ARTICLE

Effectiveness of Strategies for Preventing Acute Antineoplastic-Induced Nausea and Vomiting in Children with Acute Lymphoblastic Leukemia

L. Lee Dupuis, Robert Lau, and Mark L. Greenberg

ABSTRACT

Objective: To describe the antiemetic regimens prescribed for children receiving antineoplastic drugs for the treatment of acute lymphoblastic leukemia and the effectiveness of these regimens in preventing acute antineoplastic-induced nausea and vomiting. Evaluation of the extent of adherence to guidelines for selection of the antiemetic regimen was a secondary objective.

Methods: All children (inpatients and outpatients) receiving antineoplastics for the treatment of acute lymphoblastic leukemia during the 12-week study period were eligible for the study. For each patient, age, diagnosis, antineoplastic protocol, antineoplastic agents prescribed, antiemetic agents prescribed, and time of administration of antineoplastic and antiemetic medications were recorded. The date and time of each emetic episode were recorded in a patient diary on each day that antineoplastics were given and for 3 days thereafter. Children 3 years of age and older were asked to assess the worst degree of nausea experienced. Diet and the presence of adverse effects were also assessed. The rate of response to the antiemetic regimen, the median nausea rating, and the median diet followed were described for antineoplastic agents of high, moderate, and low emetogenicity. The responses of children who experienced anticipatory nausea and vomiting were compared with those of children who did not experience anticipatory symptoms. Proportions were compared by means of a χ^2 test or a Z-test with an a priori level of significance of 5%.

Results: Data on emetic response were collected and analyzed for 94 children receiving 133 cycles of therapy over a total of 168 days. Complete, major, and failed responses were observed on 128 (76%), 30 (18%), and 10 (6%) of the study days respectively. Most children who received moderately to highly emetogenic regimens received at least one dose of ondansetron. Children who vomited or were nauseated were given no additional antiemetic support or were given additional doses of ondansetron, dexamethasone, or dimenhydrinate.

Conclusion: The rate of complete response to the antiemetic regimen in this study was lower than that reported by other investigators. Adjustment of the emetogenicity classification, standardization of the antiemetic selection process, and development of effective management strategies for anticipatory and breakthrough nausea and vomiting will improve patients' experience.

Key words: antiemetic agents, antineoplastic-induced vomiting, leukemia, pediatrics

Can J Hosp Pharm 1999;52:350–361

RÉSUMÉ

Objectif : Décrire les traitements antiémétiques prescrits chez les enfants qui reçoivent des antinéoplasiques pour combattre la leucémie lymphoblastique aiguë, et l'efficacité de ces traitements pour la prévention des nausées et des vomissements graves dus aux antinéoplasiques. L'évaluation de la mesure avec laquelle on adhérait aux lignes directrices dans le choix du traitement antiémétique constituait un objectif secondaire.

Méthodes : Tous les enfants (hospitalisés et ambulatoires) qui recevaient des antinéoplasiques pour le traitement de leur leucémie lymphoblastique aiguë au cours de la période d'étude de 12 semaines étaient admissibles à cette étude. On a consigné l'âge, le diagnostic, le protocole d'administration des antinéoplasiques, les antinéoplasiques prescrits, les antiémétiques prescrits et l'heure d'administration des antinéoplasiques et des antiémétiques. La date et l'heure de survenue de chacun des épisodes de nausées et de vomissements ont été consignées dans un journal quotidien du patient pour chacune des journées où des antinéoplasiques ont été administrés et durant les trois jours suivants. On a demandé aux enfants de trois ans ou plus d'évaluer leurs pires épisodes de nausées et de vomissements. Le régime alimentaire et la manifestation d'effets indésirables ont également été évalués. Le taux de réponse au traitement antiémétique, la cote médiane des nausées, et le régime alimentaire moyen suivi ont été décrits pour les antinéoplasiques fortement, moyennement et faiblement émétogènes. Les réactions des enfants qui ont éprouvé des nausées et des

vomissements par anticipation ont été comparées à celles des enfants qui n'ont pas éprouvé de symptômes par anticipation. Les proportions ont été comparées au moyen du test du chi carré ou du test *Z* avec un taux de signification a priori de 5 %.

Résultats : Les données sur les réponses aux traitements antiémétiques ont été recueillies et analysées pour 94 enfants qui ont reçu 133 séances thérapeutiques au cours d'un total de 168 jours. La réponse était complète, importante et inexistante durant 128 (76%), 30 (18%), et 10 (6%) jours, respectivement, sur le total des jours d'étude. La plupart des enfants qui ont reçu un traitement antinéoplasique fortement ou moyennement émétogène ont reçu au moins une dose d'ondansétron. Les enfants qui ont éprouvé des nausées ou des vomissements n'ont reçu aucun antiémétique d'appoint ou ils ont reçu de doses additionnelles d'ondansétron, des dexaméthasone ou de dimenhydrinate.

Conclusion: Le taux de réponse complète aux traitements antiémétiques au cours de cette étude était plus faible que celui rapporté par d'autres chercheurs. Une correction de la classification de l'émétogénécité, la standardisation du processus de sélection des antiémétiques, et l'élaboration de stratégies de gestion efficaces des nausées et des vomissements par réaction d'anticipation et perthérapeutiques facilitera la vie des patients.

