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Aprepitant to control nausea and vomiting in the Pediatric ICU setting

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Keypoints

- Aprepitant is a novel anti-emetic agent that acts as a selective antagonist, blocking the binding of substance P at the neurokinin-1 receptor.
- While ondansetron is generally effective to treat nausea and vomiting, there is a need for alternative agents when ondansetron is ineffective or when its use is contraindicated due to comorbid conditions such as prolongation of the QT interval.
- Aprepitant can be administered orally (capsule or liquid formulation) or intravenously in the form of the prodrug, fosaprepitant. Given cost constraints, oral administration is the preferred route whenever feasible.

Abstract

During critical illness, various secondary end-organ adverse effects may occur related to the primary disease process, secondary end-organ involvement, or treatment regimens. Nausea and vomiting may be a particularly disturbing secondary symptom in the critically ill patient. While the pathogenesis is frequently multifactorial and an exact etiology difficult to determine, symptomatic treatment is frequently employed. We present anecdotal experience with the successful use of the novel anti-emetic agent, aprepitant (Emend®, Merck & Co, Kenilworth, NJ) in two Pediatric ICU patients. The basic pharmacology of aprepitant is discussed, its clinical use with a focus on pediatrics patients is reviewed, and dosing recommendations presented.

Keywords

Aprepitant, nausea, vomiting, pediatric, PICU

Introduction

During critical illnesses requiring Intensive Care Unit (ICU) admission and complex care, secondary symptoms may occur related to the primary disease process, secondary illnesses, or treatment modalities. Many of these issues may be related to the gastrointestinal system including nausea and vomiting. The mechanisms and structures involved in nausea and vomiting include the central nervous system (cortex and limbic system providing cognitive and emotional input), the autonomic nervous system (nucleus tractus solitarus with visceral input via the vagus nerve, cerebellar and vestibular signals), and the area postrema of the medulla (emetogenic agents in the blood).[1] While the pathogenesis of nausea and vomiting is multifactorial and an exact etiology frequently difficult to determine, symptomatic treatment is often employed. Ondansetron, a 5-hydroxytryptamine ($5HT_3$) receptor antagonist, is a commonly used anti-emetic agent that blocks the initiation of the vomiting reflex by emetogenic stimuli in the vomiting center.[2-4] Although generally effective, alternative agents may be necessary when these primary agents fail or are contraindicated due to comorbid conditions. These agents may affect cardiac

conduction and are therefore contraindicated in the patients with a prolonged QT interval due to the increased risk of life-threatening arrhythmias including polymorphic ventricular tachycardia (torsades de pointes).[5-7] These concerns may be magnified in the ICU setting where various factors may increase the incidence of arrhythmias. We present two critically ill patients from the Pediatric ICU (PICU) who required pharmacologic therapy for nausea and vomiting. The novel anti-emetic agent, aprepitant (Emend®, Merck & Co, Kenilworth, NJ) was successfully used to manage their symptoms. The basic pharmacology of aprepitant is discussed, its clinical use reviewed, and dosing recommendations presented.

Case report

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, OH) for presentation of case series with 2 or fewer patients.

