Antiemetic Medications

2.0 Contact Hours
California Board of Registered Nursing CEP# 16140
American Medical Education Center

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Title: Antiemetic Medications
Self Study Module 2.0 CONTACT HOURS
Suggestion: Read through these questions before the module as they will be the SAME questions on the required online exam.

Choose the Single Best Answer for the Following Questions and Place Answers on Form:

1. Which of the following is not a long term complication of nausea and vomiting?
   a. Dehydration
   b. Hyperkalemia
   c. Malnutrition
   d. Metabolic alkalosis

2. Which is false about risk factors for nausea and vomiting?
   a. Men are more likely than women to develop emesis
   b. Inadequate hydration can be associated with nausea
   c. Nausea and vomiting is common after general anesthesia
   d. Patients with anxiety may be prone to vomiting

3. Which of the following cancer drugs is associate with a very high risk for emesis?
   a. Vinca alkaloids
   b. Bleomycin
   c. Rituximab
   d. Cisplatinum

4. Which of the following cancer drugs has a low risk for emesis?
   a. Carmustine
   b. Cisplatinum
   c. Bleomycin
   d. Cyclophosphamide

5. In general, for treatment of chemotherapy induced nausea and vomiting, the antiemetics work well when combined with-
   a. Proton pump inhibitor
   b. Corticosteroid
   c. Local anesthetic
   d. An analgesic

6. The antiemetic of choice for patients with motion sickness is-
   a. Ondansetron
   b. Aprepitant
   c. Dimenhydrinate
   d. Chlorpromazine

7. The antiemetic drug that is often used to treat migraine associated nausea and vomiting is-
   a. Ondansetron
   b. Scopolamine
   c. Diphenhydramine
   d. Chlorpromazine

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8. When using droperidol for the treatment of nausea and vomiting, it is important to monitor-
   a. ECG
   b. Blood pressure
   c. Oxygenation
   d. Platelet count

9. The antiemetic used to prevent weight loss in AIDS patients is-
   a. Metoclopramide
   b. Granisetron
   c. Droperidol
   d. Nabilone

10. Aprepitant is a relatively new antiemetic that mediates its effects by blocking which receptor?
    a. Serotonin
    b. Neurokinin
    c. Glutamate
    d. GABA

11. Which sedative is sometimes used in combination with other antiemetics for treatment of emesis?
    a. Bupropion
    b. Lorazepam
    c. Sodium barbital
    d. Zolpidem

12. Which prokinetic agent is often used to treat emesis and gastroparesis?
    a. Diphenhydramine
    b. Chlorpromazine
    c. Ondansetron
    d. Metoclopramide
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Self Study Module 2.0 CONTACT HOURS

Objectives

At the completion of this program, the learners will:

1. Explain the causes, classification and risk factors for of nausea and vomiting.
2. Describe the classes of drugs used to treat nausea and vomiting.
3. Discuss the adverse reactions of the different class of drugs used to treat nausea and vomiting.

Nausea is described as an unpleasant sensation that is experienced at the back of the throat and or stomach that may or may not result in the act of vomiting.

Vomiting is the forceful expulsion of stomach contents via the oral cavity.

Nausea and vomiting are very common complaints in most healthcare settings. Millions of people visit the ER for prolonged nausea and vomiting. Today, there are a number of antiemetic agents used to treat symptoms of nausea and vomiting.

There are many causes of nausea and vomiting and are classified as follows:

- Postoperative nausea and vomiting
- Chemotherapy induced nausea and vomiting.
- Radiation induced nausea and vomiting.
- Opioid induced nausea and vomiting
- Miscellaneous- bowel obstruction or other GI pathology
- Hyperemesis gravidarum

Nausea and vomiting is further classified as follows:

Acute when it occurs within 24 hours after administration of radiation therapy of chemotherapy.

Delayed when it occurs more than 24 hours after radiation or chemotherapy and may last up to 5 days.

Anticipatory when it occurs before the radiation or chemotherapy has started. This often requires multiple drugs for control.