Mots clés : antiémétiques, vomissements dus aux antinéoplasiques, leucémie, pédiatrie

INTRODUCTION

Ideally, the emetogenic potential of the prescribed antineoplastic regimen as well as the therapeutic risk:benefit ratio of available antiemetics is known when antiemetic prophylaxis is selected. In pediatric practice the information determining these decisions is often extrapolated from adult literature or experience, and there is little direct evidence on which to base practice guidelines. Nevertheless, such guidelines were developed in 1985[1] by pharmacists and oncologists at The Hospital for Sick Children, Toronto, Ont., and were revised in early 1994 (Table 1). These guidelines were based on the available pediatric evidence, the published adult evidence, and the experience of the hospital's practitioners. In each instance, the guidelines were reviewed and approved by the Division of Haematology/Oncology and the Pharmacy and Therapeutics Committee. Use of these guidelines was recommended and encouraged but not mandated. The primary objective of this study was to describe the antiemetic regimens prescribed for children receiving antineoplastics at The Hospital for Sick Children for the treatment of acute lymphoblastic leukemia and the effectiveness of these regimens in preventing acute nausea and vomiting. A secondary objective was to evaluate adherence to the guidelines for selection of antiemetics. This information is a step toward refining the guidelines on the basis of their effectiveness in children.

METHODS

The protocol for this study was approved by the Research Ethics Board of The Hospital for Sick Children. All children (inpatients and outpatients) receiving antineoplastic agents for the treatment of acute lymphoblastic leukemia from May 28 to August 22, 1996, were eligible for the study. Patients who were enrolled in another antiemetic study, those who could not communicate in English (or whose parents could not communicate in English), and those who did not consent to participate were excluded. A patient was able to enter the study each time an antineoplastic cycle was undertaken, and thus one patient could contribute several data sets. Each patient's age, diagnosis, and antineoplastic protocol were recorded, as well as the prescribed antineoplastic and antiemetic drugs and the times of their administration. The emetogenicity of each antineoplastic regimen was based on the agent of highest emetogenicity (Table 1). Outpatients recorded the date and time of administration of the antiemetic regimen in a patient diary. For inpatients, this information was obtained from the health record.

Acute nausea and vomiting were defined as emetic episodes or nausea that occurred on the same day as an antineoplastic agent was given. Anticipatory nausea and vomiting were defined as emetic episodes or nausea that occurred within 24 h before administration of the first dose of an antineoplastic cycle. An emetic episode was defined as a single vomit or retch separated by the absence of both vomiting and retching for at least 1 min. Vomiting was defined as the expulsion of any stomach contents through the mouth; retching was defined as an attempt to vomit that was not productive of any stomach contents. Emetic response to the antineoplastic regimen was defined as follows: complete response = no emetic episodes, major response = up to 2 emetic episodes/ day, and failure = more than 2 emetic episodes/day. The date and time of each emetic episode

Table 1. Hospital for Sick Children Guidelines (1994) for Selecting Antiemetics for Children Receiving Antineoplastic Agents

Antineoplastic Agent	Antiemetic Agent(s) of Choice	Alternative Antiemetic Agent(s)
High emetogenicity		
Amsacrine Carmustine Busulfan (4 mg/kg for BMT) Cisplatin (90 mg/m²) Cyclophosphamide (600 mg/m²) Cytarabine (≥2 g/m²) Dacarbazine Dactinomycin (≥35 µg/kg single dose) Daunorubicin Doxorubicin (≥45 mg/m²) Etoposide (for BMT) Ifosfamide (≥3 g/m²) Mechlorethamine Melphalan	Ondansetron: 3 to 5 mg/m² IV 15 min pre-chemotherapy then IV q8h or then PO q8h as follows: <0.3 m²: 1 mg/dose 0.3 to 0.6 m²: 2 mg/dose >0.6 to 1 m²: 3 mg/dose >1 m²: 4 to 8 mg/dose *plus* dexamethasone: 10 mg/ m² per dose IV pre-chemotherapy and q12h thereafter; maximum 20 mg/dose *or* 0.2 mg/kg per dose PO pre-chemotherapy and q6h thereafter; maximum 4 mg/dose	Metoclopramide: 1.5 to 2 mg/kg per dose IV pre-chemotherapy and q2-3h for 3 doses and prn thereafter *plus* dexamethasone (*plus* diphenhydramine)
Moderate emetogenicity		
Carboplatin Cisplatin (20 mg/m²) Cyclophosphamide (<600 mg/m²) Dactinomycin (15 µg/kg) Epirubicin Ifosphamide (<3 g/m²) Methotrexate (high dose)	Dexamethasone *plus* metoclopramide (*plus* diphenhydramine)	Dexamethasone *or* ondansetron
Low emetogenicity		
L-Asparaginase Bleomycin Cytarabine (<2 g/m²) Etoposide (low dose) Hydroxyurea Intrathecal antineoplastics Lomustine Mercaptopurine Methotrexate (low dose) Procarbazine Teniposide Thioguanine Vinblastine Vincristine	None	Metoclopramide (*plus* diphenhydramine)

BMT = bone marrow transplant.

were recorded in the patient diary on each day that antineoplastics were given and for 3 days thereafter. On the day before administration of the first dose of an antineoplastic cycle, patients were asked if they experienced anticipatory nausea or vomiting.