Patient #1: The patient was a 23-year-old, 47.7 kg male who was presented with metabolic acidosis (pH 7.10) with a normal lactic acid. Given his dependence on BiPAP and the severe metabolic acidosis, he was admitted to the PICU for evaluation and treatment. The patient had Duchenne muscular dystrophy and a lengthy active problem list including chronic respiratory failure with nighttime BiPAP dependence, neuromuscular scoliosis, restrictive lung disease, left ventricular dysfunction (ejection fraction 35-40%), nephrolithiasis, clostridium difficile infection, depression, anxiety, and long Q-T syndrome. He had recently been admitted to the hospital with a 3-4 day history of anorexia, poor oral intake, and right upper quadrant pain. Evaluation revealed only the presence of starvation ketosis and the acidosis corrected quickly with intravenous fluids and bicarbonate administration. Abdominal ultrasound revealed the presence of cholelithiasis. Following admission to the Pediatric ICU, the patient complained of significant nausea and had two episodes of emesis. Given concerns regarding the baseline prolonged QT interval, aprepitant (125 mg) was administered orally. Within 30 minutes, the patient had no further complaints of nausea and no episodes of emesis. The patient had been previously scheduled for a laparoscopic Nissen fundoplication, gastrostomy, and cholecystectomy due to gastroesophageal reflux, the need for enteral access, and the diagnosis of cholelithiasis. Given the prompt resolution of his acidosis and his stable clinical status, the decision was made to proceed with the scheduled surgical procedure. His past surgeries included a childhood hernia surgery and a previous Nissen fundoplication. There were no reports of previous problems with general anesthesia. Current medications included tizanidine (2 mg) every 8 hours as needed, a lidocaine 5% topical patch for musculoskeletal pain, hydrocodone-acetaminophen every 6 hours as needed, methadone (2.5 mg) twice daily, bisacodyl (5 mg) once daily as needed, amitriptyline (50 mg) every night, clonidine (0.1 mg) every night, carvedilol (6.25 mg) twice daily, aspirin (81 mg) once daily, and omeprazole (20 mg) once daily. The patient had no known allergies. On the morning of the procedure, the patient's physical examination and preoperative vital signs were unremarkable. The anesthetic plan, risks, benefits and alternatives were discussed with the parent and informed consent obtained. The patient was held *nil per os* for 8 hours except for medications. Aprepitant (125 mg) was administered orally 60-90 minutes prior to the scheduled procedure. He was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed. Premedication included midazolam (2 mg) administered intravenously. Anesthesia was induced with etomidate and neuromuscular blockade provided by rocuronium. Although bag-valve-mask ventilation was uneventful, endotracheal intubation was difficult requiring use of indirect videolaryngoscopy. Anesthesia was maintained with a total intravenous anesthesia technique using propofol and ketamine. Additional medications included intravenous methadone (5 mg), fentanyl (100 µg), lidocaine (40 mg), dexamethasone (10 mg), and midazolam (4 mg). The procedure lasted 5-6 hours. At the completion of the procedure, the patient was transported to the ICU with his trachea intubated and sedation provided by a propofol

infusion. Residual neuromuscular blockade was reversed with sugammadex, the propofol infusion discontinued, and his trachea extubated to his usual BiPAP settings. His postoperative course was unremarkable without complaints of pain, nausea, or vomiting. His preoperative medications were resumed the evening of surgery, administered through the gastrostomy tube. G-tube feedings were gradually started and advanced. The remainder of his postoperative course was unremarkable and he was discharged home on postoperative day 5.

Patient #2: An 18-year-old 110 kg adolescent with a past history of developmental delay and a seizure disorder was admitted to an outside hospital with status epilepticus. Treatment included airway control and endotracheal intubation for 8-10 days. After successful control of the seizures, her trachea was extubated, but she continued to have respiratory difficulties and direct laryngoscopy revealed severe tracheal stenosis. Tracheostomy was recommended and she was transferred to our institution for further care. After tracheostomy placement, mechanical ventilator support was weaned. When enteral feedings were restarted, the patient began complaining of abdominal pain. A work-up for abdominal pain revealed an elevated lipase suggestive of pancreatitis. Ultrasound of the gall bladder and abdominal were negative. When enteral feedings were restarted, the patient complained of nausea and repeated bouts of emesis, unrelieved with the administration of ondansetron (8 mg). Given the ongoing nausea and vomiting, aprepitant (125 mg) was administered orally by dissolving the contents of the capsule in a small amount of water. Subjectively, the patient stated that the nausea resolved and enteral feedings were reinitiated without emesis. There was a gradual decline of the serum lipase concentration over the next 72 hours. The patient received two additional doses of aprepitant to treat nausea and vomiting during this time. The remainder of her hospital course was unremarkable.

