximately 50% of NK₁ receptors and at 100 ng/mL, occupies approximately 90%. In adults, the recommended dose of aprepitant produces plasma concentrations greater than 500 ng/mL, suggesting that more than 95% of NK₁ receptors will be occupied. The exact percentage of NK₁ receptor blockade and antiemetic efficacy is not yet known.^{2,3}

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profile of aprepitant has been established in children and adults. In adults, aprepitant is rapidly and completely absorbed, with a mean peak plasma concentration (C_{max}) of 1.6 mcg/mL on day 1 after a 125 mg dose and 1.4 mcg/mL on days 2 and 3 after 80 mg once daily.² Mean area under the concentration-time curve (AUC) for the two time points were 19.6 and 21.2 mcg•hr/mL, respectively. A study of 46 adolescents between 11 and 19 years of age

provided similar results, with a mean C_{max} of 1.2 mcg/mL and an AUC of 15.8 mcg•hr/mL.⁴ The intravenous formulation, fosaprepitant dimeglumine, is a prodrug which is rapidly converted to aprepitant upon administration.³ In adults given a 115 mg dose of fosaprepitant, the C_{max} was 3.27 ± 1.16 mcg/mL with an AUC of 31.7 ± 14.3 mcg•hr/mL, similar to the 125 mg oral dose. A dose of 150 mg fosaprepitant produced a C_{max} of 4.15 ± 1.15 mcg/mL and an AUC of 37.38 ± 14.75 mcg•hr/mL.

Aprepitant has a mean volume of distribution of 70 L in adults and is 95% bound to plasma proteins.^{2,3} It is extensively metabolized in the liver and extrahepatic tissues via cytochrome P540 (CYP) enzyme 3A4 and to a lesser extent by CYP1A2 and CYP2C19. None of the seven identified metabolites have significant pharmacologic activity. In adults, the average half-life of aprepitant is 9-13 hours.

Use in Children and Adolescents

Within two years of its approval, aprepitant was being used in adolescents to prevent CINV.⁵ The first clinical trial of aprepitant use in pediatrics was published in 2009.⁴ Gore and colleagues conducted a phase 3 randomized, double-blind, placebo-controlled study of the efficacy and tolerability of aprepitant in 46 patients between 11 and 19 years of age. Patients were randomized to receive the adult aprepitant regimen of 125 mg orally on day 1, followed by 80 mg on days 2 and 3, or placebo. All patients received dexamethasone and ondansetron. Complete response was defined as no emesis or need for rescue therapy over the first 5 days following chemotherapy. A significantly greater percentage of patients in the aprepitant group had a complete response (35.7% versus 5.6%). The percentage who did not require rescue antiemetics was also higher, 42.9% versus 22.2%. There were no serious drug-related adverse events and no patients discontinued treatment.

Several observational and retrospective studies have been published since that early report,

adding to our experience with aprepitant in younger children and different cancer types.⁶⁻¹⁰ In 2013, Bauters and colleagues analyzed the results of aprepitant use in 20 patients (mean age 14 years, range 8-16 years) receiving a total 104 cycles of moderate or highly emetogenic chemotherapy.⁶ All patients received a 5-HT₃ antagonist and dexamethasone 30 minutes prior to chemotherapy, as well as aprepitant 125 mg on day 1 followed by 80 mg on days 2 and 3. A complete response was observed in 89 cycles (85.6%). In spite of the multimodal approach, however, 13 patients still required rescue antiemetics.

Bodge and colleagues found a complete response rate of 38.9% in a group of 11 patients enrolled in their prospective observational study.⁸ The patients, ranging in age from 12 months to 17 years, all received ondansetron, dexamethasone, and aprepitant, rounded to the nearest 20 mg. Shillingburg and Biondo evaluated the tolerability of aprepitant in 26 children (11 months to 17 years of age) receiving a total of 114 chemotherapy cycles.⁹ Patients > 20 kg received the adult regimen, while patients 15-20 kg received 80 mg for 3 days and a single patient < 15 kg received 80 mg on day 1 and 40 mg on days 2 and 3. Twenty-five patients received aprepitant for CINV prevention and one patient for PONV prevention. No adverse effects believed to be related to aprepitant were reported. Although efficacy was not assessed in this report, the authors did report that only 8 patients required rescue antiemetics.

Aprepitant was also found to reduce CINV in a retrospective comparison study of 52 children and young adults (10-21 years of age) with central nervous system tumors.^{9,10} Eighteen of the patients received aprepitant with a regimen of ondansetron every 8 hours. Breakthrough vomiting was treated with the addition of lorazepam with or without diphenhydramine or promethazine. Aprepitant was given at a dose of 125 mg on day 1 followed by 80 mg on days 2 and 3. Patients who did not receive aprepitant had a significantly greater likelihood of developing grade 2 or 3 (severe) emesis during their first course of highly emetogenic chemotherapy (odds ratio 4.15, 95% CI 1.59, 10.82, $p = 0.03$). On the day after chemotherapy completion, the results remained significant, with 44% of controls having delayed grade 2 or 3 emesis, compared to only 16% of the aprepitant patients.

