Olanzapine Substitution for Dexamethasone for Prevention of Chemotherapy Induced Nausea and Vomiting Prophylaxis in Children

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Abstract

This study compared the efficacy of three-drug antiemetic regimens (olanzapine, fosaprepitant, and 5-HT3 receptor antagonist versus dexamethasone, fosaprepitant, and 5-HT3 receptor antagonist) on chemotherapy-induced nausea and vomiting (CINV) in children. Complete response (CR) was defined as no emesis or use of rescue antiemetics. In the acute phase, 52% of patients in the olanzapine group achieved a CR compared to 63% in the dexamethasone group (p=0.354). In the delayed phase, CR was 80% versus 73% (p= 0.702), respectively. Olanzapine is an acceptable agent to use in place of dexamethasone when a patient is not a candidate for corticosteroid as CINV prophylaxis.

Introduction

The Children's Oncology Group (COG) has endorsed guidelines on chemotherapy-induced nausea and vomiting (CINV) in pediatric cancer patients.[1-3] The current recommendations for the prevention of CINV in pediatric patients receiving highly emetogenic chemotherapy (HEC) include a three-drug CINV prophylaxis regimen consisting of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, and a corticosteroid.[1-3] A recently published randomized controlled trial demonstrated improved CINV control with the addition of olanzapine to this existing backbone to create a four-drug CINV prophylaxis regimen. In this study, a higher proportion of patients who received olanzapine as part of a four-drug regimen achieved a complete response (no emesis or use of rescue medication) in the acute phase (78% v 59%, p=0.001) than the control group.[4]

While evidence exists to support the addition of olanzapine to three-drug CINV prophylaxis, there are not available data to support the substitution of olanzapine in patients who are unable to receive a corticosteroid. Circumstances where clinicians may want to avoid corticosteroids as an antiemetic include patients with brain tumors and acute myeloid leukemia.[5] The COG supportive care endorsed guidelines on CINV management acknowledge such circumstances exist; however, the guidelines do not provide many alternative options to ensure appropriate prophylaxis is administered. This study aims to describe the efficacy of olanzapine, in place of dexamethasone, in combination with fosaprepitant and a 5HT3-antagonist on CINV prevention in children.

Methods

This was a single-center, retrospective, cohort study of pediatric hematology and oncology patients at Cleveland Clinic Children's from July 2016 to December 2020. Approval for the study was obtained through the Institutional Review Board at the Cleveland Clinic in Cleveland, Ohio. Eligible patients were admitted to an inpatient pediatric unit and scheduled to receive HEC defined per Children's Oncology Group CINV guidelines. Patients were included in the chemotherapy block numbers up to 4 times. Patients who received

oral olanzapine for the purpose of CINV control were identified from pharmacy dispensing records. Patients receiving conditioning chemotherapy for a hematopoietic stem cell transplant or who received four-drug CINV prophylaxis were excluded.

A chemotherapy block was defined as a series of consecutive days that chemotherapy was administered. The period of time prior to initiation, during, and up to 24 hours after completion of chemotherapy was defined as acute phase. Delayed phase was defined as greater than 24 hours after completion of chemotherapy to 120 hours after or until discharge, whichever occurred first.

The primary objective was to compare complete response (CR) between the groups in the acute, delayed and overall phases. Patients were considered to have a CR when no emesis and no use of rescue medication occurred during the respective periods. Secondary objectives olanzapine prescribing practices and safety.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Comparison between categorical values was performed using the chi-squared test or Fishers exact test. A level of significance was set at 0.05.

Results

Of the 124 patients initially screened through pharmacy dispensing records, 88 were excluded. The most common reasons for exclusion were olanzapine use as part of a four-drug CINV regimen, chemotherapy as part conditioning regimen for transplant, or chemotherapy was classified as moderately emetogenic. A total of 36 unique patients and total of 82 chemotherapy blocks met inclusion criteria. Baseline characteristics and demographic data are presented in Table 1. In the acute phase, CR was achieved in 22 (52%) patients in the olanzapine group versus 25 (63%) in the dexamethasone group (p=0.354). There was no clinically or statistically significant difference in CR rates between olanzapine and dexamethasone groups (Table 2).

Ondansetron 0.15 mg/kg (maximum 8 mg) every 8 hours was the 5-HT3 antagonist used in all but two of the chemotherapy blocks in the dexamethasone group. Palonosetron 0.02 mcg/kg (maximum 0.25 mg) for one dose was administered to those that didn't receive ondansetron. Fosaprepitant was dosed per package insert for one dose and one patient in the olanzapine group received two doses of fosaprepitant 72 hours apart. In the dexamethasone group, dexamethasone was dosed at 5 mg/m2 once daily for the duration of chemotherapy.

