NAUSEA AND VOMITING

DEFINITION

Nausea is usually defined as the inclination to vomit or as a feeling in the throat or epigastric region alerting an individual that vomiting is imminent. Vomiting is defined as the ejection or expulsion of gastric contents through the mouth, often requiring a forceful event.

PATHOPHYSIOLOGY

- The three consecutive phases of emesis include nausea, retching, and vomiting. Nausea, the imminent need to vomit, is associated with gastric stasis. Retching is the labored movement of abdominal and thoracic muscles before vomiting. The final phase of emesis is vomiting, the forceful expulsion of gastric contents due to gastrointestinal (GI) retroperistalsis.
- Vomiting is triggered by afferent impulses to the vomiting center, a nucleus of cells in the medulla. Impulses are received from sensory centers, such as the chemoreceptor trigger zone (CTZ), cerebral cortex, and visceral afferents from the pharynx and GI tract. When excited, afferent impulses are integrated by the vomiting center, resulting in efferent impulses to the salivation center, respiratory center, and the pharyngeal, GI, and abdominal muscles, leading to vomiting.
- The CTZ, located in the area postrema of the fourth ventricle of the brain, is a major chemosensory organ for emesis and is usually associated with chemically induced vomiting.
- Numerous neurotransmitter receptors are located in the vomiting center, CTZ, and GI tract. Examples of such receptors include cholinergic and histaminic, dopaminergic, opiate, serotonin, and benzodiazepine receptors. It is theorized that chemotherapeutic agents, their metabolites, or other emetic compounds trigger the process of emesis through stimulation of one or more of these receptors.

▶ CLINICAL PRESENTATION

- Nausea and vomiting may be classified as either simple or complex. The term simple applies to those episodes of nausea and/or vomiting described by one of the following criteria: (1) occur occasionally and are self-limiting or relieved by the minimal use of antiemetic methods or medications; (2) account for little patient deterioration such as fluid–electrolyte imbalances, pain, or noncompliance with prescribed therapies; or (3) are not related to the administration of or exposure to noxious agents.
- The term complex is used when describing a patient's clinical course as including symptoms that are not adequately or readily relieved by the administration of a single antiemetic method or medication; lead to progressive patient deterioration secondary to fluid–electrolyte imbalances, pain, or noncompliance with prescribed therapies; or are caused by noxious agents or psychogenic events.

One such region is the area postrema. Being in contact with the cerebrospinal fluid (CSF) in the IVth ventricle, this region can detect agents in both the blood and the CSF (Figure 1).

Stimulation of either the gastro-intestinal or central pathway results in activation of a 'vomiting centre' (VC) located in the reticular formation of the medulla close to the area postrema.

