Nausea and Vomiting

10

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Contents

10.1 **Introduction** 160

10.2 **Chemotherapy-Induced Nausea and Vomiting (CINV)** 160
10.2.1 Pathophysiology of Emesis 160
10.2.2 Principles of Emesis Control in the Cancer Patient 161
10.2.3 Emetogenicity of Chemotherapy 161
10.2.4 Classes of Antiemetics 163
10.2.5 Recommendations for Prevention and Treatment of CINV 169

10.3 **Radiation-Induced Nausea and Vomiting** 172

10.4 **Summary** 172

References 172

Abstract

Nausea and vomiting induced by antineoplastic therapy can significantly affect quality of life and continues to be a prevalent and distressing treatment-related issue faced by children with cancer and their families. Chemotherapy-induced nausea and vomiting (CINV) can result in metabolic derangements, nutritional depletion and anorexia, esophageal tears, deterioration of mental and performance status, prolonged hospitalizations, and potential poor compliance or withdrawal from anticancer treatment. Despite advances in pharmacologic and nonpharmacologic management of nausea and vomiting, prevention of CINV remains a particular issue in the pediatric population where existing guidelines are constrained by lack of robust evidence. Few studies have been carried out in children, and results obtained in adults cannot be directly applied to young children since metabolism and side effects of drugs differ. The pathophysiology of CINV, principles of antiemetic prophylaxis, emetogenicity of chemotherapy, classes of antiemetic agents, and current guidelines for prevention and treatment of CINV in children are addressed in this chapter. Specific attention is also given to nonpharmacologic strategies and approaches to anticipatory, breakthrough, and radiation-induced nausea and vomiting. This chapter provides health care providers with a summary of evidence-based information with the goal of

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J. Feusner et al. (eds.), *Supportive Care in Pediatric Oncology: A Practical Evidence-Based Approach*, Pediatric Oncology,
DOI 10.1007/978-3-662-44317-0_10, © Springer Berlin Heidelberg 2015

guiding optimal emetic control in pediatric cancer patients.

10.1 Introduction

Chemotherapy-induced nausea and vomiting (CINV) are two of the most prevalent and distressing adverse effects reported among children before, during, and after chemotherapy, with frequency reports of 20–80 % noted in the literature (Rodgers et al. 2012). CINV can significantly affect quality of life, result in metabolic imbalances, malnutrition, anorexia, decline of performance and mental status, prolonged hospitalizations, and potential discontinuation of subsequent chemotherapy cycles (Laszlo 1983; Richardson et al. 1988; Mitchell 1992). This can result in suboptimal cancer therapy and reduced survival. Additionally, chronic nausea and vomiting can occur in advanced cancer patients or patients receiving radiation therapy and may be due to gastrointestinal (GI), cranial, metabolic and drug induced-problems (Schwartzberg 2006). The incidence and severity of nausea or vomiting in patients receiving chemotherapy or radiation therapy are affected by numerous factors, including type, dose and schedule of chemotherapy, target of radiation therapy (i.e., whole body, abdomen, brain), and individual patient variability based on age, gender, or prior chemotherapy (Herrstedt 2008). Compared to adult data, there are a paucity of randomized clinical trials investigating newer antiemetic agents in pediatric cancer patients. Furthermore, recognition of symptom severity continues to be an issue as parents and health care providers tend to underestimate the occurrence of delayed nausea and vomiting (Tyc et al. 1993; Small et al. 2000). Recent evidence-based guidelines have been published to provide recommendations for antiemetic prophylaxis according to the emetogenic potential of antineoplastic therapies in pediatric patients (Basch et al. 2011; Dupuis et al. 2011; Jordan et al. 2011; Dupuis et al. 2013). Progress in relieving the symptoms of CINV will require further education of oncology physicians and nurses, aggressive use of current medications, and continued development of pharmacologic and alternative therapies for children.

10.2 Chemotherapy-Induced Nausea and Vomiting (CINV)

CINV is commonly classified as acute, delayed, anticipatory, breakthrough and refractory. Although there are no standard definitions, the following are commonly used to classify the different types of CINV (Wickham 1999):

- *Acute*: Occurs within a few minutes to several hours after drug administration and commonly resolves within the first 24 h. The intensity of acute CINV typically peaks after 4–6 h.
- *Delayed*: Arises >24 h after chemotherapy administration. Delayed CINV commonly occurs following cisplatin, carboplatin, cyclophosphamide and anthracyclines. For cisplatin, emesis reaches its maximal intensity 48–72 h after administration, but can last for 1 week.
- *Anticipatory*: Usually develops in patients who have previously experienced significant CINV as a conditioned response (Morrow 1984). Symptoms occur prior to chemotherapy administration and may be triggered by stimuli such as the smells, sights and sounds of the treatment room.
- *Breakthrough*: Breakthrough CINV results despite prophylactic treatment and requires "rescue" with additional antiemetic agents (Roila et al. 2006).
- *Refractory*: Emesis that takes place in subsequent treatment cycles when antiemetic prophylaxis and rescue have failed in prior cycles.

10.2.1 Pathophysiology of Emesis

The neurophysiologic mechanisms that control nausea and vomiting are fairly well characterized. Nausea is mediated through the autonomic nervous system. Vomiting results from the stimulation of a complex reflex that is coordinated by a putative true vomiting center, which may be located in the dorsolateral reticular formation near the medullary respiratory centers. The vomiting center receives afferent input from four neuronal pathways that carry emetogenic signals: (1) the chemoreceptor trigger zone (CTZ), (2) peripheral stimuli from the gastrointestinal tract via vagus and

splanchnic nerves, (3) cortical pathways in response to sensory or psychogenic stimuli, and (4) the vestibular-labyrinthine apparatus of the inner ear in response to body motion (Carpenter 1990).

The CTZ, located in the area postrema in the floor of the fourth ventricle, lacks a true blood-brain barrier (Miller and Leslie 1994). This allows the CTZ to sense fluctuations in the concentration of certain substances in the bloodstream, including chemotherapy and its metabolites. Several receptors have been identified in the CTZ including muscarinic, dopamine D_2, serotonin (5-HT_3), neurokinin-1 (NK_1) and histamine H_1 receptors (Dodds 1985). The CTZ may also be stimulated by posterior fossa tumors.

