Advanced Emergency Nursing Journal
Vol. 39, No. 2, pp. 97–105

APPLIED
PHARMACOLOGY

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Antiemetic Use in the Emergency Department

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ABSTRACT
Nausea and vomiting are 2 of the most common complaints of patients presenting to the emergency department (ED). In addition, antiemetics are the most commonly prescribed medications in the ED behind analgesics. Treating these conditions can be complex, especially as one considers that nausea and/or vomiting could be the primary presenting illness or simply a symptom of a more complex etiology. Although there is a wide variety of pharmacotherapeutic options in the armamentarium to treat these conditions, very few consensus recommendations exist to help guide the use of antiemetic agents in the ED, leading to wide variability in medication use. Contributing to these variations in practice is the extended spectrum of etiologies and potential physiological factors that contribute to the development of nausea or vomiting. A thorough understanding of the pharmacology and administration of these agents can help practitioners devise tailored antiemetic regimens based upon the underlying etiology. **Key words:** antiemetics, emergency department, nausea, pharmacy, vomiting

NAUSEA AND VOMITING are two of the most common complaints of patients who present to the emergency department (ED). Antiemetics are the most commonly prescribed medications in the ED behind analgesics, with ondansetron being the most common medication prescribed overall. Nausea and vomiting have been associated with 2.5 million ED visits per year in the United States (Meltzer & Mazer-Amirshahi, 2016). More than half of adults report having one episode of nausea in the last 12 months, and almost one third report one episode of vomiting during the same time frame (Singh, Yoon, & Kuo, 2016). These conditions are estimated to cost the U.S. economy upwards of $16 billion annually largely in lost productivity (Patanwala, Amini, Hays, & Rosen, 2010).

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Disclosure: *The authors report no conflicts of interest.*
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DOI: 10.1097/TME.0000000000000141

Although there are a wide variety of pharmacotherapeutic options in the armamentarium to combat nausea and vomiting, very few consensus recommendations exist to help guide the use of these agents. This leads to wide variations in managing these conditions. Recent data suggest that only around half of patients presenting with nausea and vomiting received an antiemetic in the ED (Singer, Garra, & Thode, 2016). Adding to the complexity, nausea or vomiting may be the primary presenting illness or simply a symptom of a more complex etiology. Also contributing to the variations in practice is the extended spectrum of etiologies and potential physiological factors that contribute to the development of this presentation.

PATHOPHYSIOLOGY

A complex association of nerve conduction and receptor stimulation causes nausea and vomiting. The central emesis center of the brainstem receives input from a multitude of sources including the chemoreceptor trigger zone, cerebral cortex, vagus nerve, vestibular apparatus, and the splanchnic afferent nerves. Each of these pathways also has a unique set of receptors that mediate the emesis signaling pathway and include receptors such as the dopamine (D_2), acetylcholine (muscarinic, M), histamine (H_1), and 5-hydroxytryptamine ($5\text{-}HT_3$; i.e., serotonin) receptors. Depending on the underlying etiology, different or multiple receptors may be involved. Current pharmacological therapies aimed at combating nausea and vomiting are rooted in activities at the serotonin ($5\text{-}HT_3$)/dopamine and histamine/acetylcholine, receptors (Chepyala & Olden, 2008).

THERAPEUTIC OPTIONS

One of the principal concepts to the successful termination of nausea and vomiting is the identification of the underlying etiology and the specific receptor(s) contributing to the symptoms. Prior to the initiation of any antiemetic regimen, one should address dehydration or insensible losses and ensure that the patient is adequately rehydrated with intravenous fluids if necessary. In addition, providers should evaluate whether replacement of electrolyte deficiencies is necessary. Simply restoring these two homeostatic states (fluid balance and electrolyte replacement) may resolve the symptoms of vomiting in many cases, eliminating the need for medications and the risk of side effects. The necessity of evaluating the patient's concomitant medication therapy is also critical because it can lend valuable insight into the etiology of the nausea and vomiting and hence the most appropriate antiemetic therapy. It is important to highlight the complexity of investigating appropriateness of antiemetogenic therapies. The majority of nausea and vomiting episodes are short-lived and self-limited. Also, nausea is typically more resistant to intervention than vomiting. Hence, the preponderance of investigations has explored the management of acute nausea and vomiting in specific clinical scenarios of known etiology such as pregnancy, chemotherapy, and postanesthesia. The available literature does not specifically address the complex undifferentiated patient who presents to the ED or patients with chronic nausea of unclear etiology (Quigley, Hasler, & Parkman, 2001).