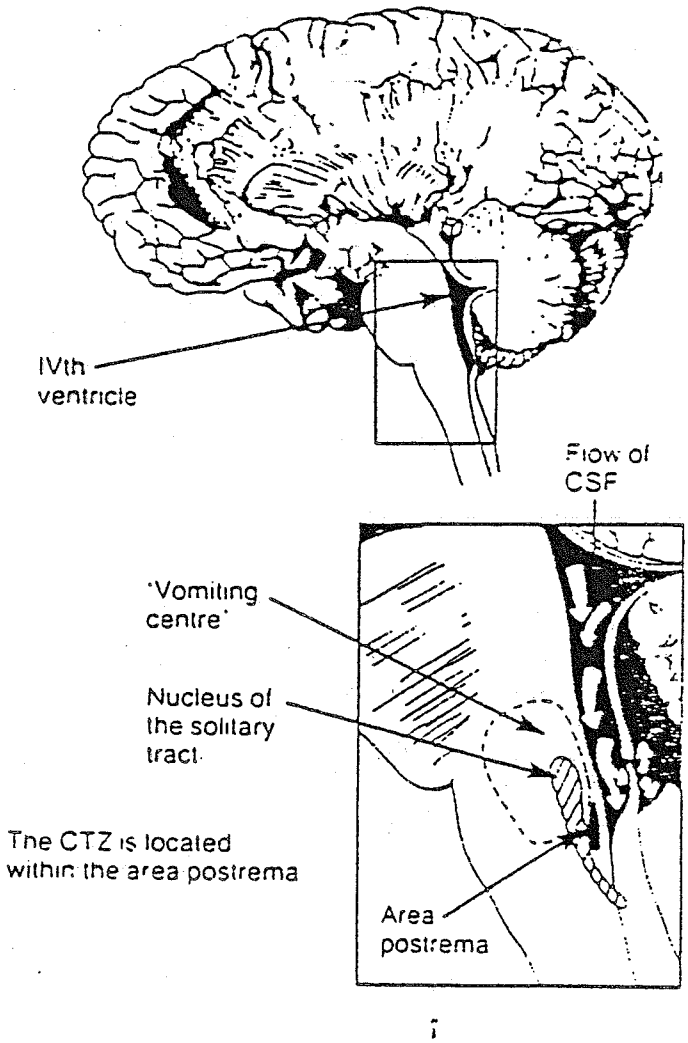


Figure 1. The anatomical location of the area postrema and the region of the vomiting centre.

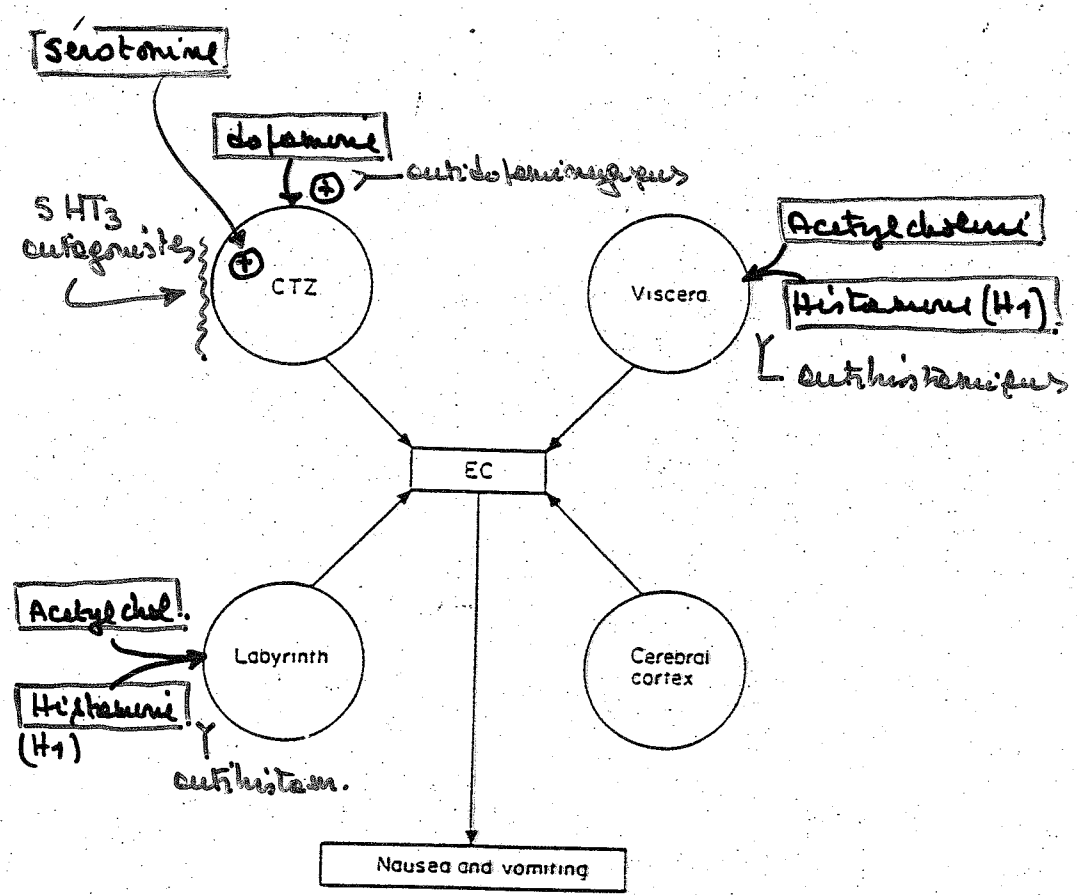


Fig. 49. Diagrammatic summary of the pathways concerned with the control of emesis. CTZ is the chemoreceptor trigger zone. EC is the emetic centre.