The emetic center (EC), located in the nucleus tractus solitarii of the brainstem, coordinates afferent pathways from the GI tract via the vagus and splanchnic nerves. Nausea may be elicited through gut irritation from medications, tumor infiltration, obstruction, distension or constipation. The EC also coordinates the efferent activities of the salivation center, abdominal muscles, respiratory center and autonomic nerves that result in vomiting (Miller and Leslie 1994). The phenomenon of anticipatory emesis suggests that inputs from the cerebral cortex may be involved. CNS or meningeal tumors, increased intracranial pressure, anxiety or uncontrolled pain can also result in cortically induced nausea and vomiting.

Current findings indicate that acute emesis following chemotherapy is initiated by the release of neurotransmitters from cells that are susceptible to the presence of toxic substances in the blood or CSF. The most critical and clinically relevant neuroreceptors involved are serotonin, dopamine and substance P. The significant advancement in antiemetic therapy came in the early 1990s when 5-HT_3 receptor antagonists became available (Jordan et al. 2007). Substance P, which binds to the NK_1 receptor, is a newer target in antiemetic therapy, and the NK_1 receptor antagonist aprepitant has demonstrated clinical utility in the pediatric population (Choi et al. 2010).

The exact mechanism by which chemotherapy and its metabolites induce emetic effects is unclear. Metabolites may directly stimulate the CTZ and serotonin, and other neurotransmitters may be released from intestinal enterochromaffin cells damaged by chemotherapy. Sensory neurons release substance P, and a number of NK_1 receptors have been identified in both the CTZ and EC. The relative contribution from these multiple pathways culminating in CINV is complex and likely accounts for the variable emetogenic profile of agents. As there is no single common pathway controlling emetic response, it is unlikely that any single agent will be able to provide complete antiemetic protection from chemotherapy.

10.2.2 Principles of Emesis Control in the Cancer Patient

The most important principle in managing CINV is the *prevention* of nausea and vomiting. The risk of CINV in patients receiving moderate to high emetogenic chemotherapy persists for at least 2–3 days after the final dose of chemotherapy, and prophylactic therapy should be given during the full period of risk (Grunberg et al. 2004). Antiemetics should be given at the minimal efficacious dose with consideration of their side effect profiles as well as the patient's prior history with specific antiemetics. Consider the use of an H_2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea. Finally, lifestyle measures such as eating small, frequent and healthy meals may help alleviate CINV.

10.2.3 Emetogenicity of Chemotherapy

Although patient factors are important, the specific chemotherapeutic agents used are most predictive of CINV risk. Several classifications have been developed to define the emetogenicity of chemotherapy; Hesketh et al. (1997) developed a widely accepted classification system for adults that divides chemotherapy into five levels of emetogenicity based on the percentage of patients experiencing CINV following administration of each particular agent without any antiemetic prophylaxis. This classification was recently updated by Grunberg et al. (2010) and has been

Table 10.1 Acute emetic potential of antineoplastic agents in pediatric cancer patients[a]

High risk (>90 % frequency of emesis in the absence of prophylaxis)		
Altretamine	[b]Cytarabine 3 g/m^2/dose	Procarbazine (oral)
[b]Carboplatin	Dacarbazine	Streptozocin
Carmustine >250 mg/m^2	[b]Dactinomycin	[b]Thiotepa ≥300 mg/m^2
[b]Cisplatin	Mechlorethamine	
[b]Cyclophosphamide ≥1 g/m^2	[b]Methotrexate ≥12 g/m^2	
Moderate risk (30–90 % frequency of emesis in absence of prophylaxis)		
Aldesleukin >12–15 million IU/m^2	Cytarabine >200 mg to <3 g/m^2	Lomustine
Amifostin >300 mg/m^2	Daunorubicin	Melphalan >50 mg/m^2
Arsenic trioxide	[b]Doxorubicin	Methotrexate ≥250 mg to <12 g/m^2
Azacitidine	Epirubicin	Oxaliplatin >75 mg/m^2
Bendamustine	Etoposide (oral)	Temozolomide (oral)
Busulfan	Idarubicin	Vinorelbine (oral)
[b]Carmustine ≤250 mg/m^2	Ifosfamide	
[b]Clofarabine	Imatinib (oral)	
[b]Cyclophosphamide <1 g/m^2	[b]Intrathecal therapy (methotrexate, hydrocortisone and cytarabine)	
Cyclophosphamide (oral)	Irinotecan	
Low risk (10–30 % frequency of emesis in the absence of prophylaxis)		
Amifostine ≤300 mg/m^2	Fludarabine (oral)	Paclitaxel
Bexarotene	5-Fluorouracil	Paclitaxel-albumin
[b]Busulfan (oral)	Gemcitabine	Pemetrexed
Capecitabine	Ixabepilone	Teniposide
Cytarabine ≤200 mg/m^2	Methotrexate >50 to <250 mg/m^2	Thiotepa >300 mg/m^2
Docetaxel	Mitomycin	Vorinostat
Doxorubicin (liposomal)	Mitoxantrone	
Etoposide	Nilotinib (oral)	
Minimal risk (<10 % frequency of emesis in the absence of prophylaxis)		
Alemtuzumab	Erlotinib	Rituximab
Alpha interferon	Fludarabine	Sorafenib
Asparaginase (IM or IV)	Gefitinib	Sunitinib
Bevacizumab	Gemtuzumab ozogamicin	Temsirolimus
Bleomycin	Hydroxyurea (oral)	Thalidomide
Bortezomib	Lapatinib	Thioguanine (oral)
Cetuximab	Lenalidomide	Trastuzumab
Chlorambucil (oral)	Melphalan (oral low dose)	Valrubicin
Cladribine	Mercaptopurine (oral)	Vinblastine
Dasatinib	Methotrexate ≤50 mg/m^2	Vincristine
Decitabine	Nelarabine	Vinorelbine
Denileukin diftitox	Panitumumab	
Dexrazoxane	Pentostatin	

Adapted from Dupuis et al. (2011)
[a]All agents given intravenously (IV) unless stated otherwise
[b]Pediatric evidence available (per Dupuis et al. [2011])

incorporated into the National Comprehensive Cancer Network (NCCN) antiemesis guidelines. Similar to the current classification system in pediatric patients, the updated guidelines divide intravenous chemotherapeutic agents into four categories of emetogenic potential, focusing on acute emesis: (1) high emetic risk, ≥90 % of patients experiencing acute emesis; (2) moderate emetic risk, 30–90 %; (3) low emetic risk, 10–30 %; and (4) minimal emetic risk, <10 % (Table 10.1) (Dupuis et al. 2010; Grunberg et al. 2010).