Nausea was self-assessed. The worst degree of nausea experienced on each day that antineoplastics were administered and for 3 days thereafter was assessed as follows by patients over 6 years of age who were able to do so: 1 = no nausea at all, 2 = did not interfere with usual activities, 3 = interfered with usual activities, and 4 = required the patient to be bedridden. Children 3 to 6 years of age used a 6-faced "happy face" analogue scale (which was converted to numeric values 0 to 6 for the analysis) to assess their worst degree of nausea.[2] Children younger than 3 years of age and those who were developmentally delayed did not assess their nausea.

Diet was assessed as follows on each day that antiemetics were administered and for 3 days thereafter: 1 = regular diet, 2 = fluids and some solids, 3 = fluids only, and 4 = nothing by mouth. Adverse reactions attributable to the antiemetic regimens were recorded. Children or their parent(s) were specifically questioned regarding the presence of diarrhea, headache, constipation, hiccups, anxiety, and restlessness.

Patients were monitored on each day that antineoplastics were given and for 3 days thereafter. While the

patient was in the hospital or the clinic, the diary was completed by either the parent, the patient, or the nurse assigned to the patient. After discharge, either the parent or the patient recorded the symptom assessments. Nausea and dietary assessments were made at bedtime and reflected the worst nausea experienced and the best diet achieved that day. Discharged patients or their parents were asked to return the completed diaries by mail (a postage-paid envelope was provided) or to bring them with them to their next clinic visit. On each day of data collection, a pharmacy student contacted the family of each participant by telephone or in person to remind them to record data and to answer their questions about study procedures.

The antiemetic response rate, the median nausea rating, and the median diet were calculated for antineoplastic regimens of high, moderate, and low emetogenicity. The responses of children who experienced anticipatory nausea or vomiting (or both) were compared with those of children who did not experience anticipatory nausea or vomiting. A χ^2 test or a Z-test with an a priori level of significance of 5% was used to compare proportions.

RESULTS

In total, 103 children or their guardians consented to participate in this study. One child withdrew during the study period, and 8 patient diaries were not returned. Therefore, data were available on the emetic response of 94 children with acute lymphoblastic leukemia, ranging in age from 1 to 17.7 years of age, who underwent a total 133 treatment cycles over 168 days. To focus on acute antineoplastic-induced nausea and vomiting, only data collected on the days on which antineoplastic agents were administered are reported here. Patient characteristics are presented in Table 2. The antiemetic prophylaxis received complied with the guidelines for antiemetic selection on fewer than half (81 or 48%) of the study days. Overall, a complete response was observed on 128 (76%) of the study days, a major response was observed on 30 (18%) of the study days, and a failed response was observed on 10 (6%) of the study days (Table 3).

Highly emetogenic antineoplastic regimens were given over 1 day (13 cycles), 3 days (1 cycle), or 4 days (5 cycles). The 1-day regimens consisted of vincristine and daunorubicin (25 mg/m^2) alone (4 cycles) or with intrathecal methotrexate (4 cycles) and/or asparaginase (9 cycles). The 3-day regimen consisted of methotrexate (1 g/m^2) and intrathecal methotrexate on day 1 and cytarabine (3 g/m^2) on days 2 and 3. The 4-day regimens consisted of cyclophosphamide (600 mg to 1 g/m^2) given on 1 or 4 days and cytarabine (75 mg/m^2) given on 4 days (4 cycles), with intrathecal methotrexate (4 cycles), or intrathecal cytarabine, doxorubicin, and vincristine (1 cycle).

Emetic response was evaluated on a total of 36 study days in children receiving highly emetogenic antineoplastic regimens (Tables 4 to 6). No course of highly emetogenic therapy was accompanied by the recommended antiemetic regimen of ondansetron q8h and dexamethasone q12h. Dexamethasone, in fact, was never given. At least 1 dose of ondansetron was given on most (27 or 75%) study days. The emetic response was complete on most study days (28 or 78%), major on 3 study days (8%), and failed on 5 study days (14%). Little or no nausea was experienced (median nausea

Table 2. Characteristics of Children with Acute Lymphoblastic Leukemia

Characteristic	Value
No. of patients	94
No. of cycles of chemotherapy (total)	133
Gender (M:F)	51:43
Mean age (years ± SD)	7.8 ± 4.5
Mean time from diagnosis (years ± SD)	1.4 ± 1.7

SD = standard deviation.

Table 3. Acute Emetic Response of Children with Acute Lymphoblastic Leukemia on Each Day that an Antineoplastic Agent was Received and During Each Antineoplastic Cycle

Emetogenicity of Antineoplastic Agent	Total No. of Study Days or Cycles	Emetic Response for No. (and %) of Study Days or Cycles		
		Complete	Major	Failed
High				
Study days	36	28 (78)	3 (8)	5 (14)
Cycles of therapy	19	15 (79)	1 (5)	3 (16)
Moderate				
Study days	28	23 (82)	4 (14)	1 (4)
Cycles of therapy	18	13 (72)	4 (22)	1 (6)
Low				
Study days	104	77 (74)	23 (22)	4 (4)
Cycles of therapy	96	73 (76)	19 (20)	4 (4)
Total				
Study days	168	128 (76)	30 (18)	10 (6)
Cycles of therapy	133	101 (76)	24 (18)	8 (6)

score: 1 for children 3 to 6 years of age and 2 for those over 6 years of age), and children maintained their usual diet on most study days (median diet score: 1). Children who vomited or complained of nausea were given no antiemetic or were given additional doses of ondansetron or dimenhydrinate (or both).