TABLE 25–1. Specific Etiologies of Nausea and Vomiting

Gastrointestinal
- Gastric outlet obstruction
- Motility disorders
- Intra-abdominal emergencies
  - Intestinal obstruction
  - Acute pancreatitis
  - Acute pyelonephritis
  - Acute cholecystitis
  - Acute cholangitis
  - Acute viral hepatitis
- Acute gastroenteritis

Cardiovascular Diseases
- Acute myocardial infarction
- Congestive heart failure
- Shock and circulatory collapse

Neurologic Processes
- Midline cerebellar hemorrhage
- Increased intracranial pressure
- Migraine headache
- Vestibular disorders
- Head trauma

Metabolic Disorders
- Diabetes mellitus (diabetic ketoacidosis)
- Addison's disease
- Renal disease (uremia)

Psychogenic Causes
- Self-induced
- Anticipatory

Therapy-Induced Causes
- Cytotoxic chemotherapy
- Radiation therapy
- Theophylline preparations (intolerance, toxic)
- Anticonvulsant preparations (toxic)
- Digitalis preparations (toxic)
- Opiates
- Amphotericin
- Antibiotics

Drug Withdrawal
- Opiates
- Benzodiazepines

Miscellaneous Causes
- Pregnancy
- Any swallowed irritant (foods, drugs)
- Noxious odors
- Operative procedures

plaintes fréquemment dues à la grossesse
référer au médecin

▶ TREATMENT

GENERAL PRINCIPLES

- Most cases of nausea and vomiting are self-limiting, resolve spontaneously, and require only symptomatic therapy.
- Antiemetic therapy is indicated in patients with electrolyte disturbances secondary to vomiting, severe anorexia or weight loss, or progression of disease either owing to refusal of continued therapy or poor nutritional status.

NONPHARMACOLOGIC MANAGEMENT

- For patients with simple complaints, perhaps related to food or beverage consumption, a change in diet may be appropriate.
- Symptoms related to labyrinthe changes produced by motion may benefit by assuming a stable position.
- Psychogenic vomiting may benefit from psychological interventions, hypnosis, behavioral modifications, and guided mental imagery.

PHARMACOLOGIC MANAGEMENT

- Antiemetic drugs [over-the-counter (OTC) and prescription] are most often recommended to treat nausea and vomiting. Provided that a patient can and will adhere to oral dosing, a suitable and effective agent can often be selected; however, for certain other patients, oral medications may be inappropriate because of their inability to retain any appreciable oral ingestion. In these patients, the rectal or injectable route of administration might be preferred.

- For most conditions, a single-agent antiemetic is preferred; however, for those patients not responding to such therapy and those receiving highly emetogenic chemotherapy, multiple-agent regimens are usually recommended.

- The treatment of simple nausea and vomiting usually requires minimal therapy. Both OTC and prescription drugs useful in the treatment of simple nausea and vomiting are usually effective in small, infrequently administered doses.
- The management of complex nausea and vomiting may require aggressive drug therapy, possibly with more than one antiemetic agent.
- For patients receiving highly emetogenic chemotherapy, antiemetic regimens may include one or more of the following agents: **prochlorperazine, metoclopramide, ondansetron, granisetron, dexamethasone,** or **lorazepam**

DRUG CLASS INFORMATION

Antacids

- Single or combination OTC antacid products, especially those containing magnesium hydroxide, aluminum hydroxide, and/or calcium carbonate, may provide sufficient relief of simple nausea/vomiting, primarily through gastric acid neutralization.
- Common antacid dosage regimens for the relief of nausea and vomiting include one or more small doses of single- or multiple-agent products.