Nausea and vomiting are very common after both radiation and chemotherapy. Past studies indicate that anywhere from 60-90% of patients suffer from varying degree of nausea and vomiting after chemotherapy/radiation. Even though several classes of drugs are available, the antiemetic efficacy is only about 70-80 % in cancer patients.¹
**Adverse Effects of Nausea/Vomiting**

Mild nausea and vomiting which is of short duration may just be an annoyance but long term symptoms can have a variety of medical consequences like:

- Dehydration
- Electrolyte disturbances (hypokalemia, metabolic alkalosis)
- Aspiration pneumonia
- Weight loss
- Malnutrition
- Delays in initiation or continuing with chemotherapy
- Poor quality of life

Nausea and vomiting can be very distressing to the patient and affect quality of life. The patient may develop anxiety, apprehension or fear of more treatment. The patient may become withdrawn and non-compliant with treatment. Countless working days are lost each year and the cost of looking after these patients is enormous.

Finally nausea and vomiting also affect finances. These patients often are not able to eat and may require additional treatment or admission to the hospital. Some patients may even require IV hydration and/or parenteral nutrition if the symptoms are severe.

**Pathology of Emesis**

Vomiting and nausea occur due to stimulation of the chemoreceptor trigger zone in the brain, vestibular apparatus, cortical structures or peripheral receptors in the stomach. Emesis may also be caused by stimulation of certain neural elements in the gastrointestinal tract. The neurotransmitters involved in emesis include serotonin, histamine, dopamine and neurokinin.

**Risk Factors for Nausea and Vomiting**

Not everyone develops emesis and there are some patient specific risk factors such as:

Age- emesis is more likely in younger patients compared to older patients.

Women are more likely to develop emesis compared to men.

Patients with a prior history of emesis after chemotherapy and radiation are more likely to have recurrence of symptoms.

Patients with a history of motion sickness are more susceptible to develop emesis.

Women who develop nausea and vomiting during pregnancy usually remain prone to further episodes.

Low consumption of alcohol is known to trigger vomiting. However, high levels of alcohol seem to lower the urge to vomit.

Inadequate hydration is also a common cause of nausea.
Post-surgery patients are prone to developing nausea and vomiting.

Patients with anxiety are also prone to developing emesis.

**Nausea and Vomiting in Malignancy**

There are several treatment specific factors that determine the potential for emesis in cancer patients.

They include the following:

- Type of chemotherapeutic agent used
- Rate of infusion
- Repetitive dosing
- Site of radiation
- Dose of radiation
- Combined radiation and chemotherapy
- Stage of tumor

Nausea and vomiting can occur after many chemotherapeutic drugs but the highest risk is with the following drugs:

- Carmustine
- Cisplatinum-most frequently associated with emesis
- Cyclophosphamide
- Dacarbazine
- Nitrogen mustard
- Streptozotocin

The lowest risk of emesis is with the following cancer drugs:

- Bleomycin
- Cladribine
- Fludarabine
- Rituximab
- Vinca alkaloids

**Antiemetic Medications**

Several types of drugs are used to treat emesis including anti histamines, dopamine antagonists, serotonin antagonists and agents which block the neurokinin receptor. In certain situation, the older antiemetics like metoclopramide and prochlorperazine may also be useful. In general, when treating patients with chemotherapy induced nausea and vomiting, combination therapy with corticosteroids is beneficial. While the newer antiemetics are effective, they are also costly.

Antiemetic drugs available today include the following:

**Antihistamines**
These agents decrease stimulation of the vomiting center in the vestibular apparatus. When used for short periods, the antihistamines are well tolerated and relatively cheap. They are best used for motion sickness. Overall, antihistamines are weak antiemetic agents. It is important to advise patients not to drive as most antihistamines can cause sedation.

**Meclizine (Antivert)** is a weak antiemetic agent and rarely works in cancer patients. It has many side effects, which include sedation, dizziness, insomnia, fatigue, poor coordination and tremors.7

**Dimenhydrinate (Dramamine)** is an effective antiemetic available as a solution and suppository. It usually takes a few hours to take effect. The disadvantage of the drug is the moderate sedation.

**Diphenhydramine (Benadryl)** is a very weak antihistamine used to treat allergies, insomnia and nausea. Because the drug is sedating, it is not much used today.