Moderately emetogenic antineoplastic regimens were given over 1 day (11 cycles), 2 days (5 cycles), 3 days (1 cycle), or 4 days (1 cycle). The 1-day regimens consisted of vincristine and doxorubicin (25 mg/m²) (10 cycles), with asparaginase (5 cycles) and intrathecal cytarabine (1 cycle), or methotrexate (8 g/m²) (1 cycle). The 2-day regimens consisted of vincristine and methotrexate (1.5 to 8 g/m²). The 3-day regimen consisted of methotrexate (1 g/m²) on day 1 and cytarabine (75 mg/m²) on days 2 and 3. The 4-day regimen consisted of methotrexate (1 g/m²) and intrathecal methotrexate on day 1 and cytarabine (1.9 g/m²) on days 2, 3, and 4.

Emetic response was evaluated on a total of 28 days in children receiving moderately emetogenic antineoplastic regimens (Tables 4, 5, 7, 8). Antiemetics were given in compliance with the guidelines on 10 (36%) of the study days. In these cases, 2 or 3 doses of ondansetron (as a single agent) were given on each study day. On 18 study days (64%), children who received moderately emetogenic antineoplastic

Table 4. Antiemetics Given and Acute Response of Children Who Received 1-Day Antineoplastic Regimens

Antiemetics Received	No. of Study Days	Emetic Response (No. of Study Days)			Median Nausea Score*		Median Diet Score†
		Complete	Major	Failed	3 to 6 years	>6 years	
For highly emetogenic regimens							
Ondansetron (1 dose)	8	6	2	0	1 (*n* = 2)	1 (*n* = 4)	1
None	2	2	0	0	0 (*n* =2)	NA	2
Ondansetron (1 dose) + dimenhydrinate (1 dose)	1	1	0	0	3 (*n* = 1)	NA	1
Ondansetron (2 doses) + dimenhydrinate (2 doses)	1	1	0	0	4 (*n* = 1)	NA	1
Metoclopramide (1 dose)	1	1	0	0	0 (*n* = 1)	NA	1
For moderately emetogenic regimens							
Ondansetron (1 dose)	5	4	1	0	0 (*n* = 1)	2 (*n* = 1)	1
Ondansetron (2 doses)	3	2	1	0	0 (*n* = 1)	3 (*n* = 2)	1
Ondansetron (2 doses) + dexamethasone (3 doses)	2	2	0	0	3.5 (*n* = 2)	NA	1
None	1	1	0	0	0 (*n* = 1)	NA	1
For regimens of low emetogenicity							
None	69	58	10	1	1 (*n* = 30)	1 (*n* = 34)	1
Dimenhydrinate (1 dose)	2	0	2	0	4 (*n* = 1)	2 (*n* =1)	3
Ondansetron (1 dose)	11	8	1	2	0.5 (*n* = 4)	2 (*n* = 6)	1
Ondansetron (2 doses)	7	6	1	0	2 (*n* = 3)	2.5 (*n* = 4)	1
Ondansetron (3 doses)	3	1	1	1	NA	2.5 (*n* = 3)	2

NA= not applicable.
*Nausea scores ranged from 0 to 5 for children 3 to 6 years of age and from 1 to 4 for children over 6 years of age. See text for complete explanation.
n values represent number of children; degree of nausea was not assessed by children under 3 years of age.
†1 = regular diet, 2 = fluids and some solids, 3 = fluids only, and 4 = nothing by mouth.

Table 5. Antiemetics Given and Acute Response of Children Who Received 3-Day Antineoplastic Regimens

Antiemetics Received	No. of Study Days	Emetic Response (No. of Study Days)			Nausea Score*		Diet Score†
		Complete	Major	Failed	3 to 6 years	>6 years	
For highly emetogenic regimens							
Day 1: None	1	1	0	0	0	NA	1
Day 2: None	1	1	0	0	3	NA	2
Day 3: None	1	1	0	0	2	NA	2
For moderately emetogenic regimens							
Day 1: Ondansetron (2 doses) + dexamethasone (2 doses)	1	1	0	0	1	NA	1
Day 2: Ondansetron (3 doses) + dexamethasone (2 doses)	1	1	0	0	1	NA	1
Day 3: Ondansetron (3 doses) + dexamethasone (2 doses)	1	1	0	0	1	NA	2

NA = not applicable.
*Nausea scores ranged from 0 to 5 for children 3 to 6 years of age. See text for complete explanation.
†1 = regular diet, 2 = fluids and some solids, 3 = fluids only, and 4 = nothing by mouth.

Table 6. Antiemetics Given and Acute Response of Children Who Received 4-Day Antineoplastic Regimens of High Emetogenicity

Antiemetics Received	No. of Study Days	Emetic Response (No. of Study Days)			Nausea Score*		Median Diet Score†
		Complete	Major	Failed	3 to 6 years	>6 years	
Day 1							
Ondansetron (1 dose)	2	2	0	0	0	1	1
Ondansetron (2 doses)	1	0	0	1	NA	4	3
Ondansetron (1 dose) + dimenhydrinate (1 dose)	1	0	0	1	4	NA	2
Ondansetron (1 dose) + dimenhydrinate (2 doses)	1	1	0	0	1	NA	1
Day 2							
Ondansetron (3 doses)	2	2	0	0	0	2	1.5
Ondansetron (2 doses)	1	0	0	1	NA	3	3
Ondansetron (1 dose)	1	0	1	0	4	NA	1
Dimenhydrinate (1 dose)	1	1	0	0	1	NA	1
Day 3							
Ondansetron (3 doses)	2	2	0	0	0	2	1
Ondansetron (2 doses)	1	1	0	0	NA	4	1
Ondansetron (1 dose)	1	1	0	0	NA	4	1
Dimenhydrinate (1 dose)	1	1	0	0	1	NA	1
Day 4							
Ondansetron (3 doses)	2	2	0	0	0	1	1
Ondansetron (1 dose)	2	1	0	1	0	2	2
Dimenhydrinate (1 dose)	1	0	0	1	4	NA	3