For those patients in whom the restoration of fluid and electrolyte homeostatic states alone is unsuccessful, multiple therapeutic options exist in the ED: phenothiazines; anticholinergics; antihistamines; butyrophenones; substituted benzamides; corticosteroids; and serotonin antagonists. Each agent has its specific receptor affinities, indications, and side effects. Regardless of the agent chosen, it is important to use the lowest total daily dose for the shortest duration possible to minimize the incidence of adverse drug effects. This is especially applicable in the ED because many patients will be discharged with a prescription for an antiemetic and consideration should be given to prescribing only enough for 24–48 hr in order to prompt reevaluation of the patient's condition if symptoms are not resolving.

Available therapies can be divided into two categories: those acting centrally (e.g., ondansetron) and those focused on altering gastrointestinal motility (e.g., metoclopramide).

Droperidol and Haloperidol

Previously, one of the most frequently used agents in the ED for the management of nausea and vomiting was droperidol. This agent has multiple sites of activity; its most significant mechanism of action is as a D_2 receptor agonist (Patanwala et al., 2010). However, in 2001, the U.S. Food and Drug Administration (FDA) labeled this medication with a black box warning, highlighting its risk for prolonging the QT interval and causing torsades de pointes in certain patients. As a result, the use of this agent declined dramatically and currently droperidol is without a manufacturer in the United States. Should manufacturer availability be restored, the FDA recommends that this agent be used in patients who have failed all other therapies. Electrocardiogram monitoring is recommended before treatment and for up to 3 hr after completing therapy to monitor for the induction of dysrhythmias. There is limited evidence that low doses such as 1.25 mg were associated with cardiac dysrhythmias (Jackson, Sheehan, & Reddan, 2007). Of the 65 individual case reports submitted to the FDA that lead to the warning, only five events were at doses less than 2.5 mg (Jackson et al., 2007). The FDA has even stated that "the boxed warning really is not about doses of droperidol less than 2.5 mg . . . " (Perkins, Ho, Vilke, & DeMers, 2015, p. 96). The lack of availability of droperidol in the United States is unfortunate because in a recent review of studies involving the management of nausea and vomiting in the ED, the investigators concluded that the only medication (including metoclopramide, ondansetron, prochlorperazine, promethazine, and droperidol) associated with a significant improvement in symptoms at 30 min was droperidol (Meltzer & Mazer-Amirshahi, 2016). Furthermore, the American Academy of Emergency Medicine has issued the following statement, "Droperidol is an effective and safe medication in the treatment of nausea, headache, and agitation. The literature search did not support mandating an electrocardiogram or telemetry monitoring for doses less than 2.5 mg given either intramuscularly or intravenously" (Perkins, Ho, Vilke, & DeMers, 2015). After the FDA's black box warning, some providers began substituting haloperidol for droperidol, usually at a lower dose (1–2 mg) than that typically used for the management of acute psychosis and agitation (5 mg). There is limited evidence to support the effectiveness of this practice, and haloperidol has been demonstrated to be inferior to other therapies in the settings of postoperative nausea and vomiting as well as in palliative care (Meltzer & Mazer-Amirshahi, 2016).

Phenothiazines

After the decline in the use of droperidol beginning in 2001, the phenothiazines (prochlorperazine and promethazine), specifically promethazine, became the most prescribed medication for nausea and/or vomiting in the ED. Through nonselective inhibition of dopamine, muscarinic, and histamine receptors, phenothiazines have a wide-ranging role in the management of nausea and vomiting (Chepyala & Olden, 2008; Sanger & Andrews, 2006). Promethazine's profound effect on the H_1 receptor leads to its characteristic sedative side effects, which can be beneficial in some circumstances. The most commonly prescribed dose is 25 mg, although doses of 6.25–12.5 mg have demonstrated equivalent efficacy with 4 mg of ondansetron while minimizing the subsequent sedation (Patanwala et al., 2010). Promethazine is not without safety considerations. Logistically, it is one of the more complex agents in this therapeutic group. There have been multiple cases of this agent causing blood vessel damage at the administration site leading to necrosis and, in some cases, limb amputation. Parenteral promethazine has a pH of 4–5.5, which can be highly irritating to

blood vessels, increasing the risk for extravasation and necrosis. The risk of tissue necrosis is elevated when it is administered undiluted or accidentally given intra-arterially.

