JPPT

Clinical Investigation

Characterization of Dronabinol Usage in a Pediatric Oncology Population

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OBJECTIVES: Chemotherapy-induced nausea and vomiting (CINV) remains an important side effect associated with administration of chemotherapy in pediatrics. The aim of this study was to retrospectively review dronabinol use in a pediatric cancer center, with the intent of characterizing its use and identifying trends such as age, sex, diagnosis, and chemotherapy that describe where dronabinol is best used as an adjuvant antiemetic.

METHODS: Patients receiving dronabinol at Riley Hospital for Children between 2000 and 2010 were identified. Patients eligible for inclusion were those with malignancy ≤18 years old, who received at least 1 dose of dronabinol for CINV during admission.

RESULTS: Ninety-five percent of patients received moderate or highly emetogenic chemotherapy. When dronabinol doses were analyzed, 95% of patients received doses that were lower than reference guidelines, 55% received dronabinol as a scheduled medication, and 19% received dronabinol 1 to 3 hours before chemotherapy. Overall, 60% of patients had a defined positive response to dronabinol. Sixty-five percent of patients received repeat courses of dronabinol, and 62% received outpatient prescriptions for dronabinol.

CONCLUSIONS: Dronabinol appears to be a viable option as an adjuvant antiemetic in pediatric CINV, but a prospective trial using patients as their own controls is necessary to truly define dronabinol's place in therapy.

INDEX TERMS: chemotherapy, dronabinol, nausea, pediatric, vomiting

J Pediatr Pharmacol Ther 2015;20(6):462–467

INTRODUCTION

As chemotherapy regimens have intensified, cure rates for oncologic disorders have increased, but so have the toxicities. Chemotherapy-induced nausea and vomiting (CINV) is one such side effect of pediatric cancer therapy.[1] Although nearly all chemotherapy recipients experience some CINV, those with poorly controlled symptoms often suffer additional physical, emotional, and psychological stress. Such debilitating effects can result in poor compliance and treatment interruptions.[2] Chemotherapy-induced nausea and vomiting ranks in the top 3 distressing side effects of cancer therapy.[3] Although CINV contributes significantly to morbidity, it remains poorly characterized in the literature.[4,5] There is a current gap in understanding the best treatment and prevention of pediatric CINV. Current pediatric supportive care guidelines are based on minimal randomized, prospective data, and often leave pediatric practitioners to extrapolate from adult studies.

Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO) guidelines for the prevention and treatment of pediatric CINV recommend that children receiving highly or moderately emetogenic chemotherapy regimens receive 5-HT_3 receptor antagonists and corticosteroids.[4,5] These guidelines do not account for special subpopulations such as patients with brain tumors, for whom corticosteroids may be contraindicated due to blood-brain-barrier disruption.[6] Recent pediatric guidelines also fail to address the various adjuvant therapies for CINV that are typically used to optimally control this side effect.[4,5] Although adjuvant options such as phenothiazines, benzodiazepines, and neurokinin-1 antagonists are often used in pediatric

patients, other adjuvant options exist that are not commonly used.

The cannabinoid dronabinol, delta-9-tetrahydrocannabinol, is one adjuvant option used, but its use is poorly characterized in the publications. It exerts an antiemetic effect through an agonistic mechanism on the cannabinoid-1 receptor and through an indirect mechanism of inhibiting emetogenic neurotransmitter release.[7] In adults, dronabinol is effective as an adjuvant antiemetic for CINV.[8,9] However, the psychotropic side effects of the medication, most often seen in the elderly population, have generally limited this cannabinoid as a second line agent for refractory CINV.[10]

Approved by the US Food and Drug Administration in 1986, dronabinol is a therapeutic alternative for pediatric CINV.[11] One small study described the use of cannabinoids in a pediatric population reporting that delta-8-tetrahydrocannabinol was efficacious and tolerable.[11] Dronabinol reportedly has more psycotropic adverse effects and has yet to be studied in the pediatric setting. Children are thought to be less sensitive to the psychotropic side effects, thus making dronabinol a reasonable option for CINV. However, it remains unclear which subset of the pediatric population would most benefit from cannabinoid therapy.