**Anticholinergic Agents**

Scopolamine is an anticholinergic alkaloid used to treat motion sickness. It is available as a transdermal patch that remains effective for up to 3 days. Adverse effects are urinary retention, blurred vision, dry mouth and exacerbation of glaucoma.7

**Dopamine Antagonists**

Drugs that block the dopamine receptor in the chemoreceptor trigger zone can reduce nausea and vomiting. Although dopamine antagonists are effective and inexpensive, they also possess a wide range of adverse effects. The dopaminergic agents are usually given intravenously. Because they tend to cause hypotension, an intravenous saline drip is usually run at the same time. Once the drug has been infused, the antiemetic effects are rapid-usually within 5-10 minutes. Repeat dosing is very rare. After the treatment is over, patients are usually observed for 30-60 minutes and vital signs are measured. The dopamine antagonists may cause sedation, neuroleptic malignant syndrome, agranulocytosis, orthostatic hypotension and extrapyramidal symptoms. Today, serotonergic antagonists have completely replaced the dopamine antagonists for treatment of emesis.7

**Chlorpromazine (thorazine)** is used intravenously for treatment of nausea. It is very effective, works rapidly and can be used alone. It is most often used to treat migraine associated nausea and vomiting. The major disadvantage of the drug are its anticholinergic side effects. These include constipation, dry mouth, slurred speech, urine retention and sedation. When used intravenously, the patient should be well hydrated as the drug does cause hypotension. It is important to know that even low dose of chlorpromazine may trigger seizures in susceptible patients.

**Droperidol (inapsine)** is one of the oldest antiemetic agent. It was once widely used but in 2001, the FDA issued a black box warning against the use of droperidol due to a concern for QT prolongation and torsade. This has led to a significant decline in its usage. Nevertheless, droperidol is very effective in reducing nausea and vomiting. If it is used, ECG monitoring is recommended for 2-3 hours after completion of therapy.7

**Prochlorperazine (Compazine)** is a weak antiemetic agent often used to treat post-operative patients. It is available as an oral liquid, injectable and as suppository. Its antiemetic effects are
rapid and often last 4-6 hours. It may cause dyskinesia.\(^7\)

**Promethazine (Phenergan)** is a 1st generation antihistamine and was in the past used to treat motion sickness and nausea. It is also found in many allergic preparations. Adverse effects are more common in elderly and range from confusion, drowsiness to tardive dyskinesia. When the drug is used parenterally, it has been associated with blood vessel irritation and even necrosis leading to amputation. It is not known if this is simply due to accidental intra-arterial administration but it is no longer a first line drug.\(^7\)

**Selective serotonin antagonists** also decrease nerve discharge from the vomiting center in the brain and are the drugs of choice. These drugs are safe, and have minimal side effects. The serotonin antagonists are primarily used to treat and prevent nausea and vomiting from chemotherapy and radiation.\(^8,9\)

The antiemetic effects of the serotonin antagonists can be enhanced by concomitant use of dexamethasone. The most common adverse effects of serotonin antagonists include diarrhea, headache and fatigue. In a few patients transient elevations of liver enzymes may be seen, which are reversible when the drug is discontinued. The one negative about these drugs is their high cost.

**Dolasetron (Anzemet)** is only used orally. IV drug use is not recommended as the drug has been associated with dose dependent QT prolongation.\(^7\)

**Ondansetron (Zofran)** is effective as an antiemetic and also used in post-surgical patients with emesis. It is also used off label for the treatment of hyperemesis gravidarum. For chemotherapy induced nausea and vomiting, the dose is 4-8 mg intravenously. A second dose may be required 6-8 hours later. The antiemetic effects of ondansetron can be augmented by dexamethasone.\(^7\)

**Granisetron (Kytril)** has same benefits as the above drugs.

**Cannabinoids**

**Nabilone (Cesamet)** is a synthetic cannabinoid, which is sometimes used as an antiemetic.\(^10\) It is also approved for treatment of anorexia and weight loss in patients with AIDS. There are some experts who advocate nabilone for chronic pain, although there is no clinical evidence that it has analgesic effects. Nabilone seems to work better as an antiemetic agent when combined with the serotonin antagonists. As monotherapy, its antiemetic effects are mild. The most common adverse effects of nabilone include vertigo, drowsiness, dry mouth, headache, ataxia and concentration difficulties. Fortunately, the effects are mild and well tolerated. Patients should be warned about consuming nabilone with sedatives, alcohol or other psychoactive agents. Finally, nabilone should be used with great caution in people with mental health disorders and a history of substance abuse.\(^7\)

**Dronabinol (Marinol)** is an extract from the cannabis plant. It is used sometimes to treat emesis in patients undergoing chemotherapy and radiation. The drug has also been approved for treatment of anorexia in AIDS patients. Dronabinol requires a prescription and is not readily available in all retail pharmacies. There is still controversy
regarding it benefits as an antiemetic agents because large scale trials have not been conducted.

