Impact of a reduced palonosetron maximum dose on the incidence of chemotherapy-induced nausea and vomiting in pediatric patients

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Abstract

Background Palonosetron is a serotonin-3 (5-HT3) receptor antagonist indicated in the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric and adult patients. Traditional dosing for palonosetron in the pediatric population has been 20 mcg/kg with a maximum dose of 1500 mcg. This study aimed to evaluate the impact of an institutional dose cap of 750 mcg on pediatric CINV. Procedure This is a retrospective chart review of admitted patients given palonosetron intended for prevention of CINV at a pediatric medical center between July 1, 2018 and June 30, 2020. Patients 1 month up to 17 years of age who received at least one dose of palonosetron prior to chemotherapy (not preceding stem cell transplant) were included. Information regarding chemotherapy, antiemetic premedication, emesis, and breakthrough antiemetic agents were recorded to quantify the instances of CINV. Results Seven hundred and seventy-one patient encounters met inclusion criteria (n=485 traditional dose, n=286 dose capped). There was no statistical difference in the instances of emesis (p=0.98) or breakthrough agents administered (p=0.65) between the two groups. Dose capping patients at 750 mcg reduced cost by approximately 34.9% compared to traditional dosing. Conclusions The use of a dose cap of palonosetron at 750 mcg maintains efficacy for prevention of CINV while reducing cost in pediatric patients receiving chemotherapy.

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Abbreviations:

5-HT3	Serotonin-3
AWP	Average wholesale price
CINV	Chemotherapy-induced nausea and vomiting

5-HT3	Serotonin-3
EMA	European Medicines Agency
EMR	Electronic medical record
FDA	Food and Drug Administration
HEC	Highly emetogenic chemotherapy
HLM	Hierarchical linear model
IRB	Institutional review board
SCT	Stem cell transplant

Background

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Procedure

This is a retrospective chart review of admitted patients given palonosetron intended for prevention of CINV at a pediatric medical center between July 1, 2018 and June 30, 2020. Patients 1 month up to 17 years of age who received at least one dose of palonosetron prior to chemotherapy (not preceding stem cell transplant) were included. Information regarding chemotherapy, antiemetic premedication, emesis, and breakthrough antiemetic agents were recorded to quantify the instances of CINV.

Results

Seven hundred and seventy-one patient encounters met inclusion criteria (n=485 traditional dose, n=286 dose capped). There was no statistical difference in the instances of emesis (p =0.98) or breakthrough agents administered (p =0.65) between the two groups. Dose capping patients at 750 mcg reduced cost by approximately 34.9% compared to traditional dosing.

Conclusions

The use of a dose cap of palonosetron at 750 mcg maintains efficacy for prevention of CINV while reducing cost in pediatric patients receiving chemotherapy.

INTRODUCTIONPalonosetron is a second generation serotonin-3 (5-HT3) antagonist, a class of medication recommended for the prevention of chemotherapy-induced nausea and vomiting (CINV) in several guidelines.[1-4] In pediatric patients age 1 month to less than 17 years, palonosetron is indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC). The manufacturer prescribing information recommends a dose of 20 mcg/kg in these patients, with a maximum dose of 1500 mcg. This maximum dose is six times the recommended dose for adult patients, which is a flat dose of 250 mcg.[5]The dosing of palonosetron in children is based on a noninferiority trial of palonosetron versus ondansetron. The study had three arms, palonosetron dosed at 10 mcg/kg up to a max dose of 750 mcg, palonosetron dosed at 20 mcg/kg up to a max dose of 1500 mcg, and three doses of ondansetron dosed at 0.15 mg/kg up to a max total dose of 32 mg. It was observed that 20 mcg/kg of palonosetron was not inferior to ondansetron, whereas the 10 mcg/kg dose was.[6] Palonosetron dosing at 20 mcg/kg with a maximum of 1500 mcg is currently licensed by the Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA).[5,7]There are few studies on alternate dosing of palonosetron in pediatric patients. A small randomized controlled trial performed in Mexico randomized patients ages 1.7-15 years to receive palonosetron dosed at 250 mcg or ondansetron 8 mg/m^2 every 8 hours. They found significant reduction in emesis in the palonosetron group compared to ondansetron at this dose.[8] Another prospective, randomized crossover study was performed in India where patients aged 2-18 years were randomized to receive either palonosetron 5 mcg/kg with no maximum dose followed by ondansetron 5 mg/m^2