This study retrospectively evaluated the use of dronabinol in a large academic pediatric cancer center, with the intent of characterizing its use and identifying trends such as age, sex, oncology diagnosis, and chemotherapy agents that might best be administered with dronabinol as an adjuvant antiemetic. This characterization will allow for more effective dronabinol use in subsets of the pediatric population in whom it appears to be most beneficial.

METHODS

Study Design

A retrospective chart review of dronabinol use at a tertiary, free-standing, academic pediatric hospital between January 1, 2000, and July 30, 2010, was completed. The study was approved by the Indiana University-Purdue University Indianapolis institutional review board.

Patients

Dronabinol recipients at Riley Hospital for Children during the study period were identified through the PharmNet reporting system, an internal pharmacy database. Eligible patients included those with malignancy diagnosed at ≤18 years of age, who received at least 1 dose of dronabinol during an inpatient stay. Patients were excluded from the study if dronabinol was ordered on their medication profile but not given or if appetite stimulation was the defined indication for dronabinol use.

Outcome Measures

Demographic information included age, sex, height, weight, body surface area, and diagnosis. Medication information collected included the chemotherapy regimen, dronabinol dosages and frequency, and additional antiemetic usage as concomitant therapy. Chemotherapy regimens were classified as high, moderate, low, or minimally emetogenic. The classifications define the risk of emesis without the use of antiemetics as >90%, 31% to 90%, 10% to 30%, and < 10%, respectively.[12] Variables intended to characterize dronabinol response included the number of emetic events from dronabinol administration until discharge, repeated courses of dronabinol, and outpatient prescriptions written for dronabinol. Response to dronabinol was divided into 3 groups (good, fair, and poor) with 0 to 1, 2 to 3, and >4 bouts of emesis, respectively. Tolerability was indirectly measured using repeat courses and outpatient prescriptions as surrogate markers.

Statistical Analysis

Statistical analysis included descriptive statistics such as means, medians, ranges, and standard deviations to test for trends in response to dronabinol.

RESULTS

A total of 66 patients received dronabinol during the study period. Eight patients were excluded because the patient did not have cancer (n=1), the patient did not receive a dose (n=3), and dronabinol was indicated for appetite stimulant (n=4). Demographics are listed in Table 1. Of the 58 patients included, 30 (52%) were male. Mean age was 13.9 years old, and only 6 patients were youger than 10 years of age. The most common malignancies in the study were leukemia and sarcoma, each consisting of 21 patients of the study population.

Table 1. Patient Baseline Characteristics

Variable	Number or Value*
Sex	
Male	30 (52%)
Female	28 (48%)
Age	
Mean ± SD	13.9 ± 3.2
Median	15
Range	6-18
Diagnosis	
Leukemia	21 (36%)
Lymphoma	9 (16%)
Sarcoma	21 (36%)
Brain tumor	5 (9%)
Miscellaneous	2 (3%)

*n=58.

Table 2 details the chemotherapy regimen each patient received while on dronabinol. Of the 58 pediatric oncology patients who received dronabinol for nausea and vomiting, 47 patients received dronabinol during a chemotherapy regimen. Upon classification of the regimens, 38% were moderately emetogenic, and 57% were highly emetogenic combinations. Only 4% were of miminal or low emetogenic risk. Twenty-eight percent of study patients did not receive an appropriate antiemetic regimen as outlined in the most recent MASCC and ASCO guidelines.[4,5] All 13 patients who did not receive appropriate antiemetics received moderately and highly emetogenic chemotherapy without the recommended combination of a 5-HT_3 receptor antagonist and corticosteroid.

