CLINICAL PRACTICE GUIDELINES

Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients

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This guideline provides an approach to the prevention and treatment of anticipatory chemotherapy-induced nausea and vomiting (CINV) in children. It was developed by an international, inter-professional panel using AGREE II methods and is based on systematic literature reviews. Evidence-based recommendations for pharmacological and non-pharmacological interventions to prevent and treat anticipatory CINV in children receiving antineoplastic agents are provided. Gaps in the evidence used to support the recommendations are identified. The contribution of this guideline to anticipatory CINV control in children requires prospective evaluation. Pediatr Blood Cancer 2014;61:1506–1512. © 2014 Wiley Periodicals, Inc.

Key words: antineoplastic agents; nausea; supportive care; vomiting

INTRODUCTION

Cancer patients who have received chemotherapy may experience nausea and vomiting in anticipation of chemotherapy administration. Evaluations of anticipatory chemotherapy-induced nausea and vomiting (CINV) have described its prevalence during widely variable time periods prior to therapy; focused on either nausea or vomiting but not both; evaluated patients at different time points during the entire treatment course; and have employed different instruments for its measurement. This variability has led to reports of widely ranging prevalence rates. The ability to accurately capture the prevalence of anticipatory CINV in children is further compounded by the use of parent or care-giver proxy report of nausea and use of non-validated nausea assessment tools. However, when anticipatory CINV was evaluated longitudinally in patients receiving 5-HT3 antagonists and corticosteroids as antiemetic agents, approximately one-third of adults experienced anticipatory CINV while anticipatory chemotherapy-induced vomiting (CIV) was reported in 6–11% [1,2].

This guideline is presented with the intention of providing clinicians caring for children 1 month to 18 years of age who are receiving antineoplastic medication with an approach to the prevention and treatment of anticipatory CINV. For the purpose of this guideline, optimal anticipatory, acute, and delayed phase CINV control is defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for CINV prevention or treatment and no nausea-related change in the child’s usual appetite and diet. This level of anticipatory CINV control is to be achieved during the 24 hours prior to administration of the first antineoplastic agent of the upcoming planned antineoplastic block.

This guideline is the third in a series of guidelines to address the need for and the selection of, antiemetic prophylaxis and intervention in children with cancer receiving antineoplastic therapy. Summaries of the first two guidelines, the Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients and the Guideline for the Prevention of Acute Nausea and Vomiting Due to Antineoplastic Medication in Pediatric Cancer Patients, have been published [3,4] and all three complete guidelines are available on the POGO website at: http://www.pogo.ca/healthcare/practice-guidelines/.

METHODS

Guideline Development Group

The Pediatric Oncology Group of Ontario (POGO) is a collaboration of the five pediatric oncology programs in Ontario, Canada. Members of the POGO CINV Guideline Development Panel were selected with a view to obtain inter-professional representation from within POGO and from internationally recognized experts in pediatric CINV and/or supportive care.

Source Guideline Selection

During August and September 2012, a systematic search of bibliographic databases and the gray literature was conducted to identify existing practice guidelines for the management of anticipatory CINV in adults or children with cancer which addressed the health questions (Table I) created to frame the development of this guideline and which could be adapted to the POGO context. Computerized searches were performed with

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1. What approaches are recommended to prevent the development of anticipatory chemotherapy-induced nausea and vomiting (CINV) in children?

Recommendation 1.1: Control of acute and delayed CINV should be optimized for each child in order to minimize the risk of the child developing anticipatory CINV.

Strength of recommendation: Strong
Level of evidence: Low

2. What interventions are recommended to control anticipatory CINV in children who develop it?

Recommendation 2.1: We suggest that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV.

Strength of recommendation: Weak
Level of evidence: Low

Recommendation 2.2: We suggest that lorazepam in a dose of 0.04–0.08 mg/kg/dose (maximum: 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children.

Strength of recommendation: Weak
Level of evidence: Very low

Decisions were taken through panel discussions and any differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the GRADE system [5,6] by one author (L.D.) and confirmed through discussion by the remaining panel members. In the GRADE system, the quality of evidence is categorized as high, moderate, or low based upon methodological considerations. Strength of recommendations may be either strong or weak depending on the balance of risks and benefits and the degree of uncertainty around these estimates.