Recent data suggest that the frequency and severity of delayed CINV are often underestimated and remain a significant problem for patients (Dupuis

et al. 2010). In order to properly manage both acute and delayed symptoms, appropriate antiemetic prophylaxis should cover the entire duration of days that symptoms are anticipated. Furthermore, for multi-agent chemotherapy regimens, antiemetic choices should be determined based on the chemotherapeutic agent with the highest emetogenic risk.

10.2.4 Classes of Antiemetics

The basis for antiemetic therapy is the neurochemical control of vomiting. Many antiemetics act by competitively blocking receptors for these substances, thereby inhibiting stimulation of peripheral nerves at the CTZ and possibly the EC. Most drugs with proven antiemetic activity in children are categorized into five groups which are discussed individually below: (1) dopamine receptor antagonists, (2) corticosteroids, (3) 5-HT_3 receptor antagonists, (4) neurokinin-1 receptor (substance P) antagonists, and (5) cannabinoids. Antihistamines such as diphenhydramine which affect histaminergic receptors in the CTZ are widely utilized but have not been systematically studied. Similarly, anticholinergics, especially scopolamine, are utilized but have not been studied specifically in CINV.

10.2.4.1 Dopamine Receptor Antagonists

There are three classes of dopamine receptor antagonists effective in the prevention and treatment of CINV: phenothiazines, butyrophenones and benzamide. The most commonly used phenothiazine is prochlorperazine and has efficacy in all classes except in highly emetogenic chemotherapy (Moertel et al. 1963). A newer agent, metopimazine has been utilized with benefit in adult patients but has not been studied in children (Croom and Keating 2006; Dupuis et al. 2013). Butyrophenones, such as the antipsychotic drug haloperidol, are infrequently used in the pediatric setting secondary to their side effect profile. Of the benzamides, metoclopramide is the best studied and most widely used in children with CINV (Roila et al. 2006). Metoclopramide blocks central and peripheral D_2 dopaminergic receptors at low doses and exhibits weak 5-HT_3 inhibition at high doses. It is also known to speed gastric emptying and increase sphincter tone at the gastroesophageal junction. Prior to the introduction of 5-HT_3 antagonists, a combination of high-dose metoclopramide and dexamethasone was the most effective prophylaxis for highly emetogenic chemotherapy (Moertel et al. 1963). Extrapyramidal effects including dystonia, tardive dyskinesia, and neuroleptic malignant syndrome (uncommon) may be seen with benzamides and thus they are not typically first-line agents (Terrin et al. 1984; Allen et al. 1985). If given for breakthrough CINV, high-dose metoclopramide at a dose of 1 mg/kg q4–6 h is typically administered in conjunction with diphenhydramine to decrease the risk of extrapyramidal symptoms (Marshall et al. 1989; Koseoglu et al. 1998). Pediatric guidelines recommend an initial metoclopramide dose of 1 mg/kg followed by 0.075 mg/kg PO q6 h for moderately emetogenic chemotherapy as a strong recommendation with minimal evidence (Dupuis et al. 2013).

10.2.4.2 Corticosteroids

Steroids, most commonly dexamethasone, are effective in preventing CINV when used alone or in combination with other antiemetic agents for all emetogenic classes of chemotherapy. The antiemetic mechanism of action is not fully understood, but they may inhibit prostaglandin synthesis in the brain (Weidenfeld et al. 1987). Clinically, steroids quantitatively decrease or eliminate episodes of CINV and may improve mood, though can also induce anxiety and insomnia.

Steroids should be given before chemotherapy for acute CINV and may or may not be repeated. Both dexamethasone and methylprednisolone have good efficacy in the prevention of acute CINV in children and are superior to low-dose metoclopramide and phenothiazines with few side effects with short-term use (Mehta et al. 1986). Dosages and administration schedules vary. Dexamethasone is also used orally for delayed CINV. Long-term corticosteroid use is inappropriate and may cause substantial morbidity. As previously shown with metoclopramide, numerous studies have demonstrated that dexamethasone potentiates the antiemetic properties of 5-HT_3-blocking agents and NK_1-blocking agents (Hesketh 1994; Hesketh et al. 2003; Gore et al. 2009; Choi et al. 2010). The combination of dexamethasone and ondansetron has been most studied and is recommended for first-line

therapy in children receiving moderately or highly emetogenic chemotherapy; the combination of a 5-HT_3 antagonist with dexamethasone has been shown to be more efficacious than a 5-HT_3 antagonist alone (Dupuis et al. 2013). In one study, the "complete protection" rates increased from 43 % with ondansetron alone to 75 % with the combination of ondansetron and dexamethasone when given prior to high-dose cytarabine (Holdsworth et al. 2006). Dexamethasone may be particularly useful in patients who have demonstrated intolerance to other antiemetics given with high-dose chemotherapy or in patients with breakthrough, refractory or delayed CINV (Alvarez et al. 1995; Holdsworth et al. 2006).

Special considerations must be made prior to choosing corticosteroids for antiemetic therapy. Steroids cannot be given for CINV if the patient receives steroids as part of their chemotherapeutic regimen, as in leukemia or lymphoma. They are also typically avoided in patients with CNS malignancies, as dexamethasone has been shown to inhibit the influx of chemotherapy into the brain in preclinical models by "sealing" the blood-brain barrier (Straathof et al. 1998). Attention to protocol guidelines should be made prior to dexamethasone initiation particularly in hematologic and CNS malignancies but also potentially in protocols that utilize immunologic and biologic therapies.