Median dronabinol doses received per hospitalization were 3.5, with a wide range (1-129 doses) received per patient (Table 3). When the dosing schedule of dronabinol was examined, the medication was scheduled in 55% of patients. Three patients included in the study received dronabinol as a 1-time order. Athough dronabinol administration is recommended 1 to 3 hours prior to chemotherapy, this occurred in only 19% of cases.[13] Similarly, when the weight-based dosing recommendations for dronabinol were examined, 55 of 58 patients (95%) received a dose lower than referred to in guidelines.[13]

When response was classified based on a predefined number of bouts of emesis, the majority of patients (60%) had a good response. In turn, 13% had a fair response, and 27% were poor responders. The 3 patients who received dronabinol as a 1-time order were excluded from this analysis due to the difficulty of ascertaining response after a single dose of the medication. Children had a similar response regardless of the emetogenecity of the chemotherapy regimen, as 59% of patients who received highly emetogenic chemotherapy had a defined "good response" compared to 56% of patients who received moderately emetogenic chemotherapy (Figure). In regard to surrogate markers of tolerability of the medication, 65% of patients received dronabinol during multiple hospital admissions, and 62% were discharged with a dronabinol prescription. Three patients included in the study either expired during hospital admission or were transferred to another facility, which precluded them from analysis of tolerability. Two additional patients did not have a discharge medication reconciliation completed, so it is unknown if they received outpatient prescriptions for dronabinol.

Table 2. Chemotherapy and Antiemetic Regimen

Variable	Number or Value*
Emetogenic potential	
Minimal risk (<10%)	1 (2%)
Low risk (10%-30%)	1 (2%)
Moderate risk (31%-90%)	18 (38%)
High risk (>90%)	27 (57%)
Appropriate antiemetic regimens	
Yes	34 (72%)
No	13 (28%)

*n=47.

DISCUSSION

This study, comprised largely of adolescents, represents the only characterization of dronabinol usage in a pediatric oncology population. This group is often more prone to the emetic effects of chemotherapy.[14] Additionally, this is a common age for sarcoma presentation, which accounted for 36% of the patients included. Sarcoma-directed chemotherapy regimens are typically highly emetogenic, and adjuvant antiemetic medications are often required. An additional 36% of dronabinol recipients had leukemia. This subgroup was composed largely of those with

Table 3. Dronabinol Regimens and Responses

Variable	Number or Value
No. of doses received	
Median	3.5
Range	1-129
Dosing frequency	
Scheduled	30 (55%)
PRN	25 (45%)
Dose given 1-3 hr prior to chemotherapy	
Yes	11 (19%)
No	47 (81%)
Received appropriate weight-based dose	
Yes	3 (5%)
No	55 (95%)
Response to dronabinol	
Good (0-1 emesis)	33 (60)
Fair (2-3 emesis)	7 (13)
Poor (>4 emesis)	15 (27)

PRN, (pro re nata) as needed.

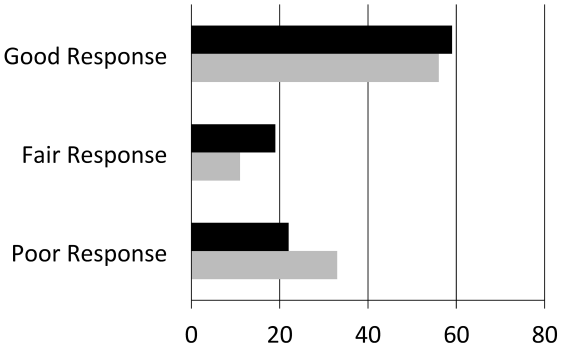

Figure. Response to dronabinol based on chemotherapy emetogenicity.
■ = highly emetogenic; □ = moderately emetogenic.

acute myeloid leukemia and those with relapsed acute lymphoblastic leukemia, both of which are typically treated with aggressive, highly emetogenic chemotherapy.

Ninety-five percent of patients who received cannabinoids received moderate or highly emetogenic chemotherpy. MASCC and ASCO guidelines indicate that antiemetic therapy for recipients of these regimens should include a 5-HT_3 receptor antagonist and corticosteroid, unless the child has a brain tumor or corticosteroids are part of their chemotherapy.[4,5] Our patients were prescribed such an antiemetic regimen 72% of the time. The 28% of children who did not receive the warranted combination of a 5-HT_3 receptor antagonist and corticosteroid were possibly at an increased risk for emesis. This increased risk could have resulted in more emetic events in patients receiving dronabinol, which effectively may underestimate the response to dronabinol.