every 8 hours for the next chemotherapy cycle, or ondansetron followed by palonosetron. No statistically significant difference was found in complete response to either antiemetic regimen.[9] There are currently no studies available for using the 20 mcg/kg palonosetron dosing with a reduced maximum dose. At Cook Children's Medical Center, our practice is to dose palonosetron at 20 mcg/kg with a capped dose of 750 mcg. In this retrospective chart review, we used instances of emesis and administrations of antiemetic breakthrough medications to quantify the occurrences of CINV in our pediatric patients receiving chemotherapy. The primary objective was to evaluate the impact of our institutional palonosetron dose cap of 750 mcg compared to traditional dosing. The secondary objective was to determine the economic impact this dose cap had compared to traditional dosing.

METHODSThis was a retrospective chart review of patients administered palonosetron at a pediatric medical center between July 1, 2018 and June 30, 2020. The study protocol was approved by the Cook Children's Medical Center Institutional Review Board (IRB). The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.1 Participants

Patients 1 month up to 17 years of age who received at least one dose of palonosetron prior to chemotherapy during an inpatient encounter were included. These were identified via the electronic medical record (EMR). Patient encounters were excluded if palonosetron was administered for indications other than prevention of CINV (i.e. post-operative nausea and vomiting), if the chemotherapy proceeded stem cell transplant (SCT), if they received multiple courses of chemotherapy in one admission, or if they received a palonosetron dose that did not qualify as a traditional dose or dose capped.

2.2 Procedure

Patient encounters were reviewed retrospectively and data collected included age, dosing weight, sex, emetogenic risk of chemotherapy regimen, antiemetic premedication in alignment with institutional acute CINV guidelines, palonosetron dose, number of palonosetron doses administered, antiemetic breakthrough agents administered, and breakthrough emesis. The institutional guidelines for emetogenic risk and acute CINV premedications can be found in the Supplemental Table S1 and Supplemental Figure S1. The encounter was considered to align with the guideline if the patient received the initial recommendation of either the correct or an increased emetogenic risk category. Further chart review was not done to determine if the patient could not receive the entirety of the initial recommendation, rather these were considered not to align with the guideline. "Traditional dose" was considered 20 mcg/kg and "dose capped" was 750 mcg. If a patient weighed around 37.5 kg and was receiving palonosetron 750 mcg, the patient would be included within the traditional dose group as this qualified as 20 mcg/kg dosing. Antiemetic breakthrough agents and emesis were recorded from the first dose of palonosetron through 48 hours after the last dose of palonosetron was administered or until discharge. For the dose capped group, the traditional dose was calculated based on patient dosing weight and the number of doses administered was also collected. These were used to calculate the estimated costs of both traditional and capped dosing, using the average wholesale price (AWP) of our institution's palonosetron.

Sample Size

An apriori power analysis was conducted using a two tailed significance value and found that we would need 264 encounters to detect a small effect with 80% power for a linear regression model with six predictors in the model. However, given that we used multilevel modeling and that we were specifically looking for null effects, we multiplied this minimum sample by two in order to maximize our power. After this adjustment, we sought to have a minimum sample size of 528 encounters.

2.4 Statistical Analysis

Most individual patients in the current dataset had multiple recorded patient encounters that qualified for inclusion. As a result, we used hierarchical linear modeling (HLM) to account for the linked dataset in which patient encounters were nested within patients. All variables were entered simultaneously into the model.

