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Original Article

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Preoperative Administration of Aprepitant to Prevent Postoperative Nausea and Vomiting in Children

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Abstract

Background: Aprepitant (Emend®), a neurokinin-receptor antagonist, has seen increased use in the treatment of nausea and vomiting in various clinical scenarios. To date, there are limited data regarding its use in the pediatric population. We retrospectively reviewed our experience with aprepitant after its addition to the operating room formulary for prevention of postoperative nausea and vomiting (PONV).

Methods: The anesthetic records of patients who received aprepitant were retrospectively reviewed. Demographic, surgical, medication, and efficacy data were retrieved.

Results: The study cohort included 144 patients ranging in age from 7 to 17 years and in weight from 24.7 to 208.9 kg. The most common surgical procedures included gastrointestinal surgery, orthopedic surgery, and otolaryngologic procedures. Reasons for the administration of aprepitant included PONV prophylaxis due to risk factors such as type of surgery, duration of surgery, previous history of significant PONV, female gender, and family history of PONV. The majority of the patients (98.6%) received aprepitant in capsule form in a dose of 40 mg (97.9%). Seventeen patients (11.8%) had PONV or received antiemetic agents postoperatively. There were no unplanned admissions related to PONV. No adverse effects related to aprepitant were noted.

Conclusions: Aprepitant was effectively introduced to the preoperative regimen as an additional agent for the prevention of PONV. The overall tolerability and efficacy of aprepitant was similar to previous studies, even in a patient population at high risk for PONV.

Keywords: Aprepitant; Postoperative nausea and vomiting; Pediatric anesthesia

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Introduction

Prior studies in pediatric patients have noted that postoperative nausea and vomiting (PONV) accounts for up to 77% of adverse events during the postoperative period and in the postanesthesia care unit (PACU) [1]. Besides causing patient discomfort, PONV can also result in a prolongation of the postoperative course, extended hospital stays for both inpatient and outpatient surgery, unanticipated hospital admission, and readmission following discharge home [2]. PONV may occur in up to 30% of pediatric patients if no prophylaxis is administered [3]. However, individual patient or procedure-related risk factors can increase this incidence up to 80% [4]. Identified risk factors include the intraoperative use of nitrous oxide, volatile-based anesthesia versus total intravenous anesthesia (TIVA) with propofol, opioid administration, female gender, a history of motion sickness, and a prior history of PONV [5]. Current techniques for prophylaxis of PONV include one or two medication regimens that include the corticosteroid, dexamethasone, and/or a 5-hydroxytryptamine$_3$ ($5HT_3$) receptor antagonist such as ondansetron [5-8]. While these medications are generally effective, they are not appropriate for all patients and all clinical scenarios [9-12]. Dexamethasone may affect adrenocortical function and alter glucose homeostasis, especially in patients with comorbid conditions such as diabetes mellitus [9-11]. Ondansetron and other 5-HT_3 antagonists have been reported to alter the QT interval and may be contraindicated in patients with long QT syndrome or when administered with other medications that affect cardiac repolarization [12, 13].

Aprepitant is a novel antiemetic agent that has been used primarily in the prevention of vomiting related to the administration of chemotherapy [14, 15]. It has also been used with increasing frequency to prevent PONV in the adult and pediatric population [15,-19]. In a prior study at our tertiary care children's hospital, we described our initial 12-month experience with the administration of aprepitant in the perioperative scenario following its introduction to our perioperative hospital formulary in a cohort of 31 pediatric patients [20]. The current study expands on that experience, outlining the preoperative use of aprepitant in a larger cohort of children, adolescents, and young adults in our tertiary care children's hospital. The intent was to provide demographic and patient data as well as information regarding the logistics of medication administration during the preoperative visit for the planning of a prospective trial in children.

Table 1. Demographic Data of the Study Cohort of 144 Patients

Variables	N (%) or mean ± SD
Age (years)	13.7 ± 2.5
≤ 3	0
4 - 7	4 (2.8%)
8 - 12	41 (28.4%)
13 - 17	99 (68.8%)
Weight (kg)	70.5 ± 36.7
Gender	
Male	67 (47%)
Female	77 (53%)
Visit type	
Inpatient surgery	87 (60.4%)
Outpatient surgery	57 (39.6%)

N: number; SD: standard deviation.