External Review and Consultation Process

The draft guideline underwent an extensive two-stage external review: first by international experts in adult and pediatric CINV and then by stakeholders from the Ontario pediatric oncology community. Nine content experts provided a review, eight of whom completed the survey; their comments were discussed in detail by the panel and a decision on each point was taken by consensus. Twenty-five stakeholder responses were received. No changes were made to the recommendations based on the stakeholders’ comments. However, guideline wording was clarified. The panel’s responses to all comments received during both stages of external review are available in the full on-line guideline.

RESULTS

The search for practice guidelines yielded 693 citations that were screened for inclusion. Nine guidelines [7–15] that were either developed for use in adults and/or for use in children met the inclusion criteria and were assessed using the AGREE II instrument. None of the highest scoring guidelines [8,14,15] were selected for adaptation, given both their adult-focus and the differences among them regarding recommendations for use of benzodiazepines and non-pharmacological interventions.

A total of 1,586 references were identified from the electronic database search for primary studies of interventions to prevent or treat anticipatory CINV. One hundred and thirteen papers were retrieved for full-text screening. Eleven studies met the inclusion criteria (Fig. 1).
The same 1,586 citations were screened for relevancy regarding the prevalence of anticipatory CINV before and after the introduction of 5-HT3 antagonist agents. One hundred ten papers were retrieved for full-text screening. Fifty studies, reported in 58 papers, met the inclusion criteria (Fig. 2).

**Literature Review**

1. What approaches are recommended to prevent the development of anticipatory CINV in children?

Recommendation 1.1: Control of acute and delayed CINV should be optimized for each child in order to minimize the risk of the child developing anticipatory CINV (strong recommendation, low quality evidence).

This recommendation places a high value on complete control of CINV across all phases (anticipatory, acute, and delayed). It is a strong recommendation because patients who experience CINV control are likely to have an improved quality of life and less distress [16–19]. Furthermore, use of guideline-informed antiemetic prophylaxis is unlikely to lead to significant adverse effects.

Anticipatory CINV appears to be a conditioned response to CINV experienced in the acute (24 hours following administration of chemotherapy) and delayed (more than 24 hours after and within 7 days of administration of chemotherapy) phases [20–26]. The anxiety and distress attendant to CINV may serve to reinforce the conditioned response [22,23]. It follows, therefore, that a higher rate of complete acute and delayed CINV control would result in lower rates of anticipatory CINV. Acute CINV control in children remains sub-optimal even when guideline-recommended antiemetic prophylaxis is provided [4,27]. It is therefore likely that children continue to experience anticipatory CINV. However, the available studies evaluating acute and delayed CINV control as a risk factor for anticipatory CINV in children are few and contradictory.

Studies which evaluate the prevalence of anticipatory CINV in adult patients who received treatment before and after the introduction of 5-HT3 antagonists are summarized in Supplementary Table I. Study design, sample size, populations, and prophylactic antiemetic regimens vary widely. In addition, study endpoints and the level of acute CINV prophylaxis provided are often not explicitly stated. Given the heterogeneity of studies, synthesis of these studies in a meta-analysis was not possible.

In the pre-5HT3 antagonist era, the reported prevalence of anticipatory chemotherapy-induced nausea (CIN) in adults ranged from 9% [28] to 65% [29] while that of anticipatory AIV ranged from 0% [30,31] to 33% [32]. In each study where the prevalence of both CIN and CIV were reported, the prevalence of CIN was higher than CIV. In the post-5HT3 antagonist era, the reported prevalence of anticipatory CIN in adults ranged from 6% [33] to 43% [34] while that of anticipatory AIV ranged from 4% [35] to 11% [2]. Again, the reported prevalence of CIN was always higher than the prevalence of CIV. Thus, the reported prevalence rates of anticipatory CIN and CIV in the post-5HT3 antagonist era compared to the pre-5HT3 antagonist era have widely overlapping ranges.