NA = not applicable.
*Nausea scores ranged from 0 to 5 for children 3 to 6 years of age and from 1 to 4 for children over 6 years of age. See text for complete explanation.
†1 = regular diet, 2 = fluids and some solids, 3 = fluids only, and 4 = nothing by mouth.

regimens received at least 2 doses of ondansetron as a single agent or in combination with dimenhydrinate or dexamethasone. Dexamethasone was given on a total of 7 study days (25%). Overall, the emetic response was complete on 23 study days (82%), major on 4 study days (14%), and failed on 1 study day (4%). Nausea was mild (median nausea score: 1 for children 3 to 6 years of age and 2 for children over 6 years of age), and diet was unaffected (median diet score: 1). Children who vomited or complained of nausea were given no antiemetic or were given dexamethasone, additional doses of ondansetron, or dimenhydrinate (or some combination).

Table 7. Antiemetics Given and Acute Response of Children Who Received 2-Day Antineoplastic Regimens

Antiemetics Received	No. of Study Days	Emetic Response (No. of Study Days)			Nausea Score*		Median Diet Score†
		Complete	Major	Failed	3 to 6 years	>6 years	
For moderately emetogenic regimens							
Day 1							
Ondansetron (1 dose)	4	4	0	0	0.5 (n = 2)	NA	1
Ondansetron (3 doses)	1	1	0	0	0 (n = 1)	NA	1
Day 2							
Ondansetron (3 doses)	3	3	0	0	0 (n = 1)	NA	2
Ondansetron (2 doses)	1	1	0	0	0 (n = 1)	NA	1
Ondansetron (3 doses) + dimenhydrinate (1 dose)	1	0	1	0	2 (n = 1)	NA	2
For regimens of low emetogenicity							
Day 1							
Ondansetron (2 doses)	1	1	0	0	NA	NA	2
Ondansetron (2 doses) + dexamethasone (1 dose)	1	1	0	0	NA	2 (n = 1)	1
Day 2							
Ondansetron (2 doses)	1	0	1	0	NA	NA	2
Ondansetron (2 doses) + dexamethasone (1 dose)	1	0	1	0	NA	2 (n = 1)	1

NA = not applicable.
*Nausea scores ranged from 0 to 5 for children 3 to 6 years of age and from 1 to 4 for children over 6 years of age. See text for complete explanation.
n values represent number of children; degree of nausea was not assessed by children under 3 years of age.
†1 = regular diet, 2 = fluids and some solids, 3 = fluids only, and 4 = nothing by mouth.

Regimens of low emetogenicity were given over 1 day (92 cycles), 2 days (2 cycles), or 4 days (2 cycles). The 1-day regimens consisted of low-dose methotrexate with (19 cycles) or without (28 cycles) vincristine; vincristine alone (13 cycles); vincristine and intrathecal methotrexate (24 cycles); vincristine and asparaginase (3 cycles); teniposide and low-dose cytarabine (2 cycles); vincristine, asparaginase, and intrathecal methotrexate (1 cycle); asparaginase and intrathecal methotrexate (1 cycle); and teniposide alone (1 cycle). The 2-day regimens consisted of low-dose cytarabine given over 2 days with (1 cycle) or without (1 cycle) intrathecal methotrexate. The 4-day regimens consisted of low-dose cytarabine for 4 consecutive days (2 cycles); intrathecal methotrexate was also given on day 1 in 1 cycle.

The emetic response of children receiving antineoplastic regimens of low emetogenicity was evaluated on a total of 104 days (Tables 4, 7, and 8). In compliance with the guidelines, antiemetics were not given on most (69 or 66%) study days. No antiemetic agents were given for most (69 or 75%) of the 1-day antineoplastic regimens, whereas children receiving antineoplastic regimens of longer duration all received at least 1 dose of ondansetron on each study day. In total, ondansetron was given on 33 study days (32%). The emetic response was complete on 77 study days (74%), major on 23 study days (22%), and failed on 4 study days (4%). On most study days, nausea was mild (median nausea score: 1 for children 3 to 6 years of age and 2 for those over 6 years of age), and diet was unaffected (median diet score: 1). Children who vomited were usually given no additional antiemetic support, although a few children were given dimenhydrinate (9 study days), dexamethasone (2 study days), or additional doses of ondansetron.