Table 2. Type of Surgical Procedure

Variable	Number
Gastrointestinal surgery	38
Upper endoscopy	1
Neurosurgery	3
Ophthalmological	6
Orthopedic surgery	27
Otolaryngologic	21
Radiologic imaging	9
Renal or urology	8
General surgery and others	31

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, OH). As a retrospective study, it was deemed that the research was associated with minimal risk and therefore informed consent was not required. Protection of patient data confidentiality and the conduct of this study was in accordance with the Declaration of Helsinki. In February 2018, aprepitant was added to the electronic medical record and perioperative formulary. The option for administration was added to the anesthesia preoperative order set for anesthesia providers to choose for either prophylaxis against or the treatment of PONV. Prior to this, education was provided, and instructions given to the anesthesia faculty and staff regarding its dosing, administration, and indications in the perioperative setting. To facilitate administration and limit delays during the preoperative process, the medication (capsules and liquid) was made available for use in the Pyxis™ MedStation™ in the preoperative unit, with an order set added to the electronic medical record with information regarding dosing. With its introduction, there were no limitations regarding the clinical scenarios in which aprepitant could be administered. As this was a retrospective study, the indication for aprepitant was not controlled, but rather left to the discretion of the anesthesia providers. Since its introduction to the operating room (OR) formulary, pharmacy services have been tracking its use every month to determine indications, adverse effects, and overall use.

The list of patients who received Emend® as prophylaxis against PONV was generated after querying the hospital pharmacy database. Patients ≥ 18 years of age and those who received aprepitant in other clinical scenarios such as nausea and vomiting prophylaxis during chemotherapy were excluded. The anesthetic records of these patients were then retrospectively reviewed for data retrieval. Demographic and patient history data included age, weight, gender, history of PONV with previous anesthetic, associated conditions known to increase the risk of PONV, and the presence of contraindications to the use of dexamethasone or ondansetron. Data regarding the type of procedure being performed, visit type (inpatient or outpatient surgery), dose and product type (capsule or liquid) of aprepitant, type of maintenance anesthesia, length of stay in the hospital postoperatively, and duration of stay in the PACU were also retrieved. Other variables included the intraoperative administration of opioids, dexmedetomidine, and use of other antiemetic agents. The postoperative records were accessed to review the occurrence of PONV and the need for the administration of postoperative antiemetic agents. For unanticipated admissions, the cause for the admission was determined. Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as the number and percentages. Analyses were performed using SAS 9.4 (Cary, NC).

Results

Our retrospective review of 24 months identified 144 patients who received aprepitant during the perioperative period (31 patients were reported in our previous study). The demographics of the study cohort are listed in Table 1. The 144 patients had a mean age of 13.7 years (range of 7 to 17 years) and a mean weight of 70.5 kg (range of 24.7 to 208.9 kg). There were 67 male (47%) and 77 (53%) female patients. The hospital visit type was listed as an inpatient surgery for 87 patients (60.4%) and outpatient surgery for 57 patients (39.6%).

The most common procedures were gastrointestinal (surgery or endoscopy), orthopedic, and otolaryngologic (Table 2). Sixty-two patients (43.1%) had a previous history of PONV while 82 (56.9%) patients did not. Reasons for the administration of aprepitant included PONV prophylaxis due to risk factors such as type of surgery, duration of surgery, previous history of significant PONV, female gender, and family history of PONV. In addition, given previous success with aprepitant, it has been added to established perioperative protocols at our institution for specific surgical procedures (posterior spinal fusion and bariatric surgery).