Promethazine is associated with more side effects such as sedation that limit its use over other agents. Lower doses also potentially help limit the incidence of sedation and other undesirable side effects such as vessel damage at the infusion site. If the maximum dose of 25 mg is ordered, it should be further diluted in 50 ml of normal saline and infused over 10–15 min to limit vascular damage (Institute for Safe Medication Practices, 2006). Promethazine is also available in suppository form and can be administered orally and intramuscularly as well. Typically, this agent is dosed every 4–6 hr.

Prochlorperazine is presumed to exert its effects through blockade of dopamine receptors and has some anticholinergic and α-adrenergic antagonist properties as well (Freedman & Fuchs, 2004). When administered intravenously or intramuscularly, it demonstrates an effect within 30–60 min. It is typically dosed 5–10 mg every 6–8 hr. It is also available as an oral and rectal formulation (25 mg). Its use is limited secondary to the risk of akathisias. These side effects are dose and infusion rate related. A 36% reduction in the incidence of this side effect was seen when 10 mg of prochlorperazine was infused over 15 min compared with a 2-min bolus (Vinson, Migala, & Quesenberry, 2001). Another option is to administer this medication with diphenhydramine, which can reduce the incidence of akathisia.

Antihistamines

Antihistamines (e.g., diphenhydramine, hydroxyzine) can have multiple roles in the management of nausea and vomiting. They are not considered first-line agents due to their high incidence of sedation. The antiemetic action of antihistamines is largely mediated through their anticholinergic and antihistamine receptor activity in the central nervous system (Chepyala & Olden, 2008). Antihistamines have a role in the management of motion sickness, given their ability to suppress labyrinthine and vestibular stimulation (Chepyala & Olden, 2008; Flake, Scalley, & Bailey, 2004). They also combat D_2 receptor antagonists to help reduce the incidence of akathisia. Diphenhydramine 12.5–25 mg intravenously/intramuscularly or hydroxyzine 25–100 mg intramuscularly can be effective antiemetic choices when primary therapies fail. It should be noted that they are most successful for motion sickness when used prophylactically. These agents can also be administered orally every 6–8 hr.

Anticholinergics

Anticholinergics, including scopolamine, do not have a large role in the management of acute nausea and vomiting in the ED. Scopolamine is available as a transdermal patch and acts as an anticholinergic agent on the central nervous system through the muscarinic receptors. Their primary role in the treatment of nausea and vomiting is in the management of motion sickness (Chepyala & Olden, 2008; Golding & Stott, 1997). Its utility in the acute setting in the ED is limited secondary to its delayed onset of action (i.e., 4 hr) and hence it is not routinely recommended outside of preventive therapy. The most common side effects associated with this agent are dry mouth and drowsiness.

Serotonin Receptor Antagonists

The serotonin receptor antagonists (e.g., dolasetron, granisetron, and ondansetron) constitute a fairly large class of agents; however, the most commonly used agent in the ED is ondansetron. These work by blocking the central 5-HT_3 receptors located in the chemoreceptor trigger zone as well as in the periphery (Chepyala & Olden, 2008; Hornby, 2001). Their efficacy is comparable with that of the other therapies and comes with a relatively low risk of side effects. The utility of these agents in postoperative nausea and vomiting and in the oncology realm is well established (Hasler & Chey, 2003). The low incidence of adverse events, specifically lower rates of sedation, has allowed

ondansetron to be considered a first-line agent in the ED for the management of nausea and vomiting. When compared directly with promethazine, ondansetron demonstrated equal efficacy in terms of nausea reduction but significantly less sedation than the promethazine group (Moser, Caldwell, & Rhule, 2006). Overall, the class has a relatively low risk of side effects, with the most common ones being headache and asymptomatic prolongation of the QT interval. Ondansetron administered 4–8 mg intravenously is the most common dose/route, although higher doses (e.g., 24 mg) may be used as part of certain oncology protocols. In the postoperative setting, comparisons of 1, 4, and 8 mg have shown no difference in efficacy, but with increasing dosages, there is an increasing risk of side effects. In the absence of compelling indications for a higher dose (e.g., chemotherapy-induced nausea and vomiting), doses greater than 4 mg are not likely to be effective and it is recommended that another agent with a different mechanism of action be considered. Ondansetron is also available in an orally dissolving formulation which is equally effective.

Although high doses of ondansetron are routinely used in the ED, doses in excess of 4 mg unnecessarily expose the patient to side effects and delay the implementation of effective therapy. Inpatients with postoperative nausea and vomiting who do not respond to prophylaxis with ondansetron are unlikely to respond to further doses (Habib & Gan, 2005). They are, however, more likely to respond to a dose of promethazine, perhaps due to its different mechanism of action. Therefore, the recommendation is that if patients do not respond to a single dose of ondansetron after 30 min, administer an agent with a different mechanism of action.