Children with Anticipatory Nausea and Vomiting

Sixteen (12%) antineoplastic cycles studied in 14 patients (15%) were complicated by nausea or vomiting (or both) during the 24 h preceding the first antineoplastic dose (Table 9). Relative to cycles for which no anticipatory nausea or vomiting was experienced, these cycles had a significantly higher proportion of study days on which the antiemetic regimen failed (5 [3%] and

Table 8. Antiemetics Given and Acute Response of Children Who Received 4-Day Antineoplastic Regimens of Moderate or Low Emetogenicity

Antiemetics Received	No. of Study Days	Emetic Response (No. of Study Days)			Nausea Score*		Median Diet Score†
		Complete	Major	Failed	3 to 6 years	>6 years	
For moderately emetogenic regimens							
Day 1: Ondansetron (2 doses) + dexamethasone (1 dose)	1	1	0	0	0	NA	1
Day 2: Ondansetron (3 doses) + dexamethasone (1 dose)	1	1	0	0	0	NA	1
Day 3: Ondansetron (3 doses)	1	0	1	0	2	NA	2
Day 4: Ondansetron (3 doses)	1	0	0	1	2	NA	3
For regimens of low emetogenicity							
Day 1							
Ondansetron (3 doses) + dimenhydrinate (2 doses)	1	0	1	0	NA	2	1
Ondansetron (3 doses) + dimenhydrinate (1 dose)	1	1	0	0	NA	2	2
Day 2							
Ondansetron (2 doses) + dimenhydrinate (1 dose)	2	1	1	0	NA	2.5	3
Day 3							
Ondansetron (3 doses) + dimenhydrinate (2 doses)	1	0	1	0	NA	2	3
Ondansetron (2 doses) + dimenhydrinate (2 doses)	1	0	1	0	NA	4	4
Day 4							
Ondansetron (3 doses) + dimenhydrinate (4 doses)	1	0	1	0	NA	2	3
Ondansetron (2 doses)	1	0	1	0	NA	4	3

NA = not applicable.
*Nausea scores ranged from 0 to 5 for children 3 to 6 years of age and from 1 to 4 for children over 6 years of age. See text for complete explanation.
†1 = regular diet, 2 = fluids and some solids, 3 = fluids only, and 4 = nothing by mouth.

Table 9. Characteristics and Acute Response of Children with Anticipatory Nausea and Vomiting

Characteristic	Value
No. of patients	14
No. of cycles of chemotherapy (total)	16
Gender (M:F)	7:7
Mean age (years ± SD)	9.5 ± 3.4
Mean time from diagnosis (years ± SD)	2.2 ± 2.0
Acute emetic response (% study days)	
Complete	36
Major	40
Failed	24

SD = standard deviation.

Table 10. Adverse Reactions Noted by Children or Parents during Study Period

Reaction	No. of patient days reported
Fatigue	15
Abdominal pain	4
Diarrhea	4
Rectal pruritis	4
Headache	3
Constipation	1
Hiccups	1
Hives	1
Sore back	1

6 [24%], respectively) and a significantly higher incidence of vomiting at least once on any day on which antineoplastic agents were administered (24 [17%] and 16 [64%], respectively) (χ^2 test; $p < 0.05$).

Adverse Reactions

The adverse reactions reported by children or their parents on days when antineoplastic agents were given are listed in Table 10.

DISCUSSION

Despite the provision of guidelines for selecting antiemetic regimens for children who receive antineoplastic agents, the choice of antiemetic during this study remained highly dependent on the individual prescriber. Antiemetic selection complied with the guidelines on only 48% of study days. Furthermore, administration of no antiemetic in courses of low emetogenicity represented 86% of the compliant activity. Acute antineoplastic-induced vomiting was well controlled in children who received antineoplastic agents of moderate and low emetogenicity (complete plus major response rates: 96% for both). However, the overall complete response rate was lower than that reported previously for both adults and children. For example, Nolte and colleagues,[3] using a combination of dexamethasone and a serotonin antagonist, obtained a complete response rate of 73% to 87% and 83% to 93% in adults receiving highly and moderately emetogenic antineoplastic therapy, respectively. Similarly, Foot and Hayes[4] reported complete control in 82% of first courses of antineoplastics of unspecified emetogenicity and on 90% of study days in children.

Some of the deviation from the guidelines for selecting antiemetics may have arisen from the prescribers' lack of confidence in the emetogenicity classification, particularly in the assignment of the high and moderate emetogenicity rankings. There is no direct information that can be used to classify the emetogenic potential of antineoplastics in children. In fact, there is little direct information for adults in this regard. Hesketh and colleagues[5] have proposed a 5-level classification (none, mild, moderate, high, very high), which is based on adult experience and which takes both antineoplastic dose and drug combination into account. If we were to adopt this system, several major changes in our approach, including the following, would occur:

- doxorubicin at the doses given in our treatment protocols for acute lymphoblastic leukemia would be classified as moderately emetogenic rather than highly emetogenic (the fact that most children in our study who received doxorubicin had a complete antiemetic response when given a single dose of ondansetron supports the classification of doxorubicin as a moderate emetogen in children);
- methotrexate at doses greater than 1 g/m^2 would be classified as highly emetogenic rather than as moderately emetogenic; and
- antiemetics would be selected on the basis of the emetogenicity of the combination of antineoplastic agents rather than on the emetogenicity of the most highly emetogenic agent in the combination.

Administration of both ondansetron and dexamethasone to children receiving highly emetogenic antineoplastic agents would likely have improved emetic control. However, our hematologists and oncologists are apparently reluctant to prescribe dexamethasone for this purpose. Dexamethasone was given on a total of 9 study days: 7 study days during moderately emetogenic therapy and 2 study days during therapy of low emetogenicity. The explanations for this reluctance may include:

- the risk of serious, nonreversible morbidity associated with the use of adrenocorticosteroids;
- the potential influence of dexamethasone on the clinical response of the underlying leukemia; and
- the potential effect of dexamethasone on the pharmacokinetics or pharmacodynamics (or both) of the antineoplastics given concurrently.