Clinical information regarding the use of aprepitant and other intraoperative data are outlined in Table 3. The majority of the patients (142 patients or 98.6%) received aprepitant in

Table 3. Perioperative Clinical Data of the Study Cohort

Variable	N (%) or mean (SD)
History of PONV following previous surgical procedures	
Yes	62 (43.1%)
No	82 (56.9%)
Aprepitant product	
Capsule	142 (98.6%)
Liquid	2 (1.4%)
Dose of aprepitant administered	
40, 80 or 125 mg	141 (97.9%), 2 (1.4%), 1 (0.7%)
Average dose of aprepitant (mg/kg)	0.7 (0.3)
Contraindications to use of ondansetron or dexamethasone	
None	142 (98.6%)
Prolonged QT interval, first-degree heart block	1 (0.7%)
Yes (ondansetron allergy)	1 (0.7%)
Intraoperative dexmedetomidine (yes/no)	83 (57.6%)/61 (42.4%)
Number of additional antiemetic agents administered intraoperatively	
0, 1, 2, 3	2, 24, 98, 20
Other antiemetic agents administered intraoperatively	
Diphenhydramine	1
Dexamethasone	130
Metoclopramide	15
Ondansetron	123
Promethazine	3
Scopolamine patch	8
Antiemetic agents required postoperatively (yes/no)	17 (11.8%)/127 (88.2%)
Antiemetic agents administered postoperatively	
Dexamethasone	2
Ondansetron	12
Palonosetron	2
Promethazine	2
Other	9
Intraoperative opioids (yes/no)	115 (79.9%)/29 (20.1%)
Intraoperative opioids	
Fentanyl	83
Hydromorphone	69
Methadone	6
Morphine	7
Remifentanil	6
Sufentanil	2
PONV in PACU/postoperatively (yes/no)	17 (11.8%)/127 (88.2%)
Duration of stay in PACU (min)	116.5 (99.9)
Length of stay postoperatively (days)	1.5 (3.9)

Data presented as n (%) or mean (SD). N: number; SD: standard deviation; PONV: postoperative nausea and vomiting; PACU: postanesthesia care unit.

capsule form. As is our routine practice, the option was given for the patients to swallow the capsule with a small sip or water or for the capsule to be opened and diluted in 5 - 10 mL of water. One hundred forty-one (97.9%) patients received 40 mg, two patients (1.4%) received 80 mg, and one (0.7%) received 125 mg. The average dose of aprepitant was 0.7 ± 0.3 mg/kg.

Following intravenous induction with propofol or inhalation induction with sevoflurane and nitrous oxide, maintenance anesthesia was provided by an inhalational anesthetic agent in air and oxygen. Nitrous oxide was used only to facilitate induction for less than 5 min and not for maintenance anesthesia. One hundred fifteen patients (79.9%) received opioids intraoperatively. Fentanyl (n = 83), hydromorphone (n = 69), and morphine (n = 7) were used most commonly. Eighty-three patients (57.6%) received dexmedetomidine intraoperatively. During the procedure, almost all of the patients (142 of 144 patients or 98.6%) received additional antiemetic agents, while two patients received only aprepitant. Twenty-four patients received one other antiemetic agent, 98 patients received two other antiemetic agents, and 20 patients received three other antiemetics intraoperatively. Dexamethasone (n = 130), ondansetron (n = 123), and metoclopramide (n = 15) were the most commonly administered supplemental antiemetic agents intraoperatively.

Seventeen patients (11.8%) had PONV or received antiemetic agents postoperatively compared to 127 patients (88.2%) who did not. The mean duration of stay in the PACU was 116.5 min. The total incidence of PONV during the first 24 postoperative hours was 11.8% (17 of 144 patients). PONV was not listed as a cause of unplanned admission for any of the patients. There were no other adverse effects that could be attributed to aprepitant.

Discussion

The current retrospective study provides preliminary information regarding our perioperative practices for the use of aprepitant following its addition to our perioperative practice. Our intermittent reviews of the use of aprepitant were primarily intended, due to cost constraints, to ensure appropriate use of this novel medication. As part of an ongoing quality assurance project within the Department of Anesthesiology & Pain Medicine, educational information regarding aprepitant was provided to all anesthesia providers. This included pediatric anesthesiology attendings, certified registered nurse anesthetists (CRNAs), and pediatric anesthesiology fellows. These education initiatives included email education as well as presentations at our monthly departmental outcomes conferences. During these encounters, perioperative indications for aprepitant were discussed, dosing reviewed, adverse effects and contraindications presented, and cost information provided.