At present there are legal concerns regarding the prescribing of marijuana related products. Medically, these products are not recommended by the oncologists for treatment of emesis in cancer patients. although, marijuana related products are available. In some states, the federal government has been clamping down on pharmacies that sell these drugs.7

**Neurokinin Antagonists**

**Aprepitant (Emend)** is a relatively new antiemetic that block substance P.11,12 The drug is known to mediate its effect by blocking the neurokinin1 receptor. Aprepitant has been approved for the treatment of chemotherapy-induced nausea and vomiting. It is also used for post-surgical patients who fail to respond to the serotonin antagonists. For chemotherapy induced nausea, aprepitant capsules are prescribed for 3 days as part of a regimen that includes a serotonin antagonist and dexamethasone. The pill is taken 1 hour prior to chemotherapy and then continued once daily on days 2 and 3.

**Fosaprepitant** is the intravenous formulation of aprepitant.

Side effects reported include hiccups, fatigue and slight elevation of liver enzymes.

**Other Agents**

Dexamethasone is a potent corticosteroid that has been used to treat postoperative nausea and vomiting, especially in surgery patients. Doses of 2-8 mg are usually used intravenously to prevent opioid induced nausea and vomiting. When given 1 hour prior to general surgery procedures, it has also been shown to reduce post-operative fatigue and nausea. Dexamethasone is also widely used to prevent chemotherapy induced nausea and vomiting for high risk patients. It works best when combined with other antiemetic agents.13

**Trimethobenzamide (Tigan)** is an old antiemetic agent. It was once frequently used to treat postoperative nausea and vomiting. Because it does not have any serotonergic or antidopaminergic effects, it also has fewer side effects. The drug is safe and can be used orally or IV. The rectal suppositories are no longer available because they are ineffective.7

**Haloperidol (Haldol)** is known to possess antiemetic properties. Studies show that 1-1.25 mg of haloperidol administered IV can help reduce postoperative nausea and vomiting. Haloperidol also has a rapid onset of action. The antiemetic effects of haloperidol are attributed to its strong peripheral antidopaminergic effects and inhibition of the chemoreceptor trigger zone. Haloperidol is also used for treatment of chemotherapy-induced nausea and vomiting. The one major negative about haloperidol includes its ability to induce extrapyramidal symptoms. The risk of tardive dyskinesia of the face is about 4-6% in young patients. The drug can also induce akathisia, which can manifest itself with dysphoria, anxiety and inability to remain still.7

**Lorazepam (Ativan)** is a moderately effective benzodiazepine for the treatment of emesis. it is never used alone but in combination with either dexamethasone or serotonin antagonists. It is often used to treat anticipatory nausea and vomiting from chemotherapeutic drugs. The drug is also used to treat acute symptoms of dizziness and vertigo in people with Meniere’s disease. Adverse effects of lorazepam include sedation and hypotension. When the drug is administered
intravenously, it is vital to monitor the patient. Vital signs should be obtained frequently (every 2-5 mins) and the patient should be hooked to pulse oximetry. Lorazepam is effective for short-term use but long-term use is associated with tolerance and dependence. Tolerance is known to occur after 3-5 months of regular use.7

Metoclopramide (Reglan) is not a first line agent for nausea and vomiting. It is classified as a prokinetic agent and moderately effective for diabetic gastroparesis. It is also used to treat nausea and vomiting in post-surgical patients, uremia, labor, migraine and malignancy. The drug is known to increase peristaltic movements of the proximal small bowel and also relaxes the pyloric sphincter-which facilitates gastric emptying. The major limitations of metoclopramide are its adverse effects that include drowsiness, fatigue, and focal dystonia.7

Metoclopramide is commonly associated with extrapyramidal effects, especially in young people. The risk of tardive dyskinesia is increased with prolonged therapy or high doses. Once tardive dyskinesia develop, the disorder is almost impossible to cure. Hence, it is highly recommended that metoclopramide only be used at low doses (5 mg 2-3 times a day) and for less than 12 weeks.

Anticipatory Nausea and Vomiting

Antiemetic drugs usually do not help control anticipatory nausea and vomiting once the symptoms have developed. Behavior therapy may help some patients. For other patients, the disorder can be managed with combination of ondansetron, aprepitant, lorazepam or a corticosteroid. This combination needs to be administered 30-45 minutes prior to initiating chemotherapy.