Certainly the biological effects of adrenocorticosteroids are far-reaching. Most feared perhaps are the effects of these agents on bone, since they may lead to significant disability. We have observed osteonecrosis in 4.4% of children with acute lymphoblastic leukemia receiving prednisone and dexamethasone as part of their treatment protocol.[6] Concurrent administration of a second corticosteroid may increase the risk of toxic effects.

Corticosteroids have cytotoxic activity and for this reason are integral to the therapy of acute lymphoblastic leukemia. In vitro studies with leukemic cell lines indicate that these agents induce apoptosis.[7] Exposure to corticosteroids may select steroid-resistant clones or lead to down-regulation of the glucocorticoid receptors and thus may create steroid-resistant disease, at least temporarily.[8] The impact of the use of dexamethasone as an antiemetic on the outcome of patients or on long-term sequelae has not been determined.

Investigations of the impact of corticosteroids on the pharmacokinetic disposition of antineoplastics are also lacking. The conversion of cyclophosphamide to its active metabolite may be affected by corticosteroids, but data are conflicting and the clinical impact of this purported interaction has not been determined.[9] Dexamethasone has been shown to interfere with the cytotoxic and antiproliferative actions of several antineoplastic agents on cultured malignant glioma cells.[10] Mechanisms for this interaction include the production of subcellular resistance as well as a reduction in the distribution of the antineoplastic agents to the tumour through the effects of dexamethasone on the

blood–brain barrier and edema. In summary, it seems reasonable to reserve dexamethasone for those children with acute lymphoblastic leukemia in whom the benefits outweigh the known risks, that is, for those children who are receiving very highly emetogenic antineoplastic regimens and for those in whom emetic prophylaxis without dexamethasone has failed in prior treatment cycles.

Although the antiemetics administered in this study controlled vomiting in most cases, the children in whom prophylaxis failed were not adequately identified or treated. Central to improvement in the control of antineoplastic-induced nausea and vomiting is the education of children and their families about what can be reasonably expected with respect to the degree, duration, and severity of nausea and vomiting. Several parents of children enrolled in this study accepted their children's severe vomiting as an inevitable effect of therapy that could be neither prevented nor treated. Treatment or more effective antiemetic prophylaxis were therefore not requested. Nurses, physicians, and pharmacists must also be educated regarding the limits of tolerance of nausea and vomiting. Appreciation of the extent of a child's nausea and the need to respond are especially important.

Conversely, children who received antineoplastic regimens of low emetogenicity received ondansetron on 32% of study days. Some of these children may well have vomited during previous cycles of low emetogenicity and therefore deserved to receive antiemetics with subsequent cycles. However, many parents and children expect to receive antiemetics with every antineoplastic cycle, regardless of its emetogenic potential. Caregivers must ensure that parents and children understand that all antineoplastic agents do not cause vomiting so that children do not receive antiemetics unnecessarily.

In many cases of breakthrough nausea and vomiting, no additional support was provided or dimenhydrinate was given. Antihistamines such as dimenhydrinate do little to prevent or treat antineoplastic-induced vomiting.[11,12] Caregivers must have specific, effective management strategies when first-line antiemetics fail. The addition of lorazepam or scopolamine (or both) has been recommended for the treatment of breakthrough vomiting, despite the lack of documentation to support their use for this purpose.[13] Administration of antiemetics usually reserved for antineoplastics of higher emetogenic potency has also been recommended.[14] Further investigation in this area is required to identify appropriate treatment.

A small proportion of children (15%) enrolled in our study reported symptoms of anticipatory nausea and vomiting. Other investigators have reported anticipatory nausea and vomiting in up to 59% of children undergoing antineoplastic treatment.[15] In our study, the presence of anticipatory nausea and vomiting was associated with a higher rate of antiemetic failure. To address this situation, children should be specifically questioned before each antineoplastic course about symptoms of anticipatory nausea and vomiting. Those who experience such symptoms should be offered management strategies aimed at controlling both anticipatory and antineoplastic-induced nausea and vomiting. Unfortunately, evidence regarding specific, effective interventions is lacking. Lorazepam has been recommended for this purpose despite the lack of documentation of its efficacy.[4,13] Improved control of post-antineoplastic nausea and vomiting may well decrease the incidence of anticipatory nausea and vomiting.[16]

The adverse effects reported by children and their parents in this study are similar to those reported by others for children who received ondansetron-based antiemetic regimens.[17-19] Given the large number of drugs given concurrently to these children and their underlying illnesses, it is impossible to determine the cause of the adverse effects reported.

Despite considerable recent improvement in its control, antineoplastic-induced vomiting continues to be ranked by adult cancer patients as among the most distressing adverse effects of therapy.[20] Although no specific evidence exists, it is likely that the opinions and experience of children are similar. Our results indicate that compliance with the 1994 antiemetic selection guidelines of The Hospital for Sick Children was poor and the overall emetic response of our patients was lower than that reported in other centres. Adjustment of our emetogenicity classification, standardization of our antiemetic selection process, and the development of effective management approaches for anticipatory and breakthrough nausea and vomiting will improve the experience of our patients. Children receiving highly emetogenic antineoplastic regimens must be specifically targeted for further study. Guidelines at our institution have been revised on the basis of these observations. The full extent of their effectiveness can only be assessed if the guidelines are vigorously promoted and compliance is achieved. The effectiveness of these guidelines as well as management strategies for anticipatory and breakthrough emesis must be rigorously evaluated.