Two recent prospective studies have provided more detailed information on aprepitant use in children.^{11,12} In the April 2015 issue of *Lancet Oncology*, Kang and colleagues published the results of a phase 3 study evaluating the safety and efficacy of aprepitant for prevention of CINV in children.¹¹ Three hundred and seven patients between 6 months and 17 years of age

were enrolled in this international randomized, double-blind study which compared aprepitant 3 mg/kg (maximum 125 mg) on day 1 with 2 mg/kg (maximum 80 mg) on days 2 and 3 plus ondansetron on day 1 to placebo for 3 days plus ondansetron on day 1. Younger patients received an investigational oral aprepitant suspension. Patients were grouped by age and the emetogenic potential of their chemotherapy. The primary endpoint was the proportion of patients with a complete response and no need for rescue medication during the delayed phase (25-120 hours after chemotherapy). Secondary endpoints included response during the acute phase (0-24 hours) and overall response.

Fifty-one percent of the patients in the aprepitant group achieved the primary endpoint, compared to only 26% of the controls ($p < 0.0001$). Sixty-six percent of the aprepitant group experienced no acute CINV, compared to 52% of controls ($p = 0.014$) and overall efficacy was seen in 47% of the aprepitant group and 21% of the controls ($p < 0.0001$). Fewer patients in the aprepitant group required dexamethasone (32% versus 48%) and they had a longer time to the first dexamethasone dose ($p = 0.0024$). There were no differences among age groups. Adverse effects were similar in the aprepitant group and controls.

A subsequent randomized, double-blind, placebo-controlled study focused on response to aprepitant as add-on therapy during the acute phase after chemotherapy administration.¹² Ninety-three children between 5 and 18 years of age were enrolled in this single-center study. All patients received ondansetron (0.15 mg/kg) and dexamethasone (0.15 mg/kg), with the first dose given intravenously and the subsequent doses given orally. Aprepitant was given to patients weighing 15-40 kg as an 80 mg dose on days 1-3 and to patients 41-65 kg as 125 mg on day 1 followed by 80 mg on days 2 and 3. Patients in the control group received a placebo. Doses were given 1 hour before chemotherapy. A complete response was defined as no more than 2 episodes of emesis in the first 24 hours after administration of the first chemotherapy dose until 24 hours after the last dose. A significantly greater proportion of patients in patients in the aprepitant group had a complete response compared to the controls (48% versus 12%, $p < 0.001$). The incidence of acute moderate to severe vomiting was also less with aprepitant (38% versus 72%, $p = 0.001$). No major adverse effects were reported.

Merck is currently enrolling patients in two phase IIb clinical trials that will provide additional information on the use of aprepitant and fosaprepitant in children within the next several years.^{13,14} The first study will evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of fosaprepitant for CINV in children.¹³ Patients (newborn to 11 years of

age) will receive 3 doses of a weight-adjusted fosaprepitant dose or placebo, in combination with ondansetron prior to their first cycle of chemotherapy. Fosaprepitant may then be continued in an open-label phase for cycles 2-6. The results of this study should provide optimal dosing for future efficacy studies. The second clinical trial will evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of aprepitant in the prevention of pediatric PONV. Patients from birth to 17 years of age will be randomized to receive aprepitant in one of 4 doses, ondansetron, or placebo prior to induction of anesthesia. The anticipated completion time for both studies is mid to late-2016.

Adverse Effect

The most commonly reported adverse effects in clinical trials of adults receiving aprepitant for highly emetogenic chemotherapy have been fatigue (in 17.8% of patients from pooled data), nausea (12.7%), hiccups (10.8%), constipation or diarrhea (10.3%), anorexia (10.1%), headache (8.5%), and emesis (7.5%). Other less common adverse effects include dizziness (6.6%), dehydration (5.9%), heartburn (5.3%), abdominal pain (4.6%), gastritis or epigastric discomfort (4.2%), tinnitus (3.7%), neutropenia (3.1%), fever or insomnia (2.9%), and mucositis (2.6%). These values were reported by similar percentages of patients in the standard therapy comparator groups.²

The most frequently reported adverse effect in the recent phase 3 pediatric trial was anemia (seen in 17% of children compared to 25% of controls), followed by febrile neutropenia (16% in both groups), vomiting (15% in both) neutropenia (14% versus 12%), thrombocytopenia (10% versus 11%), decreased neutrophil count (9% versus 13%), and nausea (9% versus 11%).¹¹ Two patients in the aprepitant arm withdrew from the study because of a serious adverse event related to their chemotherapy: one allergic reaction with carboplatin and one anaphylactic shock with etoposide. Five of the aprepitant patients (3%) and three controls (2%) were thought to have an adverse effect directly related to a study drug, including hiccups, a *C. difficile* infection, vomiting, constipation, decreased serum calcium and potassium, and T-wave inversion on an electrocardiogram in the aprepitant group and increased alanine and aspartate aminotransferases and nausea in the controls.