Dexamethasone dosing for CINV is not well-studied. The most current pediatric CINV guidelines developed by the Pediatric Oncology Group of Ontario (POGO) suggest that dexamethasone should be dosed at 6 mg/m^2 IV/PO q6 h for highly emetogenic chemotherapy (Dupuis et al. 2013). For moderately emetogenic chemotherapy, dexamethasone can be dosed at 2 mg IV/PO q12 h for patients $\leq$0.6 m^2 and 4 mg q12 h for patients >0.6 m^2. If given concurrently with aprepitant, guidelines suggest reducing dexamethasone doses by half (Dupuis et al. 2013).

10.2.4.3 5-HT_3 Receptor Antagonists

Four serotonin receptor antagonists—ondansetron, granisetron, dolasetron and palonosetron—are available in the United States. Tropisetron is only available internationally and has not yet been approved by the Federal Drug Administration (FDA). When first approved in the early 1990s, these agents revolutionized the antiemetic prophylaxis of highly and moderately emetogenic chemotherapy, largely replacing phenothiazines and benzamides as first-line therapy due to superior efficacy and significantly fewer side effects (Grunberg et al. 2010). 5-HT_3 receptor antagonists are thought to prevent CINV by inhibiting serotonin, which is released from enterochromaffin cells in the gastrointestinal mucosa, from initiating afferent transmission to the CNS via vagal and spinal sympathetic nerves (Jordan et al. 2007). They may also work by blocking serotonin stimulation at the CTZ and other CNS structures. Prior to 2003, there were three FDA-approved 5-HT_3 receptor antagonists: ondansetron, granisetron and dolasetron. Numerous clinical trials demonstrated their clinical equivalence and showed there was no significant difference whether given orally or intravenously (Corapcioglu and Sarper 2005; Dupuis et al. 2013).

Ondansetron

Ondansetron is highly effective in controlling acute emesis induced by moderately and highly emetogenic chemotherapy in pediatric oncology patients (Carden et al. 1990; Hewitt et al. 1993). Used alone, ondansetron is superior to combination therapy with metoclopramide and dexamethasone or chlorpromazine and dexamethasone and is free of extrapyramidal and sedative side effects (Dick et al. 1995; Jimenez et al. 1997; Koseoglu et al. 1998). Ondansetron used in combination with corticosteroids has been shown superior to ondansetron monotherapy in control of CINV with highly emetogenic chemotherapy in pediatric cancer patients (Alvarez et al. 1995; Roila et al. 1998). Alvarez et al. (1995) conducted a small but significant double-blind, placebo-controlled, randomized crossover trial comparing ondansetron and dexamethasone to ondansetron and placebo in 25 children 3–8 years of age receiving highly emetogenic chemotherapy for solid tumors. Complete emetic control was achieved in 61 % receiving both ondansetron and

dexamethasone versus 23 % in those treated with ondansetron alone ($p = 0.04$).

The lowest fully effective dose of ondansetron is 0.45 mg/kg/day, with a single daily dose schedule no less efficacious than a multiply divided dose schedule (Sandoval et al. 1999). Oral and intravenous (IV) drug administration has also been found statistically equivalent (White et al. 2000). White et al. (2000) conducted a double-blind, parallel-group, multicenter study comparing the efficacy and safety of IV and liquid ondansetron (both arms with oral dexamethasone) in the prevention of CINV in pediatric patients receiving moderately to highly emetogenic chemotherapy. Complete control of emesis was achieved in 89 % of patients in the IV group and 88 % of patients in the oral syrup group during the worst day of chemotherapy treatment and was well tolerated in both arms (White et al. 2000). For highly emetogenic chemotherapy, the recommended dose of ondansetron is 0.15 mg/kg 30 min prior to initiation of chemotherapy and repeated q8 h, although other regimens (such as 0.45 mg/kg as a single daily dose) have been shown equally effective (Dupuis et al. 2013). When giving multiple-daily dosing, ondansetron can potentially be spaced to q12 h for moderately emetogenic chemotherapy (Dupuis et al. 2013). A single-center retrospective chart review has reported ondansetron-loading doses of 16 mg/m^2 (maximum, 24 mg) IV, followed by two doses of 5 mg/m^2 q8 h, to be safe in infants, children and adolescents (Hasler et al. 2008).

Currently, the oral and injectable ondansetron formulations are approved for use without dosage modification in patients >4 years, including patients with renal insufficiency. Ondansetron clearance is diminished in patients with severe hepatic insufficiency; therefore, such patients should receive a single injectable or oral dose ≤8 mg. The major adverse effects include: headache, constipation or diarrhea, fatigue, dry mouth and electrocardiographic (ECG) abnormalities including QTc prolongation (Culy et al. 2001). Buyukavci et al. (2005) monitored ECGs in 22 children with acute lymphoblastic leukemia randomized to receive a single dose of either ondansetron (0.1 mg/kg) or granisetron (40 mcg/kg). The granisetron group demonstrated a significant decrease in mean heart rate at 1 and 3 h post dosing and a significant QTc prolongation at 1 h post dosing although all values eventually returned to baseline; no significant changes were seen in the ondansetron group (Buyukavci et al. 2005). Pinarli et al. (2006) randomized 38 children to either ondansetron or granisetron, and patients were monitored with a 24-h ECG post antiemetic administration. Compared to baseline, patients who received granisetron (but not ondansetron) demonstrated a significant prolongation of the QTc interval and shortening of the PR interval and QRS complex, though none of these abnormalities were clinically significant (Pinarli et al. 2006).

Granisetron

Granisetron has demonstrated efficacy in preventing and controlling CINV due to moderately to highly emetogenic chemotherapy in children and when used alone is superior to combination therapy using metoclopramide and promethazine, metoclopramide and dexamethasone, and chlorpromazine and dexamethasone (Hählen et al. 1995; Komada et al. 1999). In a small study, Hirota et al. (1993) showed no significant difference between the combination of granisetron and methylprednisolone compared with granisetron alone in pediatric oncology patients. Effective granisetron doses in children range from 20 to 40 mcg/kg/day, often administered IV once daily prior to chemotherapy or orally q12 h (Dupuis et al. 2011). In the United States, granisetron injection, transdermal patch, and oral tablets are approved for initial and repeat prophylaxis in patients receiving emetogenic chemotherapy, including high-dose cisplatin. Granisetron is pharmacologically and pharmacokinetically distinct from ondansetron; however, clinically it appears equally efficacious and safe (Gebbia et al. 1994). Current pediatric guidelines recommend granisetron at 40 mcg/kg IV as a single daily dose for moderately to highly emetogenic chemotherapy or 40 mcg/kg/dose PO q12 h for prevention of CINV from moderately emetogenic chemotherapy (Dupuis et al. 2013).