Our data collection allowed for a characterization of dronabinol-prescribing habits within our single institution. Specifically, we analyzed dosages, timing of administration, and duration of therapy. The recommended pediatric dosage of dronabinol is 5 mg/m^2 given orally 1 to 3 hours prior to chemotherapy and continued every 2 to 4 hours thereafter.[13] There are no recommendations for PRN (as-needed) use; all guidelines recommend scheduled dosing. Therefore, the ordering of dronabinol as a PRN medication in 45% of our population was notable. The institutional prescribing habits in our population were such that 81% of patients received dronabinol outside of the 1- to 3-hour pre-chemotherapy window as well. These trends are consistent with dronabinol being used most prominently as a rescue antiemetic, prescribed after patients are already experiencing nausea and vomiting.

Ninety-five percent of patients did not receive the recommended weight-based dose of 5 mg/m^2 dronabinol.[13] The most commonly prescribed regimen at our institution was 2.5 mg/m^2 oral solutin every 6 hours as needed. Although labeled dosing for dronabinol allows for the medication to be increased up to a maximum of 15 mg/m^2 as tolerated, no patient received a dose greater than 5 mg/m^2 in this characterization. Initial underdosing may have been an attempt to first assess tolerability and to minimize the psychotropic effects before increasing to the recommended dose level. Because only 2 patients in this study received a dose of 5 mg/m^2, we were unable to claim efficacy in comparison with those who received lower doses of dronabinol versus those who received the labeled dose of dronabinol. However, it remains notable that in this characterization, there was a favorable outcome when response to the 2.5 mg/m^2 dosing scheme alone was examined.

Patients received a median of 3.5 dronabinol doses, but the range was quite large, from 1 to 129 doses. Patients with extended hospitalizations, such as stem cell-transplant recipients,

Table 4. Tolerability of Dronabinol

Variable	Number (%)
Repeat courses of dronabinol	
Yes	36 (65)
No	19 (35)
Outpatient Rx given for dronabinol	
Yes	33 (62)
No	20 (38)

accounted for those with the highest number of doses. If the 3 patients who received the largest number of doses (129, 38, and 24 doses) are excluded from data analysis, the average number of doses patients received throughout the study was 5.5 ± 5.1.

Sixty-percent of patients were noted to have a "good" response to dronabinol. When response was further examined based on emetogenicity of chemotherapy, no trend was identified. Recipients of highly emetogenic chemotherapy maintained an equally "good" response to dronabinol compared to recipients undergoing less emetogenic chemotherapy. The maintenance of response to dronabinol in highly emetogenic chemotherapy is notable, as these regimens would be expected to result in more CINV than moderately emetogenic chemotherapy regimens.

Dronabinol use is often limited due to concerns of tolerability. As Table 4 suggests, it can be extrapolated that our study population tolerated dronabinol well on the basis of the 65% of children who received repeated courses and 62% who received an outpatient prescription. Although 62% of patients received a prescription for dronabinol at time of discharge, it is unknown whether these prescriptions were filled.

Several limitations can be drawn from this characterization. The retrospective nature precludes an ability to truly analyze efficacy and safety, although early trends were identified. Although emetic events were quantifiable, severity of nausea could not be ascertained. An extended duration of the study was necessary. During the reporting period, additional CINV therapies, such as the neurokinin-1 antagonists, were introduced. Importantly, however, supportive care guideline recommendations remained consistent during the study period. Finally, the lack of a comparison group, lack of chemotherapy standardization, and lack of standardized antiemetic regimens were all barriers to interpretation. These differences in treatment make it impossible to solely credit dronabinol for improvement in CINV although this report encourages a more detailed investigation into the use of dronabinol.

CONCLUSIONS

Despite the limitations of this exploratory study, it begins to characterize cannabinoid use in pediatric cancer patients. This is the largest study of its type in this population. This characterization unveils interesting findings, and based on results, dronabinol appears to be a viable option in pediatric CINV, but a prospective trial using patients as their own controls would be necessary to truly define dronabinol's place in therapy.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Acknowledgments This work was presented previously in poster format by Joshua J. Elder and Holly M. Knoderer, entitled *Characterization of Cannabinoid Usage in a Pediatric Oncology Population*, at the 2011 Annual Meeting of the American College of Clinical Pharmacy, Pittsburgh, PA, October 2011.

Abbreviations ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; MASCC, Multinational Association of Supportive Care in Cancer

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