All intercepts and slopes were allowed to vary randomly (although fixing the slopes and intercepts did not change the overall results). Finally, covariances were estimated using unstructured estimation. Using HLM, we entered dosing condition (dummy coded, 0 = traditional dose; 1 = dose capped), weight (grand mean centered; Level 2), age (grand mean centered; Level 2), premedication alignment, emetogenic risk, and sex (dummy coded, 0 = female; 1 = male) simultaneously to predict breakthrough agents (dichotomous, 0 = no breakthrough agents, 1 = breakthrough agents used), number of different breakthrough agents, total number of all breakthrough agents, emesis (dichotomous, 0 = no emesis; 1 = emesis), and total number of emesis. Inferential statistics were used for these analyses, and ap -value of less than 0.05 was considered significant. All analysis were done using IBM SPSS Statistics 24.

RESULTS

Seven hundred and seventy-one encounters were included in the final analysis, which were divided into groups of either traditional dose (n=485) or dose capped (n=286). Refer to Figure 1 for the flow diagram of patient encounter inclusion. Patients ranged in age from 0 to 16 years old. A total of 552 (71.6%) patient encounters received a highly emetogenic chemotherapy regimen, and 424 (55.0%) patient encounters had antiemetic premedications that aligned with a correct or increased emetogenic risk (Supplemental Table S1 and Supplemental Figure S1). Between groups, there were no significant differences for sex, high emetogenic risk, or premedication alignment. There was a significant difference in age and weight between the groups. These patient characteristics can be found in Table 1. There was no statistically significant difference in the dichotomous emesis (p=0.98) or dichotomous breakthrough agents administered (p=0.65) between dose groups. Similarly, when looking at those patients with emesis and antiemetic breakthrough agents administered, there was no statistically significant difference in the number of emesis (p=0.32), the number of different agents administered (p=0.42), or the number of doses administered (p=0.75) between the groups. The coefficient table for this analysis can be found in Table 2. When reviewing the secondary outcome, we found that there were 531 palonosetron doses given to the "dose capped" group. The estimated cost of these capped doses was $95,580. If the same doses were instead administered using traditional dosing, the estimated cost increased to $146,760. Dose capping reduced our cost for this group by $51,180 or 34.9%.

DISCUSSION

This retrospective chart review evaluated the impact of our institutional dose cap on pediatric CINV. There are currently no studies available for using the 20 mcg/kg palonosetron dosing with a reduced maximum dose. The present study found no difference in emesis or antiemetic breakthrough agents required when capping the dose at 750 mcg in pediatric patients while controlling for weight, sex, age, emetogenic risk, and premedication alignment. When evaluating the economic impact of this dose cap, there was a relatively significant cost savings compared to the same amount of palonosetron dosed traditionally. Our institution's current dosing recommendation was chosen as somewhat of an arbitrary dose between the manufacturer's recommended maximum dose of 1500 mcg among pediatric patients and the adult dose of 250 mcg. Per provider discretion, palonosetron may be started at 20 mcg/kg even if it is above the institutional dose cap, or may be switched to a higher dose later within the encounter. For this review, there were only 34 (4.4%) patient encounters in which we used a dose higher than the dose cap and there were no encounters in which the dose was changed to a higher dose later in the encounter. We believe that this was because a higher dose was not thought to be necessary in these patients by providers, which further demonstrates the efficacy of our reduced maximum dose. It is possible that this dose could be reduced further and still show similar efficacy, but more research would need to be done in this area. We considered the inclusion of encounters that received multiple courses of chemotherapy in a single encounter, but ultimately decided to exclude these patients as they were "different" at baseline than the patient encounters that were admitted for just one course of chemotherapy. It was determined that removing these patients would constitute a more relevant data sample to draw our conclusions. With these encounters excluded, the study was still adequately powered at 771 patient encounters to evaluate for difference in clinical outcomes. A few limitations should be noted. The number used in our analysis refers to the number of patient encounters, not individual patients. The number of individual patients included in our analysis is 182 patients, which is still relatively large