Palonosetron

A second-generation 5-HT_3 receptor antagonist palonosetron was FDA approved in 2003 and boasts advantages over first-generation 5-HT_3 receptor antagonists including a higher binding affinity to the 5-HT_3 receptor and longer elimination half-life (i.e., 40 h in adults versus 4–8 h for first-generation agents). Large drug company sponsored adult trials have demonstrated at least non-inferiority and potential superior control of acute emesis with single-dose palonosetron compared with single-dose ondansetron or dolasetron (Eisenberg et al. 2003; Gralla et al. 2003). Gralla et al. (2003) randomized 570 adult patients receiving moderately emetogenic chemotherapy to either 0.25 or 0.75 mg palonosetron or 32 mg ondansetron on the first day of chemotherapy and showed a significantly increased prevention of acute CINV (81 % vs. 68.8 %, $p=0.009$) for the 0.25 mg palonosetron arm compared with ondansetron. Of note, there was no significant difference in response to acute nausea comparing 0.75 mg palonosetron and 32 mg of ondansetron (Gralla et al. 2003). Eisenberg et al. (2003), on the other hand, showed only non-inferiority of both 0.25 and 0.75 mg palonosetron as compared with 100 mg of dolasetron. Although both studies showed significant improved response in delayed CINV for palonosetron compared with single-dose ondansetron as a secondary outcome measure, this conclusion is confounded by the inappropriate utilization of single-dose (with a 4–8 h half-life) ondansetron as a comparison dosing schedule for the prevention of delayed CINV (Eisenberg et al. 2003; Gralla et al. 2003). In a meta-analysis of adult studies of palonosetron in CINV, Likun et al. (2011) showed a significant benefit to 0.25 and 0.75 mg palonosetron in acute, delayed, and overall CINV prevention compared with first-generation agents although due to the methodologic concerns described above, it is difficult to conclude the superiority of palonosetron in delayed and overall control of CINV. However, Geling and Eichler (2005) have shown in a meta-analysis of adult patients that first-generation 5-HT_3 antagonists may not be effective in the prevention of delayed CINV no matter the dosing schedule. Palonosetron's three- to fourfold increased cost versus ondansetron must be weighed with a need for significantly less total doses (Geling and Eichler 2005; De Leon 2006; Likun et al. 2011).

Only two studies of efficacy of palonosetron in children have been published. A randomized trial of 60 pediatric patients 2–17 years of age showed 3 mcg/kg (maximum dose 0.25 mg) and 10 mcg/kg (maximum dose 0.75 mg) of palonosetron were well tolerated and equally effective (Kadota et al. 2007). Sepulveda-Vildosola et al. (2008) conducted a randomized comparison of palonosetron (0.25 mg single dose 30 min before chemotherapy) and ondansetron (8 mg/m^2 every 8 h beginning 30 min before chemotherapy) in children 2–15 years, evaluating 50 chemotherapy courses in each arm and showing a significant reduction in emetic events and intensity of nausea during the acute phase of therapy (days 1–3) in the palonosetron group. Due to the decreased number of doses, they found that palonosetron was more inexpensive as well (Sepulveda-Vildosola et al. 2008). The study was limited by the fact that palonosetron was given as a standard dose rather than weight and age adjusted and also that determination of emesis and intensity of nausea was based on family report and therefore subject to potential inaccuracy (Sepulveda-Vildosola et al. 2008). Though palonosetron appears to be well tolerated, further research is needed to evaluate the optimal dose, cost-effectiveness and its relative efficacy in children based on the chemotherapeutic emetogenicity and in delayed CINV.

Comparison of Agents

Studies suggest that there are no major differences in efficacy or toxicity of the three first-generation 5-HT_3 receptor antagonists (dolasetron, granisetron and ondansetron) in the treatment of acute CINV when used at appropriate doses (Hesketh 1994). Although these agents have been shown effective for the treatment of acute CINV, they have not demonstrated efficacy in alleviating symptoms of delayed CINV in adult patients (Hickok et al. 2003; Geling and Eichler 2005). The second-generation 5-HT_3 receptor antagonist palonosetron has been approved for the control of delayed emesis for adult patients receiving moderately emetogenic chemotherapy, though

definitive safety and efficacy has not been established in children and methodologic concerns exist in the comparison with first-generation agents for the treatment of delayed CINV.

The 5-HT_3-receptor antagonists remain the cornerstone of prophylaxis for both moderately and highly emetogenic chemotherapy in children although a recent Cochrane review concluded that our knowledge of effective antiemetics in children with CINV is quite incomplete (Phillips et al. 2010). Despite the advent of 5-HT_3 receptor antagonists, the control of acute and delayed CINV is suboptimal with highly emetogenic chemotherapeutic regimens, and there is considerable opportunity for improvement with either the addition or substitution of new agents in current regimens (Dupuis et al. 2011). Although lacking evidence, the recent pediatric guidelines suggest either ondansetron or granisetron can be given although no dose recommendation is given for granisetron and evidence is lacking to recommend doses or regimens with dolasetron or palonosetron (Dupuis et al. 2013).

10.2.4.4 Substance P Antagonists (NK_1 Receptor Antagonists)

NK_1 receptors are found in the nucleus tractus solitarii and the area postrema and are activated by substance P (Saito et al. 2003). Inhibitors of NK_1 receptors have demonstrated beneficial antiemetic effects and represent a new target for antiemetic therapy. Aprepitant and its prodrug fosaprepitant have been shown to prevent both acute and delayed CINV from moderately to highly emetogenic chemotherapy in adults (Hesketh et al. 2003). Current Multinational Association of Supportive Care in Cancer (MASCC), European Society of Medical Oncology (ESMO), NCCN, and American Society of Clinical Oncology (ASCO) guidelines recommend the use of aprepitant in adults receiving highly emetogenic chemotherapy or those receiving a combination of anthracycline and cyclophosphamide (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012). When compared to ondansetron and dexamethasone alone, the addition of aprepitant has been shown to increase the rate of complete emetic control (i.e., no acute emesis or need for rescue medication) from 52–73 % in chemotherapy-naïve adults during a 5-day period after single-day cisplatin therapy (Hesketh et al. 2003). Subsequent randomized clinical trials in adults have demonstrated superior efficacy for the prevention of delayed CINV when aprepitant is added to a 5-HT_3 antagonist and dexamethasone, recently summarized in a pooled analysis by Jin et al. (2012). These results led to FDA approval of aprepitant for adults in March 2003 for highly emetogenic chemotherapy and in 2006 for moderately emetogenic chemotherapy.