Pediatric studies which describe the prevalence of anticipatory CINV (Supplementary Table II) vary not only in the features listed earlier with respect to adult prevalence studies but also in the
methods used to evaluate the presence or severity of nausea. Of the 11 available pediatric studies, nausea severity was determined by child or parent report (five studies); [36–40] child report (four studies); [21–23,41–43] by child, parent or nurse report (one study); [44] or by parent or guardian report (one study) [45]. None of the studies where the child reported the severity of their nausea used a validated pediatric nausea assessment tool. The pediatric studies are also limited by their small sample size (median sample size: 52; range: 19–150).

A single group of investigators has evaluated anticipatory CINV in children in the pre-5HT3 antagonist era. Dolgin et al. reported anticipatory CIN in 29% of children (23/80) and anticipatory AIV in 20% (16/80) who had received 11 cycles of antineoplastic therapy, on average, before evaluation [36]. The same investigators observed anticipatory CINV in 13% (12/94) in another group of children 7 months after diagnosis [37]. In the post-5HT3 era, the reported prevalence of anticipatory CIN in children ranges from 0% [39] to 59% [22,23]. Similar to observations in adult patients, the reported prevalence of CIN was always higher than that of CIV, with one exception: Stockhorst et al. [21] report an equivalent prevalence (26%; 5/19) of CIN and CIV.

In conclusion, it is not clear that the use of 5HT3 antagonists and the presumed resulting improvements in acute CINV control have led to improved control of anticipatory CINV. However, the inconsistent approach to measurement of anticipatory CIN and AIV and the use of unvalidated instruments preclude comparison of results across studies. Furthermore, no study directly evaluated the relationship between acute CINV control itself and anticipatory CINV control. The applicability of the results of these studies to patients receiving modern, guideline-consistent antiemetic prophylaxis is also unclear. The strength of the relationship between anticipatory CINV control and acute CINV control in the setting of modern, guideline-informed antiemetic prophylaxis is therefore uncertain.

Adherence to evidence-based guideline recommendations regarding CINV prevention has been shown to substantially improve complete acute CINV control [46,47]. Given that anticipatory CINV appears to be a conditioned response, optimization of acute and delayed CINV control may help to minimize exposure to the negative stimuli required for conditioning to occur. The guideline development panel therefore recommends that clinicians select antiemetic interventions using guidelines such as the POGO Guideline for the Prevention of Acute CINV in Children Receiving Antineoplastic Agents [4,27] for antineoplastic agent-naive patients. Once antineoplastic therapy has been initiated, the selection of antiemetic interventions should be informed by evidence-based guidelines and tailored based on the extent of CINV control experienced by the patient as well as any adverse effects associated with antiemetic agents.

2. What interventions are recommended to control anticipatory CINV in children who develop it?

Recommendation 2.1: We suggest that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV. (weak recommendation; low quality evidence)

Recommendation 2.2: We suggest that lorazepam in a dose of 0.04–0.08 mg/kg/dose (maximum: 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children. (weak recommendation; very low quality evidence)

Recommendation 2.1 places a high value on the possible improvement in anticipatory CINV control and the lack of harm conveyed by the recommended interventions. It is a weak recommendation because of concerns regarding the lack of standard and distinct methodologies for many of these interventions, the applicability of the evidence base underpinning the recommendation in patients receiving modern guideline-consistent antiemetic prophylaxis and the additional resources required for its implementation. Systematic desensitization is recommended based on the experience in adults. Recommendation 2.2 places a high value on the possible improvement in anticipatory CINV control and the evidence of efficacy of benzodiazepines in adult cancer patients. It is a weak recommendation because direct evidence of lorazepam efficacy at this dose and frequency in children is lacking. Furthermore, there are concerns regarding the applicability of this recommendation to patients receiving modern, guideline-consistent antiemetic prophylaxis.