for this patient population. The traditional dose group had more encounters and individual patients than our dose capped group, which was an expected outcome within the pediatric patient population. Another detail to note is that our traditional dose group was both younger and had a lower dosing weight than their dose capped counterparts, which was another expected outcome due to the nature of dose capping in pediatrics, and could not be controlled for retrospectively. In agreement with previous studies, we did find that age was not significantly associated with a higher risk of chemotherapy-induced nausea in the acute phase for pediatric patients.[10] For the covariate of premedication alignment, we found a significant difference in the both dichotomous emesis (p=0.01) and number of emesis (p=<0.0001), and non-alignment was associated with more emesis. This finding may help to validate our institutional guideline for acute CINV premedications. Furthermore, this was retrospective in nature, and the data is reliable and valid to the extent that the health care providers accurately and consistently recorded medical information in the EMR. Another potential limitation is that our institution does not currently use a tool to measure nausea, so surrogate markers of antiemetic breakthrough medications and episodes of emesis were used. This means that no analysis of nausea without emesis or an antiemetic breakthrough medication could be made. Overall, this retrospective chart review contributes to the evidence that a lower maximum palonosetron dose in pediatric patients may maintain efficacy for acute CINV. At a reduced palonosetron maximum dose of 750 mcg, we found no difference in emesis or antiemetic breakthrough agents administered. Using the reduced maximum dose can also reduce cost and drug exposure to pediatric patients receiving chemotherapy.

1. **CONFLICT OF INTEREST STATEMENT**There are no conflicts of interest disclosures from any of the authors.
2. **ACKNOWLEDGEMENTS**The authors would like to thank Mackenzie Creamer for her contribution to the institutional acute CINV guideline included in the supplemental material.
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4. **LEGENDS**FIGURE 1 Flow diagram of study patient encounter inclusion

SUPPLEMENTAL TABLE S1 Emetogenic risk of oncologic agents per Cook Children's Medical Center institutional guidelines SUPPLEMENTAL FIGURE S1 Acute CINV premedications per Cook Children's Medical Center institutional guidelines

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`PBC Table 1.docx` available at https://authorea.com/users/420290/articles/526647-impact-of-a-reduced-palonosetron-maximum-dose-on-the-incidence-of-chemotherapy-induced-nausea-and-vomiting-in-pediatric-patients

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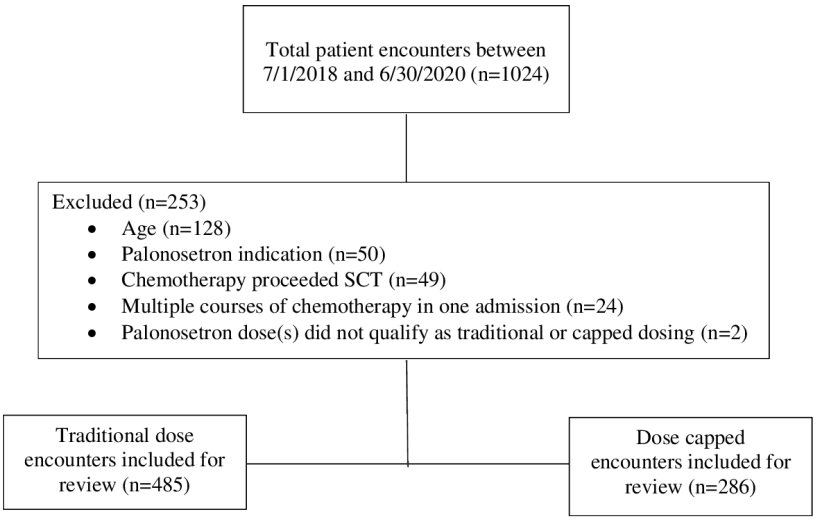

SCT = stem cell transplant