Studies of aprepitant in the pediatric population have been limited to retrospective reviews and case reports with the exception of one randomized controlled trial (Gore et al. 2009; Choi et al. 2010; Bauters et al. 2013). Gore et al. (2009) conducted a randomized, double-blind, placebo-controlled multicenter phase III trial studying aprepitant in adolescent patients. In addition to ondansetron and dexamethasone, patients were randomized 2:1 to receive either aprepitant or placebo. Forty-six patients from 11 to 19 years of age participated, with overall complete response rates of 28.6 % in the aprepitant group versus 5.6 % in the control group (though not significantly different). Serious adverse events were 32.1 % in the aprepitant group versus 16.7 % in the control group (not statistically significant) and pharmacokinetic data showed increased aprepitant metabolism as compared to historical adult data (Gore et al. 2009). Further study is required to understand the efficacy, appropriate dose and side effect profile with aprepitant in pediatric patients.

In an effort to balance access to an apparently effective antiemetic with the lack of pediatric dosing and safety information, some centers are administering aprepitant to children ≥12 years of age, weighing ≥40 kg and receiving highly emetogenic chemotherapy. The usual adult dose is administered in conjunction with a 5-HT_3 receptor antagonist and dexamethasone for 3 days (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012). Based on the limited available data, pediatric guidelines recommend 125 mg of aprepitant on day 1 and 80 mg on days 2 and 3 (adult dosing) with a 5-HT_3 antagonist

and dexamethasone for patients ≥12 years receiving highly emetogenic chemotherapy (Dupuis et al. 2013). Although variable dosing regimens have been utilized in children <40 kg and reported to be well tolerated, optimal dosing is yet to be determined in this population (Choi et al. 2010; Bauters et al. 2013; Bodge et al. 2014).

As aprepitant is a moderate inhibitor of and a substrate for CYP3A4, drug interactions are an important consideration, and, as mentioned, the dose of concomitant dexamethasone or methylprednisolone (utilized as an antiemetic) is recommended to be halved. Multiple chemotherapy agents including etoposide, ifosfamide, imatinib, irinotecan, paclitaxel, vinca alkaloids and steroids are metabolized by CYP3A4 (Shadle et al. 2004). As such, aprepitant should be avoided in patients receiving these chemotherapeutic agents because of the potential for unintended increases in the dose intensity and toxicity of these antineoplastic agents. More complete references should be consulted regarding the nature and extent of drug interactions with aprepitant, as interactions with non-chemotherapeutic agents (e.g., warfarin, phenytoin, midazolam, carbamazepine, erythromycin, ketoconazole) have been described (Shadle et al. 2004). Additional NK_1 receptor antagonists casopitant and rolapitant have been shown effective and safe in adult CINV but have not been studied in pediatric patients.

10.2.4.5 Cannabinoids

The plant *Cannabis* contains more than 60 different types of cannabinoids which have physiologic activity. There are two FDA-approved products for CINV: dronabinol (a synthetic isomer, *-trans-Δ9-tetrahydrocannabinol*) and nabilone. Cannabinoids likely exert antiemetic effects by targeting cannabinoid-1 (CB-1) and CB-2 receptors in the CNS (Abrahamov et al. 1995; Tramer et al. 2001). These agents have demonstrated modest efficacy in the prevention of acute CINV in children and are superior to low-dose metoclopramide and prochlorperazine, though with side effects which include euphoria, dizziness (i.e., postural hypotension) and hallucinations (Chan et al. 1987, Tramer et al. 2001). Dronabinol is dosed at 5 mg/m^2 q6 h prn (max 15 mg/m^2/dose) orally and is typically reserved for refractory patients. Pediatric guidelines recommend nabilone (<18 kg, 0.5 mg/dose PO twice daily; 18–30 kg, 1 mg/dose PO twice daily; >30 kg, 1 mg/dose PO three times daily) in patients for whom corticosteroids are contraindicated receiving moderately to highly emetogenic chemotherapy (Dupuis et al. 2013).

10.2.4.6 Other Antiemetic Agents

Antihistamines

Antihistamines such as diphenhydramine are commonly used as adjunctive agents in the treatment and prevention of CINV although systematic review of their potential benefit is not reported in the literature. Antihistamines theoretically impact the histaminergic receptors in the CTZ and should also be utilized in combination with metoclopramide to prevent extrapyramidal side effects. Adult and pediatric guidelines do not discuss antihistamines beyond utilization with metoclopramide (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012; Dupuis et al. 2013).

Benzodiazepines

Benzodiazepines such as lorazepam and midazolam have become recognized as valuable adjuncts in the prevention and treatment of anticipatory nausea and vomiting associated with chemotherapy. Benzodiazepines have not demonstrated intrinsic antiemetic activity as single agents and thus should be used with other antiemetics, primarily for the treatment of anticipatory and breakthrough CINV (Triozzi et al. 1988; Hesketh 2008; Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012). Benzodiazepines are thought to act on higher CNS structures, the brainstem, and spinal cord, and they produce anxiolytic, sedative, and anterograde amnesic effects. Administration of lorazepam may be oral, IV or sublingual. Doses range from 0.03 to 0.05 mg/kg (max dose 2 mg) in children every 6–12 h (Van Hoff and Olszewski 1988). The adverse effects of lorazepam include sedation, visual disturbance, confusion and ataxia. Benzodiazepines as adjunct agents are not mentioned in the recent pediatric guidelines (Dupuis et al. 2013).