In our current retrospective review of our clinical practice, several findings were noted. The capsule formulation was used in most patients with the majority of patients receiving a dose of 40 mg. Although weight-based dosing is generally used in the practice of pediatric anesthesiology, as the majority of patients in the current cohort were ≥ 13 years of age, standard adult dosing of 40 mg was chosen. Intraoperatively, all patients received volatile-based anesthesia with nearly all receiving opioids, and more than half receiving dexmedetomidine intraoperatively. Although TIVA with a propofol-based technique may be chosen most commonly in adult practice in patients at high risk for PONV based on patient or surgery-related concerns, this is not considered routine in our OR. As such, the potential for PONV may have been higher given the choice to use a volatile-based technique rather than TIVA. Given its cost and our current perioperative practices, aprepitant was generally used only for high-risk patients and high-risk surgical procedures with a reported higher incidence of PONV. This also explains the reason that aprepitant was administered with other antiemetic agents. All except two patients received at least one additional antiemetic, while 83% of patients received at least two additional antiemetics. Dexamethasone and ondansetron were administered to 130 and 123 patients in this cohort, respectively.

Even in this high-risk population, PONV determined by documentation in the medical record of vomiting, complaints of nausea, or the need to administer an additional antiemetic agent postoperatively, occurred in fewer than 12% of the patients. Furthermore, PONV was not listed as the primary indication for any unplanned admissions. Our study cohort had an incidence of PONV of 11.8%, which was at the lower end of the reported range for children post-surgery. This result was consistent with results from studies of aprepitant preoperative use in adults that ranged from 9.7% to 22% [17, 18], suggesting aprepitant is as effective an antiemetic in children as it is in adults. In addition, our study found no serious adverse effects of aprepitant in the 144 children who received it.

As the majority of the patients were ≥ 13 years of age, dosing was generally extrapolated from adult data, with 141 of 144 patients receiving the 40 mg capsule. Given the overall weight of the study population, this arbitrarily resulted in a dose of approximately 1 mg/kg when considering the entire cohort. Aprepitant was administered orally following the preoperative evaluation of the patient in the preoperative surgical unit. Despite standard *nil per os* (NPO) practices, oral medications such as routine morning medications, premedication (oral midazolam), oral adjuncts for analgesia (acetaminophen), and prophylaxis for PONV may be preoperatively administered. This practice is in accordance with NPO guidelines for the OR. The need to administer aprepitant orally did not appear to limit its use by the anesthesia providers.

This study was limited by its retrospective design and the absence of a control group to clearly define the efficacy of aprepitant. As such, descriptive information is available with limited inferential statistics regarding efficacy when compared to other antiemetic agents. Given the variation in practice, patient demographic, type of anesthetic agents administered, and the administration of various adjunctive agents for prevention of PONV, we did not believe that even a case-matched controlled study would be feasible. Furthermore, the inability to obtain objective data on nausea in a validated manner must be considered. The primary efficacy end-points included documentation of PONV in the electronic medical record (EMR) and the need for the administration of antiemetic agents in the PACU or during the postoperative period. It is possible that episodes of PONV may have been missed due to charting deficiencies.

As this was a high-risk group for PONV, one or more additional antiemetic agents were administered to 142 of 144 patients. This precluded our ability to evaluate aprepitant as the sole agent for prevention of PONV. We believe that the only way to effectively answer these questions will be with a prospective randomized trial, preferably in a relatively homogenous surgical population.

In conclusion, this study in a large pediatric cohort provides clinical experience with the use of aprepitant for PONV in the pediatric population. It also outlines our process of introducing this novel agent to our perioperative arena. We noted that the overall tolerability and efficacy of aprepitant was similar to previous studies. It should be considered when choosing a preoperative regimen to prevent PONV in high-risk patients. Future prospective studies are needed to determine appropriate dosing regimens, based on a mg/kg basis, in children. Trials also appear warranted to demonstrate its efficacy when used as the sole agent for PONV as opposed to its addition to other antiemetic medications such as dexamethasone and ondansetron. It may have a role in surgical procedures at high risk of PONV or when there are clinical contraindications to the use of more commonly chosen medications.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

As a retrospective study, it was deemed that the research was associated with minimal risk and therefore informed consent was not required.