Antihistamines, Anticholinergics

- Antiemetic drugs from the antihistaminic–anticholinergic category may be appropriate in the treatment of simple symptomology. However, when used alone, each provides little efficacy in patients with more complex complaints such as those caused by cytotoxic chemotherapy.
- Adverse reactions that may be apparent with the use of the antihistaminic–anticholinergic agents primarily include drowsiness or confusion, blurred vision, dry mouth, urinary retention, and possibly tachycardia, particularly in elderly patients.

Phenothiazines

- Phenothiazines are most useful in patients with simple nausea and vomiting or in those receiving mildly emetogenic doses of chemotherapy.
- Rectal administration is most preferred when parenteral administration is impractical or oral medications cannot be retained and are therefore ineffective.
- In many patients, low doses of phenothiazine drugs may not be effective, while larger doses may produce unacceptable risks.
- Problems associated with these drugs include troublesome and potentially dangerous side effects, including extrapyramidal reactions, hypersensitivity reactions with possible liver dysfunction, marrow aplasia, and excessive sedation.

Butyrophenone (Haloperidol and Droperidol)

- Preoperative doses may range from 2.5 to 10 mg, while dosage regimens during cytotoxic chemotherapy have been documented as low as 0.5–2.5 mg by intermittent injection to as great as 1.0–1.5 mg/h by IV infusion.
- Adverse reactions resulting from the use of the butyrophenone compounds primarily include sedation and the possibility of dystonic reactions.

Corticosteroids

- Corticosteroids have been used successfully in the management of CINV with few problems.
- Reported adverse effects have included mood changes ranging from anxiety to euphoria as well as headache, a metallic taste in the mouth, abdominal discomfort, hyperglycemia, and itchy throat.

Metoclopramide

- **Metoclopramide** increases lower esophageal sphincter tone, aids gastric emptying, and accelerates transit through the small bowel, possibly through the release of acetylcholine.
- Because the adverse reactions to metoclopramide include extrapyramidal effects, IV **diphenhydramine** 25–50 mg should be prophylactically administered or provided on-call for its anticipated need.

Serotonin Antagonists (Ondansetron, Granisetron, Dolasetron)

- 5-HT_3 selective serotonin antagonists act by blocking serotonin receptors located in the area postrema and possibly vagal afferent fibers in the upper GI tract.
- Although potentially important agents for cancer patients, 5-HT_3 serotonin receptor antagonists have provided no beneficial effects in reducing motion sickness when compared with placebo.