Olanzapine

Olanzapine nonspecifically antagonizes D_2 and 5-HT_3 receptors and has been shown in nonrandomized adult studies to be effective in preventing acute and delayed CINV (Navari et al. 2005; Navari et al. 2007; Hesketh 2008). Adult guidelines include olanzapine as a suggested adjunct agent in patients with delayed or refractory CINV (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012). Pediatric data are lacking (Dupuis et al. 2013).

10.2.4.7 Alternative Therapies

Ginger

Ginger has been traditionally utilized as a treatment for upset stomach and is considered safe by the FDA. A Cochrane review of pregnant women showed limited and inconsistent results of ginger on the treatment of nausea (Matthews et al. 2014). Studies in CINV are limited and mixed. In randomized controlled adult trials, Zick et al. (2009) showed no benefit to ginger in the reduction of severity of acute or delayed CINV, while Ryan et al. (2012) found significant benefit of 0.5 and 1.0 g ginger in acute CINV when given 3 days prior to chemotherapy initiation. One randomized placebo-controlled study in pediatric patients found significant improvement in both acute and delayed CINV with the addition of ginger root powder in bone sarcoma patients receiving ondansetron and dexamethasone (Pillai et al. 2011). Further work is required to determine if ginger is a potentially beneficial adjunctive agent (Dupuis et al. 2013).

Acupressure/Acupuncture

Chinese medicine has for centuries utilized acupressure and acupuncture for the treatment of emesis induced by pregnancy and surgery (Jindal et al. 2008). Traditionally, the P6 acupuncture point above the wrist between the palmaris longus and flexor carpi radialis muscles of the forearm is targeted for prevention of nausea and vomiting. The role of acupuncture and acupressure has been studied systematically; in a pooled analysis of CINV, Ezzo et al. (2006) demonstrated mild reduction in acute emesis (RR = 0.82, 95 % CI 0.69, 0.99; $p = 0.04$), but no change in acute or delayed nausea severity compared with controls. A Cochrane review showed no benefit to acupuncture and limited evidence for acupressure in pregnant women with nausea (Matthews et al. 2014). Continuous pressure to the P6 acupuncture point can be administered continuously using acupressure wrist bands (Sea-Band®) (Molassiotis et al. 2008).

Studies of acupressure and acupuncture in the pediatric population are limited due to difficulties in patient accrual, particularly in younger patients who might fear this modality. One study was only able to enroll 11 patients ≥10 years of age in a 2-year period and demonstrated a significantly reduced need for additional antiemetics when acupressure was combined with 5-HT_3 antagonists ($p = 0.024$) (Reindl et al. 2006). This conclusion was confounded by the fact that episodes of vomiting were not reduced ($p = 0.374$) (Reindl et al. 2006). Small sample sizes continue to be a barrier to future research, though efforts for stronger evidence-based studies are ongoing including a randomized controlled trial of acupressure to control CINV in children receiving cisplatin sponsored by the Children's Oncology Group. A validated pediatric nausea assessment tool (PeNAT) will be utilized to assess response to therapy in both acute and delayed phases (Dupuis et al. 2006).

Hypnosis and Other Therapies

Limited data are available in the literature regarding hypnosis although a meta-analysis of five pediatric studies in the prevention of CINV showed significant reduction in anticipatory CINV (Richardson et al. 2007). Benefit of hypnosis as well as other behavioral modification techniques such as cognitive-behavior therapy, guided imagery, music therapy, muscle relaxation, virtual reality and psychoeducational support have not been systematically studied (Dupuis et al. 2013).

10.2.5 Recommendations for Prevention and Treatment of CINV

The advent of new and improved pharmacologic antiemetic agents, accumulation of clinical

experience, and ability to stratify chemotherapy regimens according to their emetogenicity has made it possible to construct guidelines for a logical approach to prevention and treatment of CINV in adults (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012). However, due to important differences in treatment intensity, drug metabolism and toxicity, adult guidelines cannot simply be extrapolated to the pediatric population. Evidence-based guidelines for antiemetic selection in children receiving chemotherapy have been developed by ASCO, ESMO, and MASCC; however, recommendations were based on few randomized controlled trials and extrapolation of adult data (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012). The recent Pediatric Oncology Group of Ontario guidelines represent a comprehensive systematic review of the pediatric literature and recommendations here are largely based on these guidelines (Dupuis et al. 2013).

10.2.5.1 Management of CINV

Management of CINV (Table 10.2) is based on the emetogenic potential of the chemotherapeutic regimen that each individual is undergoing as well as their previous history of CINV. For patients receiving regimens with high emetogenic risk such as cisplatin or cyclophosphamide (Table 10.1), the combination of a 5-HT_3 receptor antagonist, aprepitant and dexamethasone is recommended prior to chemotherapy. Aprepitant and dexamethasone are recommended to continue >24 h after chemotherapy (i.e., for 3 total days) for the prevention of delayed CINV. Close attention should be paid to potential drug interactions when considering use of aprepitant, and aprepitant cannot currently be recommended in children <12 years of age or <40 kg (Dupuis et al. 2013). If aprepitant cannot be used, patients should at minimum receive a 5-HT_3 receptor antagonist and dexamethasone. If aprepitant and corticosteroids are contraindicated, a 5-HT_3 receptor antagonist plus a cannabinoid (dronabinol or nabilone) or dopamine receptor antagonist (promethazine, metopimazine or metoclopramide with diphenhydramine) can be used although typical pediatric oncology practice has utilized diphenhydramine and lorazepam prior to cannabinoids or D_2 antagonists. An anticholinergic such as scopolamine may also be used for adjuvant therapy especially in adolescents although data in CINV are lacking.

For patients receiving moderate emetogenic risk chemotherapy, the combination of a 5-HT_3 receptor antagonist and dexamethasone is recommended prior to chemotherapy. If corticosteroids are contraindicated, a 5-HT_3 receptor antagonist plus a cannabinoid (dronabinol or nabilone) or dopamine receptor antagonist (promethazine, metopimazine or metoclopramide with diphenhydramine) can be used although typical pediatric oncology practice has utilized diphenhydramine and lorazepam prior to cannabinoids or D_2 antagonists. An anticholinergic such as scopolamine may also be used for adjuvant therapy especially in adolescents. For regimens with low emetogenic risk, monotherapy with a 5-HT_3 receptor antagonist is recommended. For regimens with minimal emetogenic risk, no prophylaxis is recommended.