Two pediatric and nine adult studies met the criteria for inclusion in the evidence base that informed the recommendations formulated by the panel (Supplementary Table III). In keeping with the theory that anticipatory CINV is a conditioned response to CINV experienced in the acute and delayed phases, the majority of these studies (8/11) evaluated psychological interventions. Hypnosis was the most common intervention (4/8) evaluated and was the only intervention studied in children. Systematic desensitization is a strategy where the conditioned behavior is thought to be reciprocally inhibited by a state of induced progressive muscle relaxation. For example, when in a state of deep relaxation, patients imagine situations which elicit adverse sensations of increasing intensity. They then imagine that the situation dissolves and floats away. In adult cancer patients, systematic desensitization has been associated with a significantly higher rate of complete anticipatory CINV control compared to interventions such as relaxation alone, counseling, or usual care [48–50]. No pediatric study of systematic desensitization met criteria for inclusion in the evidence base to inform this recommendation. Pediatric studies of hypnosis are summarized here.

Hypnosis. Hypnosis has been defined as an intervention that “provides suggestions for changes in sensation, perception, cognition, affect, mood, or behavior” [51]. Interestingly, the two randomized trials of interventions aimed at controlling anticipatory CINV were both pediatric trials and both evaluated hypnosis [39,52]. Zeltzer et al. [52] recruited 54 children 5–17 years of age who had reported experiencing anticipatory CIN and/or CIV in a previous study and who were about to receive at least two identical antineoplastic treatment courses. On average, children were 15.8 months (range: 0.5–118 months) from their cancer diagnosis at the time of the study. The control group had received antineoplastic therapy for much longer than the other two groups (29.5 months vs. 8 or 11.5 months). Although it is not possible to precisely ascertain the emetogenicity of the antineoplastic therapy that children received, it appears that most received highly emetogenic treatment as assessed by the POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients [3,53]. The antiemetic agents received for CINV prophylaxis were not reported but children’s antiemetic regimens were unchanged during the trial. CINV severity was assessed through semi-structured interviews of the child. Children were
randomized to receive one of three possible interventions: hypnosis training (imagination-focused therapy), active cognitive distraction (relaxation), or contact with a therapist (control). The authors report a significant improvement in complete control of anticipatory CINV in the group who received hypnosis training [57% (12/21) at baseline vs. 86% (18/21) after hypnosis training; \( P < 0.05 \)]. Complete control of anticipatory CINV increased from 24% (5/21) at baseline to 38% (8/21) after hypnosis training.

Jacknow et al. [39] evaluated hypnosis as a means of preventing anticipatory CINV in 20 children 6–18 years old who were naïve to chemotherapy. Controls were matched for age (±3 years) and the emetogenicity of their antineoplastic treatment. Insufficient information is available to determine the emetogenicity of the antineoplastic regimens. Children randomized to receive hypnosis did not receive antiemetic prophylaxis but received antiemetic agents as needed. Children in the control group received standard antiemetic prophylaxis for 4–6 hours after antineoplastic therapy. Ondansetron was given to more children in the control group (7/10 vs. 3/10). Children randomized to receive hypnosis were taught self-hypnosis during the initial antineoplastic treatment; children in the control group spent equivalent time in conversation with a therapist. CINV was assessed by means of a daily structured interview of the child. The presence of anticipatory CINV was assessed at 1–2 months, and at 4–6 months after diagnosis. At the time of first assessment of anticipatory CINV, children who had been taught self-hypnosis reported significantly less anticipatory CIN than did the control group although the incidence is not reported. The rate of anticipatory CIV was identical in each group (1/10). By the time of the second assessment, there was no difference in the rate of anticipatory CIN between the groups. The rate of anticipatory CIV was also similar between the groups (hypnosis: 0/10 vs. control: 2/10).

**Pharmacological interventions.** Pharmacological interventions that have been evaluated for the treatment of anticipatory CINV are few and are limited to benzodiazepines. No pediatric trials of the use of pharmacological treatments of anticipatory CINV met our criteria for inclusion. Since patients who experience anticipatory CINV have been observed to be more anxious than patients who do not experience anticipatory CINV [54], the use of anxiolytic agents in this setting seems reasonable. Three studies in adults (two randomized trials) have evaluated the contribution of benzodiazepines as a treatment of anticipatory CINV [55–57].