Prokinetic Agents

The therapies listed up to this point are primarily antiemetics without any prokinetic properties. Depending on the etiology of the nausea and vomiting, an agent with prokinetic agent may provide some targeted benefit. Some agents possess only prokinetic properties (e.g., erythromycin), whereas others possess both prokinetic and antiemetic properties (e.g., metoclopramide). By acting on the motilin receptors on the smooth muscle of the gastrointestinal tract, erythromycin helps modulate the vagal pathways concerned with emesis (Javid et al., 2013). At doses of 50–100 mg, this agent has some utility in managing nausea and vomiting associated with delayed gastric emptying. However, at higher doses of 250–500 mg, it can induce nausea and vomiting through contraction of the gastric fundus and inducing gastric dysrhythmias (Javid et al., 2013). Metoclopramide acts on vagal and central 5-HT_3 and D_2 receptors and results in dopamine antagonism and 5-HT_4 receptor agonist activity in the gastrointestinal tract (Singh et al., 2016). Unfortunately, this agent crosses the blood–brain barrier, leading to extrapyramidal side effects. Metoclopramide has demonstrated efficacy in the setting of migraine-associated nausea. It may also have some utility in the management of nausea and vomiting related to gastroparesis secondary to its ability to modulate gastrointestinal motility. The typical dosing of metoclopramide for this indication is 10 mg intravenously/intramuscularly every 6–8 hr.

Similar to prochlorperazine, the use of metoclopramide is limited secondary to the risk of akathisias. These side effects are dose and infusion rate related. Doses of metoclopramide greater than 10 mg have not been found to confer any additional benefit. Infusing the medication over 15 min has been found to reduce the incidence of akathisias compared with a bolus over 2 min by almost 20% ($p < 0.001$; Parlak et al., 2007). Also, like prochlorperazine, this medication can be administered concomitantly with diphenhydramine in an attempt to reduce the incidence of akathisia. This approach has been shown to reduce the incidence of this side effect by 61%, however, with an increase in the rate of sedation (Vinson et al., 2001). Administering either of these agents over 15 min obviates the need for coadministration with

diphenhydramine. Metoclopramide is also available in an orally disintegrating formulation. According to the American Geriatric Society, promethazine, prochlorperazine, and metoclopramide should be avoided in elderly patients and those with Parkinson's disease due to their anticholinergic side effects and potential to cause confusion or aggravate symptoms of confusion (Glare, Miller, Nikolova, & Tickoo, 2011).

Cost

The costs of these agents in the intravenous formulation are relatively low ranging from $0.54 to $3 for standard doses (*Red Book: Pharmacy's Fundamental Reference*; Thompson Healthcare, 2009). It is important to evaluate these costs in light of the cost of drug failure or the cost of drug side effects, which can often be high. These costs, however, can change dramatically on the outpatient side when branded formulations are utilized. Ondansetron orally disintegrating tablets are a great example ($26/4 mg) compared with regular release tablets ($0.20/4 mg) (Thompson Healthcare, 2009). Metoclopramide, promethazine, and prochlorperazine tablets are priced similarly to ondansetron regular release tablets and therefore are affordable to most patients without insurance. Scopolamine patches can also be somewhat cost prohibitive and so their use should be critically evaluated.

SPECIAL POPULATIONS

Pediatric

Although the list of potential etiologies of nausea and vomiting in pediatric patients is as extensive as it is in adults, in children younger than 5 years, acute gastroenteritis is common and results in 220,000 hospitalizations per year, with 8.9% of patients younger than 18 years receiving a prescription for an antiemetic despite it not being recommended (American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis, 1996; Li, DiGiuseppe, & Christakis, 2003). Antiemetic use in this population is approached with caution because of the concern regarding extrapyramidal side effects that can occur with dopamine receptor antagonism. Hence, similar to the adult population, ondansetron is a first-line agent in this population. In an evaluation of 54 trials that included ondansetron, droperidol, and metoclopramide, a subgroup analysis of pediatric patients found that ondansetron was more effective than droperidol (Domino, Anderson, Polissar, & Posner, 1999). The dose of intravenous ondansetron in the pediatric population is 0.15 mg/kg, with a maximum dose of 4–8 mg depending on the indication (Freedman & Fuchs, 2004).