10.2.5.2 Special Considerations

Anticipatory Nausea and Vomiting

Prevention of anticipatory nausea and vomiting (Table 10.2) is achieved through the use of optimal antiemetic prophylaxis with each cycle of chemotherapy. Once symptoms have developed, benzodiazepines can be added to the prophylactic antiemetic regimen for anxiolysis. Patient expectancy of nausea and vomiting is an often underrecognized factor and alternative therapies have been shown to effectively treat anticipatory CINV especially when used in combination with antiemetics (Figueroa-Moseley et al. 2007; Richardson et al. 2007).

Breakthrough Nausea and Vomiting

Breakthrough emesis (Table 10.2) presents a difficult scenario as correction of refractory ongoing CINV is challenging to reverse. Prevention is far easier than treatment. The general principle of breakthrough treatment is to give an additional agent from a different drug class. Some patients require several agents utilizing differing mechanisms of action. Around the clock dosing is

Table 10.2 Management of chemotherapy-induced nausea and vomiting in pediatric cancer patients[a]

Emetogenic risk[b]	Drug	Dosing	Level of evidence[c]
High emetogenic risk	Corticosteroids permitted[d]: ondansetron or granisetron + dexamethasone + aprepitant[e]	Ondansetron 0.15 mg/kg/dose (max 8 mg/dose) IV/PO pretherapy and then q8 h	1B
		Granisetron 40 mcg/kg/dose IV daily	1B
	Corticosteroids contraindicated[d]: ondansetron or granisetron + breakthrough agent + aprepitant[e]	Dexamethasone 6 mg/m^2/dose IV/PO q6 h; if given concurrently with aprepitant, reduce dexamethasone dose by half	1C
		Aprepitant 125 mg PO on day 1, 80 mg daily on day 2 and 3	1C
Moderate emetogenic risk	Corticosteroids permitted[d]: ondansetron or granisetron + dexamethasone	Ondansetron 0.15 mg/kg/dose (max 8 mg/dose) IV/PO pretherapy and then q8-12 h	1B
	Corticosteroids contraindicated[d]: ondansetron or granisetron + breakthrough agent	Granisetron 40 mcg/kg/dose IV daily OR 40 mcg/kg/dose PO q12 h	1B
		Dexamethasone ≤0.6 m^2: 2 mg/dose IV/PO q12 h >0.6 m^2: 4 mg/dose IV/PO q12 h	1C
Low emetogenic risk	Ondansetron or granisetron	Same dosing as above	1B
Minimal emetogenic risk	No routine prophylaxis		1C
Breakthrough nausea and vomiting	Ondansetron or granisetron	Same dosing as above (ordered prn if not already scheduled)	1B
	Lorazepam	0.05 mg/kg/dose IV q6 h prn (max 2 mg/dose)	2B
	Metoclopramide	1 mg/kg/dose IV pretherapy (max 10 mg/dose) then 0.075 mg/kg/dose PO q6 h; give diphenhydramine concurrently	1C
	Promethazine	0.125 mg/kg/dose IV q6 h (do not use in children <2 years of age)	2C
	Dronabinol	5 mg/m^2/dose PO q6 h prn (may increase in 2.5 mg increments to max 15 mg/m^2/dose)	2B
Anticipatory nausea and vomiting	Lorazepam	0.05 mg/kg/dose IV q6 h prn (max 2 mg/dose)	2B

IV intravenous, *PO* by mouth, *prn* as needed
Adapted from Ettinger et al. (2012), Dupuis et al. (2013)
[a]See text for full detail
[b]See Table 10.1 for chemotherapy emetogenicity classification
[c]Level of evidence per Guyatt et al. (2006); see Preface
[d]Corticosteroids as antiemetic generally contraindicated with treatment of brain tumors, leukemia and lymphoma
[e]Recommended for children ≥12 years old, investigate potential drug interactions prior to use

typically preferred rather than as needed dosing, particularly in children who may not know how to properly convey nausea. Typical breakthrough agents include lorazepam, diphenhydramine, scopolamine, metoclopramide (with diphenhydramine), promethazine or metopimazine, and cannabinoids. One can consider maximizing the starting dose of the 5-HT$_3$ antagonist or switching

to an alternative 5-HT_3 antagonist (e.g., from ondansetron to granisetron or palonosetron). If the patient has dyspepsia, adding an H_2 blocker or proton pump inhibitor may be beneficial. Adequate hydration is imperative. Alternative therapies should be explored and may be of benefit. The patient should also be assessed for other non-chemotherapy-associated etiologies of nausea and vomiting such as electrolyte imbalances, GI obstruction or gastroparesis, tumor infiltration of bowel or brain, effect of total parenteral nutrition, and other potential diagnoses.

10.3 Radiation-Induced Nausea and Vomiting

Radiation-induced nausea and vomiting (Table 10.2) is seen in nearly all patients receiving total body irradiation prior to hematopoietic stem cell transplant and in >80 % of those receiving radiation to the upper abdomen (Feyer et al. 2005). Studies have demonstrated efficacy of 5-HT_3 receptor antagonist prophylaxis in this setting as well as superiority to metoclopramide (American Society of Health-System Pharmacists 1999). Adult guidelines recommend prophylaxis with ondansetron or granisetron prior to each radiation fraction delivered (Basch et al. 2011; Jordan et al. 2011; Ettinger et al. 2012).

10.4 Summary

Dramatic progress has been made in the prevention of CINV, especially with the introduction of the 5-HT_3 receptor antagonists in the early 1990s. Utilization of second-generation 5-HT_3 receptor antagonists such as palonosetron requires further study in children but will also likely be beneficial in the prevention of delayed CINV as compared to first-generation agents. The utility of NK_1 receptor antagonists is evident in the adult literature and dedicated pediatric studies are necessary to allow further improvement of CINV outcomes in children with cancer. Heightened awareness of patient symptoms, assessment and modification of risk factors, adherence to current guidelines for prophylaxis based on emetogenic risk, and the use of novel strategies such as long-acting and sublingual formulations, transdermal patches, and complimentary alternative therapies will ensure that fewer pediatric patients experience nausea and vomiting from antineoplastic therapy.

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