Discussion

Aprepitant is a selective high-affinity antagonist, blocking the binding of substance P at the neurokinin-1 receptor.[8] Since its initial approval by the United States Food & Drug Administration in 2003 for clinical use in adults, it has been reported to be effective in reducing nausea and vomiting induced by chemotherapy, radiotherapy, and surgical procedures or anesthesia.[9-11] The majority of the literature regarding aprepitant's efficacy highlight its effect on controlling chemotherapy-induced nausea and vomiting when it is combined with the already existing regimen of ondansetron and dexamethasone. Head-to-head trials comparing aprepitant to ondansetron to prevent PONV in adults have shown it to be comparable or more effective than ondansetron for PONV at 24 and 48 hours after surgery in adults.[11-14]

Outside of its use to control chemotherapy-induced nausea and vomiting, there are limited clinical data regarding the use of aprepitant in the pediatric population. A recent report in children involved a multicenter, randomized, partially-blinded study evaluating the pharmacokinetics, pharmacodynamics, safety, and tolerability of aprepitant to treat PONV in pediatric patients up to 17 years of age.[15] The study used a control group of subjects who received intravenous ondansetron and three study groups who received a single oral dose of aprepitant adjusted to be equivalent to adult doses of 10, 40, and 125 mg. The authors reported that aprepitant was generally well tolerated among pediatric patients, there was dose-dependent relationship in serum concentrations, and that the complete response and no vomiting rates were high (>80%) across treatment groups, which was similar to intravenous ondansetron. Complete response was defined as no emesis, retching, or dry heaves and no rescue therapy within 0-24 hours following surgery while no vomiting was defined as no emesis, retching, or dry heaves within 0-24 hours following surgery.

Cristofori et al. reported the potential efficacy of aprepitant in managing cyclic vomiting syndrome (CVS) in children that is resistant to conventional therapy.[16] The retrospective review included 41 children with an average age of 8 years who received aprepitant either prophylactically or for the acute treatment of CVS symptoms.

Eighty-one percent of those receiving aprepitant prophylactically and 76% receiving it acutely achieved a complete or partial clinical response. These patients also experienced a decrease in hospital admissions/year, CVS episodes/year, and an increased symptom-free interval duration and school attendance percentage.

We present anecdotal experience with the use of aprepitant in two Pediatric ICU patients. In our first patient, a history of a prolonged QT interval was a relative contraindication to the routine use of ondansetron. Although anecdotal, several reports demonstrate the potential for QT interval prolongation and an arrhythmogenic effect with ondansetron and other $5HT_3$ antagonists.[17-19] These effects have not been reported with aprepitant.[20] Therefore, in our first patient, we chose to use aprepitant given our concerns regarding the use of ondansetron in a patient with an established prolonged QT interval. In our second patient, we chose to use aprepitant because the administration of ondansetron to treat this patient's vomiting related to pancreatitis was ineffective.

Aprepitant can be administered orally (capsule or a liquid) or intravenously in the form of the prodrug, fosaprepitant. Given cost constraints, oral administration is the preferred route whenever feasible. Acquisition costs (data from 2019) are approximately $110, $204, and $319 for the 40, 80, and 120 mg capsules respectively and $319 the liquid (125 mg in a single dose bottle). Dosing for the pediatric patient is extrapolated mainly from the adult literature with oral dosing ranging from 40 to 125 mg or approximately 1 mg/kg.

To date, the adverse effect profile of aprepitant has been limited. Aprepitant demonstrates a clinically significant interaction with several medications that are CYP3A4 or CYP2C9 substrates, which is consistent with the pharmacology of aprepitant and fosaprepitant as moderate and weak inhibitors of CYP3A4, respectively.[21] However, other CYP3A4 or CYP2C9 substrates do not have clinically significant interactions with aprepitant or fosaprepitant as alternative elimination pathways may exist for those medications that compensate for the inhibition of CYP3A4 by aprepitant and fosaprepitant. The other issue regarding aprepitant is its potential to decrease the efficacy of oral contraceptive agents.[22,23] Patients should use a non-hormonal form of birth control during treatment with aprepitant and for 1-2 months after the last dose.

In summary, our anecdotal experience demonstrates the potential efficacy of aprepitant in the treatment of nausea and vomiting of various etiologies in the Pediatric ICU patient. We found it effective when there are contraindications to the administration of ondansetron or when it was ineffective. To date there are limited data regarding its use in pediatric-aged patients; however, the adverse effect profile appears limited. Dosing has been largely extrapolated from the adult population and given cost constraints, oral administration is suggested when feasible.

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