Treatment of Nausea/Vomiting in Pregnancy

Pregnancy is often associated with nausea and vomiting. It is believed that nausea and vomiting occur in 50-90 percent of women during some point in the pregnancy. While this is nothing more than a transient nuisance for some women, in others it is often persistent and lasts for many weeks. The most severe form of nausea and vomiting during the first trimester of pregnancy is known hyperemesis gravidarum. The nausea and vomiting are typically seen in the first trimester and start around the 8-10th week of pregnancy, peak at 11-13 weeks and resolve in the majority of cases by the 14th week. In about 1-10% of pregnancies, the nausea and vomiting may persist until the 22nd week of pregnancy.14

Besides nausea and vomiting, hyperemesis is also associated with ketosis and weight loss. If the disorder is prolonged and severe, it may result in dehydration, acid base imbalance and loss of electrolytes. Nutritional deficiencies and even deaths have been reported. Anywhere from 0.3-2% of pregnant women with hyperemesis need hospital admission.

Pharmacologic Therapy of Hyperemesis Gravidarum

If possible, the use of drugs should be minimized in hyperemesis gravidarum. Because of the issue of teratogenicity, there have been no randomized clinical trials to compare the effectiveness of drugs in this disorder. To date, there is no evidence that one class of drugs is superior to another with regard to effectiveness.

The disorder commonly occurs during the first trimester which is known to be the most critical
time for the growth of the fetus- any insult to the growing fetus by an external factor such as a drug can be disastrous.

Pyridoxine

If pharmacological therapy is deemed necessary, the first treatment of choice is vitamin B6 (pyridoxine). This vitamin B supplement plays a role in the synthesis of many substrates and also acts as a cofactor for enzymes. It is administered at 10-25 mg three to four times a day. Vitamin B6 has been found to be effective in several clinical trials for the treatment of nausea and vomiting during pregnancy. Some physicians administer it with doxylamine, which is an old anti histamine. Doxylamine is available as Dilectin. The older formula, benedectin, has been taken off the market in the USA, but is available in other countries. Doxylamine has been used for many decades and is considered safe during pregnancy.

Antihistamines

Antihistamines have empirically been used to treat nausea and vomiting during pregnancy for many years. Several studies show that these drugs do provide relief of symptoms in over 80% of patients. The older generation of antihistamines are sedating and thus, the lowest dose should be used.

Meclizine (Antivert) is a very old antihistamine that is used to treat motion sickness and also provides relief from nausea and vomiting. Only an oral formula is available and it may not work well in patients with continuous waves of nausea and vomiting. The dose for mild nausea is 12.5 mg orally every 6-8 hours.

Diphenhydramine (Benadryl) is another old antihistamine, which has been used to treat insomnia, pruritis and nausea. The drug also has mild anticholinergic effects and induces sedation. The dose is 12.5 - 25 mg every 4-6 hours.

Herbal Supplements

Even though there are many herbals sold in food stores as a treatment for hyperemesis gravidarum, the majority of these products have not been approved by the FDA. Only ginger has been shown to be effective for nausea and vomiting during pregnancy. Clinical studies do show that ginger extracts are effective when compared to placebo. The herb ginger is available as a capsule and is effective in the treatment of hyperemesis gravidarum. It is administered at 250 mg four times a day.\(^{15}\)

Other agents used for treatment of hyperemesis gravidarum include prochlorperazine (compazine), promethazine (phenergan) and chlorpromazine (thorazine, ormazine).

Ondansetron (Zofran) is used if the nausea still persists. The drug is may be administered at 4-8 mg orally or IV every 8 hours. Methylprednisolone (Medrol, Solu-Medrol) may improve symptoms of nausea and vomiting. For emesis the initial dose is 15- 30 mg IV twice a day, and then rapidly tapered over the next few days. Steroids should only be used for recalcitrant cases and when the above treatments have failed.

Selection of Antiemetic based on Clinical Scenario
Migraine Metoclopramide, prochlorperazine or serotonin antagonists
Motion sickness Antihistamines or Anticholinergics
Pregnancy Ginger, vitamin B6
Gastroenteritis Dopamine antagonists
Post-Surgery Serotonin antagonists, dopamine antagonists, Dexamethasone
Chemotherapy Usually a cocktail of serotonin antagonists, steroid and a dopamine antagonist.

References


10. Kranke P, Eberhart LH. Possibilities and limitations in the


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