Author Contributions

S. Kukura, NS, SZS performed the chart reviews and prepared drafts and final version of the manuscript. S. Kim performed the data analysis and reviewed drafts and final version of the manuscript. JDT provided project oversight and administration as well as editing drafts and final version of the manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

References

1. Murat I, Constant I, Maud'huy H. Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. Paediatr Anaesth. 2004;14(2):158-166.
2. Edler AA, Mariano ER, Golianu B, Kuan C, Pentcheva K. An analysis of factors influencing postanesthesia recovery after pediatric ambulatory tonsillectomy and adenoidectomy. Anesth Analg. 2007;104(4):784-789.
3. Franck M, Radtke FM, Apfel CC, Kuhly R, Baumeyer A, Brandt C, Wernecke KD, et al. Documentation of postoperative nausea and vomiting in routine clinical practice. J Int Med Res. 2010;38(3):1034-1041.
4. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91(3):693-700.
5. Tateosian VS, Champagne K, Gan TJ. What is new in the battle against postoperative nausea and vomiting? Best Pract Res Clin Anaesthesiol. 2018;32(2):137-148.
6. Cao X, White PF, Ma H. An update on the management of postoperative nausea and vomiting. J Anesth. 2017;31(4):617-626.
7. Hohne C. Postoperative nausea and vomiting in pediatric anesthesia. Curr Opin Anaesthesiol. 2014;27(3):303-308.
8. Obrink E, Jildenstal P, Oddby E, Jakobsson JG. Postoperative nausea and vomiting: update on predicting the probability and ways to minimize its occurrence, with focus on ambulatory surgery. Int J Surg. 2015;15:100-106.
9. Purushothaman AM, Pujari VS, Kadirehally NB, Bevinaguddaiah Y, Reddy PR. A prospective randomized study on the impact of low-dose dexamethasone on perioperative blood glucose concentrations in diabetics and non-diabetics. Saudi J Anaesth. 2018;12(2):198-203.
10. Herbst RA, Telford OT, Hunting J, Bullock WM, Manning E, Hong BD, D'Alessio DA, et al. The effects of perioperative dexamethasone on glycemic control and postoperative outcomes. Endocr Pract. 2020;26(2):218-225.
11. Bacigalupo Landa A, Viswanath O, D'Mello J. Acute adrenal insufficiency after an antiemetic dose of dexamethasone: a case report. A A Pract. 2019;12(11):424-425.
12. Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology. 2005;102(6):1094-1100.
13. Freedman SB, Uleryk E, Rumantir M, Finkelstein Y. Ondansetron and the risk of cardiac arrhythmias: a systematic review and postmarketing analysis. Ann Emerg Med. 2014;64(1):19-25.e16.
14. He M, Xu R, Liu M, Zhang Y, Yi F, Wei Y, Liu Q, et al. Use of dexamethasone and a 5-HT3 receptor antagonist with or without aprepitant to prevent chemotherapy-induced nausea and vomiting among patients with lung cancer who are treated with platinum-based chemotherapy: a systematic review and meta-analysis of randomized controlled trials. Ann Palliat Med. 2021;10(4):4308-4319.

15. Bodge M, Shillingburg A, Paul S, Biondo L. Safety and efficacy of aprepitant for chemotherapy-induced nausea and vomiting in pediatric patients: a prospective, observational study. Pediatr Blood Cancer. 2014;61(6):1111-1113.
16. Habib AS, Keifer JC, Borel CO, White WD, Gan TJ. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. Anesth Analg. 2011;112(4):813-818.
17. Okafor D, Kaye AD, Kaye RJ, Urman RD. The role of neurokinin-1 (substance P) antagonists in the prevention of postoperative nausea and vomiting. J Anaesthesiol Clin Pharmacol. 2017;33(4):441-445.
18. Singh PM, Borle A, Rewari V, Makkar JK, Trikha A, Sinha AC, Goudra B. Aprepitant for postoperative nausea and vomiting: a systematic review and meta-analysis. Postgrad Med J. 2016;92(1084):87-98.
19. Diemunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, Irwin MG, Pueyo J, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth. 2007;99(2):202-211.
20. Kanaparthi A, Kukura S, Slenkovich N, AlGhamdi F, Shafy SZ, Hakim M, Tobias JD. Perioperative Administration of Emend((R)) (Aprepitant) at a Tertiary Care Children's Hospital: a 12-month survey. Clin Pharmacol. 2019;11:155-160.