The mean initial olanzapine dose was 0.07 mg/kg/dose (range 0.02-0.1, maximum 5 mg). Doses were rounded to nearest 1.25 mg. The median duration of olanzapine was 2 days (range 1-7 days). Olanzapine was initiated on day 1 of chemotherapy for all blocks and was continued for the duration of each chemotherapy block or longer in 28 (67%) blocks. No patients required a dose reduction of olanzapine due to intolerance; 3 patients required a dose increase to maximize efficacy. Olanzapine was discontinued in one of two patients for over-sedation.

Discussion

This single-center, retrospective, cohort study showed that olanzapine, fosaprepitant, and a 5-HT3 receptor antagonist had similar control of CINV in pediatric patients receiving HEC compared to dexamethasone, fosaprepitant, and a 5-HT3 antagonist in the acute (53% v 63%, p=0.354) and delayed (80% v 73%, p=0.702) phases. The CR rates in this study are similar to other studies using three-drug antiemetic regimens in children. Bakhshi and colleagues demonstrated a CR in the acute phase of 48% v 12% when aprepitant was added to dexamethasone and ondansetron, and Kang and colleagues found CR rates of 51% v 26% in the delayed phase when aprepitant was added to ondasetron with or without dexamethasone. [6, 7]

Most studies continued olanzapine for 3-4 days after completion of chemotherapy; however, that was not the practice found in this study.[4, 8] To maximize olanzapine benefit, one could consider continuing olanzapine for up to 4 days after completion of chemotherapy. Additionally, when dexamethasone is not used, providers should consider using palonosetron instead of ondansetron as recommended in the COG CINV endorsed

guidelines.[2] This recommendation is based on a meta-analysis demonstrating increased acute CINV control with palonosetron compared to other 5-HT3 antagonists in the absence of dexamethasone. [9]

This study was limited by its retrospective design and incidence of nausea and vomiting and other toxicities relied on documentation in the electronic medical record. As a result, mild adverse events may have been unreported. In this study, only one patient required a dose modification due to over-sedation. The incidence of over-sedation in other studies range from 35-40%.[4, 8] The limited sedation experienced in this study may be due to the lower starting dose of olanzapine use compared to other studies (0.07 mg/kg v 0.14 mg/kg).[4, 8] In this study, the standard dose of 0.05 mg/kg/dose was chosen to allow for an additional as needed dose without exceeding the maximum daily dose of olanzapine that has been studied in the pediatric population.

In conclusion, olanzapine appears to be a safe and effective alternative to dexamethasone as part of a three-drug prophylaxis regimen for both acute and delayed CINV. Future studies are warranted to determine the benefit of olanzapine in combination with palonosetron and fosaprepitant when dexamethasone must be avoided.

Table 1. Baseline characteristics

	Olanzapine group n=17	Dexamethasone group n=19
Median age (range), years	17 (8-24)	16 (1-23)
Sex Male Female	12 5	13 6
Diagnosis Lymphoma Sarcoma Leukemia Brain tumor Other	4 3 3 6 1	5 6 3 0 5
Duration of chemotherapy block Single day Multiday	4 13	2 17
Median chemotherapy blocks received per patient	2	2

Table 2. Complete response rates per chemotherapy block

	Olanzapine Group n = 42 N (%)	Dexamethasone Group n = 40 N (%)	*p-value*
Acute Phase	22 (52)	25 (63)	0.354
Delayed Phase	32 (76%)	29 (73)	0.702
Overall Response	21 (50)	20 (50)	0.829

1. Paw Cho Sing, E., et al., *Classification of the acute emetogenicity of chemotherapy in pediatric patients: A clinical practice guideline.* Pediatr Blood Cancer, 2019. **66** (5): p. e27646.

2. Patel, P., et al., *Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update.* Pediatr Blood Cancer, 2017. **64** (10).

3. Hesketh, P.J., et al., *Antiemetics: ASCO Guideline Update.* J Clin Oncol, 2020. **38** (24): p. 2782-2797.

4. Naik, R.D., et al., *Olanzapine for Prevention of Vomiting in Children and Adolescents Receiving Highly Emetogenic Chemotherapy: Investigator-Initiated, Randomized, Open-Label Trial.* J Clin Oncol, 2020. **38** (32): p. 3785-3793.

5. Patel, P., et al., *Dexamethasone dosing for prevention of acute chemotherapy-induced vomiting in pediatric patients: A systematic review.* Pediatr Blood Cancer, 2020. **67** (12): p. e28716.

6. Bakhshi, S., et al., *Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: a randomized, double-blind, placebo-controlled trial.* Support Care Cancer, 2015.**23** (11): p. 3229-37.

7. Kang, H.J., et al., *Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial.* Lancet Oncol, 2015. **16** (4): p. 385-94.

8. Flank, J., et al., *Olanzapine for prevention of chemotherapy-induced nausea and vomiting in children and adolescents: a multi-center, feasibility study.* Support Care Cancer, 2018.**26** (2): p. 549-555.

9. Popovic, M., et al., *Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials.*Support Care Cancer, 2014. **22** (6): p. 1685-97.