Hyperemesis Gravidarum

Approximately 75% of women experience nausea during pregnancy, and 50% experience both nausea and vomiting (Goodwin, 2008). Hyperemesis gravidarum (HG) is a condition characterized by persistent vomiting, weight loss, ketonuria, electrolyte abnormalities, and dehydration. It occurs in less than 1% of pregnancies (Goodwin, 2008). Following fluid and electrolyte replacement, about 10% of women still require pharmacotherapy (Goodwin, 2008). The mainstays of therapy for HG include vitamin B_6 and antihistamines as well as other agents. The American College of Obstetricians and Gynecologists (2015) recommends the combination of vitamin B_6 and the antihistamine doxylamine as first-line therapy for nausea and vomiting in pregnancy. The combination product of 10 mg of doxylamine succinate and 10 mg of pyridoxine (Diclegis) can be cost prohibitive, especially for patients lacking insurance. Each individual component is available over the counter (OTC) without a prescription. However, it should be noted that the strengths of the OTC tablets differ slightly. Other antihistamines are also options, and none have been shown to be teratogenic (e.g., diphenhydramine, meclizine, hydroxyzine; Niebyl, 2010). In patients who are refractory to this combination, often a phenothiazine or

metoclopramide are prescribed (Niebyl, 2010). Both have demonstrated similar efficacy with metoclopramide yielding less sedation, and neither showed significant associations with birth defects (Park-Wyllie et al., 2000). The 5-HT_3 antagonist ondansetron has been used extensively in this population; however, limited data exist regarding its safety in pregnancy and its routine use is controversial (Einarson et al., 2004). The evidence available has mixed results on ondansetron use in this population, and there is concern for an increased risk of adverse fetal outcomes such as cleft palate and neural tube defects, especially when used in the first trimester of pregnancy (Danielsson, Wikner, & Kallen, 2014; Pasternak, Svanstrom, & Hviid, 2013). Although recent literature has provided conflicting recommendations regarding the use of ondansetron in the setting of pregnancy, the American Academy of Family Physicians acknowledges that these data exist but says that the risk is very low (Herrell, 2014). The authors of a recent review of the literature regarding the use of ondansetron therapy in this role concluded that the maternal benefit outweighed the current proposed risks in the setting of pregnancy.

Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting are theorized to occur secondary to stimulation of a wide array of receptors that are both centrally and peripherally located, as well as multiple neurotransmitters and receptors (Tageja & Groninger, 2016). This condition is also traditionally broken down into three categories: acute (occurring within minutes to hours after chemotherapy administration), delayed (occurring more than 24 hr after chemotherapy administration), and anticipatory (preceding administration) (Tageja & Groninger, 2016). Although unique agents may be utilized in the oncology clinic to manage these conditions, upon presentation to the ED, the most common approach will be the coadministration of a 5-HT_3 antagonist such as ondansetron combined with a steroid such as dexamethasone (Tageja & Groninger, 2016). Although the exact mechanism remains to be elucidated, the combination of corticosteroids with 5-HT_3 antagonists (i.e., ondansetron) has been found to have a role in both acute and delayed chemotherapy-induced nausea and vomiting. In the postoperative arena, steroids may even have equivalent efficacy compared with ondansetron alone (Chepyala & Olden, 2008; Sanger & Andrews, 2006). Benzodiazepines (e.g., lorazepam) are also commonly used in the management of chemotherapy-induced nausea and vomiting. Benzodiazepines have demonstrated utility in the area of anticipatory nausea and vomiting associated with chemotherapy owing to their anxiolytic, amnestic, and sedative properties (Chepyala & Olden, 2008; Rodola, 2006).

Cannabinoid Hyperemesis Syndrome

Although it is unclear what causes cannabinoid hyperemesis syndrome, the incidence is increasing as cannabinoid use gains popularity. Patients may return frequently to the ED, and the diagnosis is often missed because of unfamiliarity with this as a cause of nausea and vomiting and patients being reluctant to share drug use history. What seems to be consistent in presentation is long-term cannabinoid use, profound abdominal pain, and propensity to take frequent hot showers. Care is largely supportive; correcting dehydration and electrolytes may be helpful. Ultimately, the symptoms are self-limiting, ceasing after several days if cannabinoid use stops (Galli, Sawaya, & Friedenberg, 2011).

CONCLUSION

There are a variety of potential etiologies for patients presenting to the ED with nausea and vomiting. Fortunately, there is also a variety of therapeutic agents with multiple mechanisms of action to combat this often challenging presentation. Ensuring that the most effective agent with the fewest accompanying side effects is prescribed is critical to the

successful management of these symptoms. It is also important that these agents be dosed and infused as safely as possible so as not to not cause potentially devastating side effects.

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