Lorazepam 2 mg by mouth the night before antineoplastic treatment, the morning of treatment and at bedtime for the next 5 days or placebo was given to adult cancer patients over 180 antineoplastic treatment courses containing cisplatin [55]. Patients also received metoclopramide 2 mg/kg/dose, clemastine and dexamethasone for antiemetic prophylaxis. At the time of randomization, approximately two-thirds of patients were naïve to antineoplastic agents. Anticipatory CINV was defined as nausea and/or vomiting that occurs within 12 hours prior to antineoplastic therapy or 1 hour after the start of antineoplastic therapy. A significantly higher proportion of treatments where lorazepam was given were associated with complete anticipatory CINV control compared to the control group (52 vs. 32%; \( P < 0.05 \)). Few adverse effects were attributed to lorazepam; mild sedation occurred in 76% of the treatments where lorazepam was given and 32% of the control treatments. Patients were entered into this trial more than once and were randomized independently at each entry. The experience of individual patients longitudinally over time or the effect of receipt of lorazepam/placebo during previous study enrollments on study outcomes was not described.

Women with breast cancer naïve to antineoplastic treatment were enrolled in a double-blind, placebo-controlled trial comparing the incidence of anticipatory CINV after relaxation training plus either alprazolam (29 patients) or placebo (28 patients). Alprazolam 0.25 mg or placebo was given twice daily by mouth for 6–12 months. Triazolam was also given on an as needed basis to patients in both study arms to manage insomnia. The proportion of patients who experienced complete control of anticipatory CIN and CIV before the fourth antineoplastic treatment was similar in both study arms (26% vs. 25% and 4% vs. 0%, respectively).

Diazepam 5 mg twice daily was given to 29 adult cancer patients with anticipatory CINV for 3 days before each of four consecutive antineoplastic treatment courses [57]. Thirteen patients (45%) experienced complete CINV control at some time over the four antineoplastic treatment courses.

**Conclusions.** While the improvement in complete anticipatory CINV control provided by psychological interventions such as hypnosis or systematic desensitization may not be dramatic, these interventions may convey benefit to individual patients with minimal risk. For this reason, the guideline development panel recommends that it be offered to age-appropriate patients who experience anticipatory CINV where the expertise and resources exist to deliver these interventions.

Despite the lack of evidence to support the use of benzodiazepines for the treatment of anticipatory CINV in children, the guideline development panel acknowledged the experience with benzodiazepines in adults. The panel’s choice of lorazepam as the recommended benzodiazepine in children with anticipatory CINV was based on the greater overall experience with lorazepam in the pediatric oncology setting [58–61] compared to alprazolam and diazepam. The recommended initial lorazepam dose was based on current pediatric dosing recommendations with the usual adult dose as the maximum dose [62]. This dose should be titrated to the needs of each child. For example, if this dose is associated with an unacceptable degree of sedation, lower doses are recommended for subsequent antineoplastic blocks. It is the opinion of the guideline development panel that the duration of benzodiazepine administration in the three adult trials above (3 days, 6 days and continuously) was longer than would be acceptable for children. The recommended lorazepam dosing schedule was based on the NCCN Antiemesis Guideline [63].

**RESEARCH GAPS**

The published literature describing the prevalence of anticipatory CINV in children and the risk factors associated with it is very limited. Much of it may no longer be relevant due to the evolution of more effective antiemetic strategies to prevent acute CINV and newly available tools to evaluate nausea severity by children. The prevalence of anticipatory CINV and risk factors for its development in children must be systematically evaluated across the spectrum of common antineoplastic regimens using validated child self-report measures of nausea severity and modern, guideline-directed antiemetic interventions. Similarly, the efficacy of both new and old interventions aimed at managing anticipatory CINV must be prospectively and rigorously evaluated. In particular, the optimal pediatric dose and dosing schedule of lorazepam needs to

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be determined to ensure optimal anticipatory CINV control (Table II).

**CONCLUSIONS**

Recommendations aimed at preventing and treating anticipatory CINV in children 1 month to 18 years of age who are receiving antineoplastic treatment are presented in Table I. We encourage individual clinicians and institutions to adapt these recommendations to their local context and to periodically audit adherence to the recommendations and the extent of anticipatory CINV control in their population.

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