References

1. Dupuis L, Chan HSL, Lacey C, McBride J. The management of chemotherapy-induced nausea and vomiting in children. *Can J Hosp Pharm* 1986;39:38-40.
2. Wong D, Baker C. Pain in children: comparison of assessment scales. *Pediatr Nurs* 1988;14:9-17.
3. Nolte MJ, Berkery R, Pizzo B, Baltzer L, Grossano D, Lucarelli CD, et al. Assuring the optimal use of serotonin antagonist antiemetics: the process for development and implementation of institutional antiemetic guidelines at Memorial Sloan-Kettering Cancer Center. *J Clin Oncol* 1998;16:771-8.
4. Foot ABM, Hayes C. Audit of guidelines for effective control of chemotherapy and radiotherapy induced emesis. *Arch Dis Child* 1994;71:475-80.
5. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;15:103-9.
6. Murphy RG, Greenberg ML. Osteonecrosis in pediatric patients with acute lymphoblastic leukemia. *Cancer* 1990;65:1717-21.
7. Gaynon PS, Lustig RH. The use of glucocorticoids in acute lymphoblastic leukemia of childhood: molecular, cellular, and clinical considerations. *J Pediatr Hematol Oncol* 1995;17:1-12.
8. Ito C, Evans W, McNinch L, Coustan-Smith E, Mahmoud H, Pui C-H, et al. Comparative cytotoxicity of dexamethasone and prednisolone in childhood acute lymphoblastic leukemia. *J Clin Oncol* 1996;14:2370-6.
9. Faber OK, Mouridsen HT. Cyclophosphamide activation and corticosteroids [letter]. *New Engl J Med* 1974;291:211.
10. Weller M, Schmidt C, Roth W, Dichgans J. Chemotherapy of human malignant glioma: prevention of efficacy by dexamethasone? *Neurology* 1997;48:1704-9.
11. Moertel CG, Reitemeier RK, Gage RP. A controlled clinical evaluation of antiemetic drugs. *JAMA* 1963;186:116-8.
12. Morran C, Smith DC, Anderson DA, McArdle CS. Incidence of nausea and vomiting with cytotoxic chemotherapy: a prospective randomised trial of antiemetics. *BMJ* 1979;1:1323-4.
13. Billett AL, Sallan SE. Antiemetics in children receiving cancer chemotherapy. *Support Care Cancer* 1994;2:279-85.
14. Osoba D, Warr DG, Fitch MI, Nakashimia L, Warren B. Guidelines for the optimal management of chemotherapy-induced nausea and vomiting: a concensus. *Can J Oncol* 1995;5:381-400.
15. Tyc VL, Mulhern RK, Barclay DR, Smith BF, Bieberich AA. Variables associated with anticipatory nausea and vomiting in pediatric cancer patients receiving ondansetron antiemetic therapy. *J Pediatr Psychol* 1997;22:45-58.
16. Morrow GR, Roscoe JA, Hickok JT, Stern RM, Pierce HI, King DB, et al. Initial control of chemotherapy-induced nausea and vomiting in patient quality of life. *Oncology* 1998;12 (Suppl 4):32-7.
17. Alvarez O, Freeman A, Bedros A, Call SK, Volsch J, Kalbermatter O, et al. Randomized double-blind crossover ondansetron-dexamethasone versus ondansetron-placebo study for the treatment of chemotherapy-induced nausea and vomiting in pediatric patients with malignancies. *J Pediatr Hematol Oncol* 1995;17:145-50.
18. Brock P, Brichard B, Rechnitzer C, Langeveld NE, Lanning M, Soderhall S, et al. An increased loading dose of ondansetron: a northern European, double-blind randomised study in children, comparing 5 mg/m² with 10 mg/m². *Eur J Cancer* 1996;32A:1744-8.
19. Stevens R, Voltan B, Lane R, Schaison G. A randomized study of ondansetron syrup in children: evaluation of taste acceptability and tolerance. *Pediatr Hematol Oncol* 1996;13:199-202.
20. de Boer-Dennert M, de Wit R, Schmitz PIM, Djontono J, Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer* 1997;76:1055-61.

L. Lee Dupuis, MScPhm, FCSHP, is Manager, Clinical Services, Research and Education, Department of Pharmacy, The Hospital for Sick Children, and Assistant Professor, Faculty of Pharmacy, University of Toronto, Toronto, Ont.

Robert Lau, MB, BS, FRCPC, is Staff Oncologist, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ont.

Mark L. Greenberg, MB, ChB, FRCPC, FAAP, is Senior Staff Oncologist, Division of Haematology/Oncology, The Hospital for Sick Children, and Professor of Pediatrics and Surgery, Faculty of Medicine, University of Toronto, Toronto, Ont.

Address correspondence to:
Lee Dupuis
Department of Pharmacy
The Hospital for Sick Children
555 University Avenue
Toronto ON
M5G 1X8
e-mail: lee.dupuis@sickkids.on.ca

Acknowledgements
The assistance of Deborah Chong with data collection is acknowledged. Funding for this study was provided by the CSHP Research and Education Foundation.