Immediate hypersensitivity reactions have been reported with the administration of intravenous fosaprepitant, resulting in flushing, erythema, dyspnea, and anaphylaxis.³ If a reaction occurs, the drug should be immediately discontinued and not reintroduced. Rare cases of severe dermatologic reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis, have also been reported.

Drug Interactions

Aprepitant is a dose-dependent CYP3A4 inhibitor and should be used with caution in patients receiving other medications metabolized through this pathway.^{2,3} The risk for clinically significant interactions is greatest with the 80 mg or 125 mg regimens. Studies of aprepitant in patients receiving midazolam, a CYP3A4 substrate, have demonstrated up to a 1.5-fold increase in the midazolam AUC, but the clinical significance of the interaction has not been determined.

Concentrations of aprepitant may be elevated in patients taking other agents that inhibit CYP3A4, such as clarithromycin, diltiazem, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, or troleandomycin, or reduced in patients taking strong CYP3A4 inducers such as rifampin.^{2,3} Several chemotherapeutic agents are metabolized by CYP3A4 and have the potential for a reduction in metabolism, including docetaxel, etoposide, ifosfamide, imatinib, irinotecan, paclitaxel, vinblastine, vincristine, and vinorelbine. Studies of the administration of aprepitant with docetaxel or vinorelbine have shown no significant clinically changes in the pharmacokinetic parameters of either drug.

Coadministration of aprepitant and warfarin has been shown to produce a 34% reduction in warfarin concentrations with a clinically significant 14% decrease in prothrombin time, reported as the International Normalized Ratio (INR).^{2,3} It is recommended that patients taking warfarin have an INR monitored 7-10 days after initiation of aprepitant regimen in patients expected to receive multiple chemotherapy cycles. Aprepitant may also reduce plasma concentrations of tolbutamide. Coadministration of aprepitant with paroxetine has resulted in a 25% reduction in the AUC of both drugs.

Administration of aprepitant or fosaprepitant and hormonal contraceptives, including oral, transdermal, implanted, or intrauterine products, may reduce their efficacy.^{2,3} Studies of oral contraceptive administration with aprepitant have shown a 64% reduction in ethinyl estradiol and norethindrone concentrations lasting up to 3 weeks after treatment. An alternative or back-up method of contraception is recommended throughout treatment and for a month after aprepitant discontinuation.

Concomitant use of aprepitant or fosaprepitant with either methylprednisolone or dexamethasone or has been shown to increase the concentration of the corticosteroid approximately 2- to 2.5-fold.^{2,3} The manufacturer recommends reducing the dose of methylprednisolone by 25% when given on day 1 of an aprepitant or fosaprepitant regimen. Oral doses of prednisone or dexamethasone should be reduced by 50%.

Availability and Cost

Aprepitant is available in 40 mg, 80 mg, and 125 mg capsules.^{2,3} Fosaprepitant dimeglumine injection is available in 115 mg and 150 mg single-dose vials. The average wholesale unit price for aprepitant ranges from approximately \$90 for the 40 mg capsule to \$250 for the 125 mg capsule. A vial of fosaprepitant costs approximately \$300.

Dosing and Administration

When used for the prevention of CINV, aprepitant is typically given in a 3-dose regimen that includes a 5-HT₃ antagonist and a corticosteroid.^{2,3} In adults, the recommended dose is 125 mg on day 1, followed by 80 mg on days 2 and 3. This dose is currently being used in many centers for older children and adolescents ≥ 40 kg. While limited information is available on doses for infants and younger children, the recent phase 3 study conducted by Merck used a regimen of 3 mg/kg on day 1 with 2 mg/kg given on days 2 and 3, with the adult dose serving as the maximum. The recommended adult dose for prevention of PONV is 40 mg within 3 hours of the induction of anesthesia. No pediatric dosing recommendations are currently available for this indication. Aprepitant should be administered one hour prior to chemotherapy and may be taken with or without food. No dosage adjustment is recommended for aprepitant or fosaprepitant in patients with renal impairment or mild to moderate hepatic impairment. There are no clinical data regarding dosing in severe hepatic impairment. Aprepitant is not removed by hemodialysis.^{2,3}

In adults, fosaprepitant is administered to adults as either a single 150 mg dose for highly emetogenic chemotherapy or a 3-dose regimen of 115 mg on day 1 followed by oral doses of 80 mg on days 2 and 3.^{2,3} Fosaprepitant should be infused over 15 to 20 minutes. The intravenous form is stable for 24 hours at room temperature and should not be mixed with fluids containing divalent cations, including Lactated Ringer's solution.

Summary

Aprepitant, with its unique mechanism of action, has the potential to be a valuable tool in the prevention of CINV or PONV in children who continue to have nausea and vomiting in spite of the use of 5-HT₃ antagonists and corticosteroids. It has been shown to be effective and generally well tolerated in children; however, more studies are needed to evaluate repeated use and to establish its role in pediatric PONV. With additional research and the availability of an oral liquid dosage form, aprepitant may develop into a useful addition to standard therapy for children at risk for severe nausea and vomiting.

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