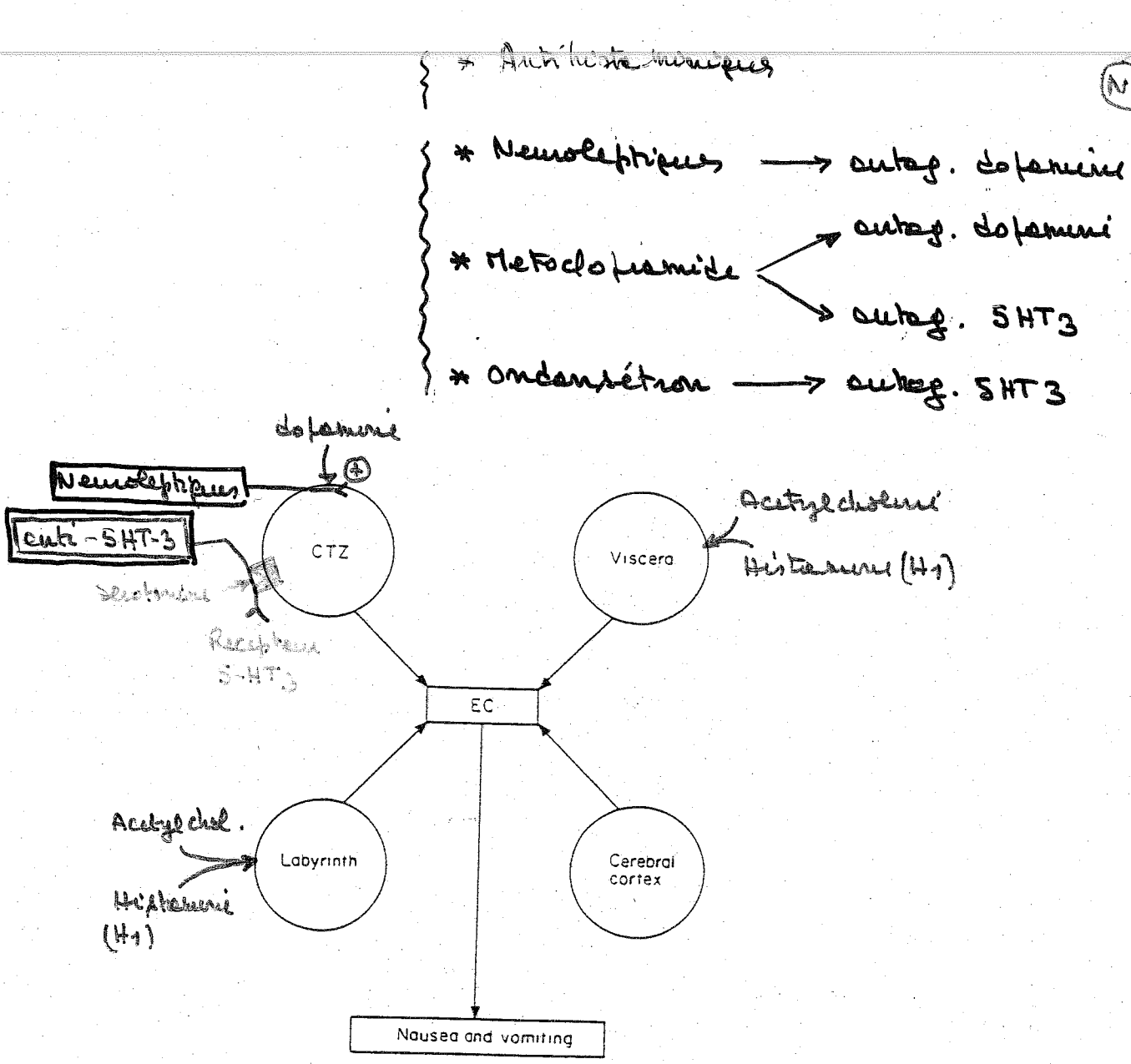
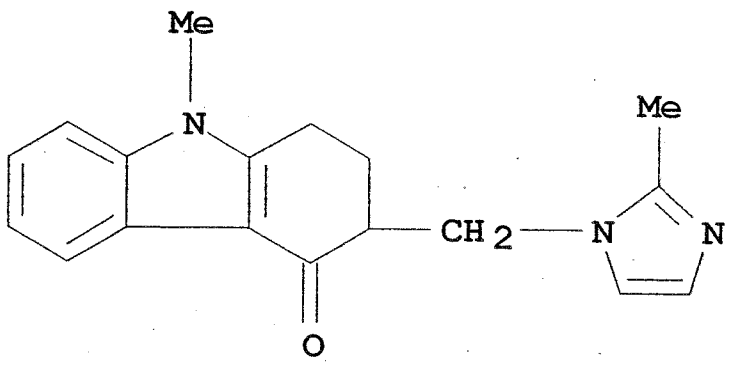
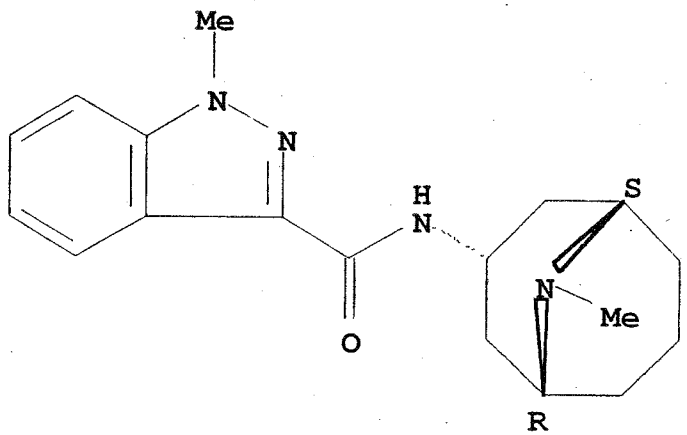


Fig. 49. Diagrammatic summary of the pathways concerned with the control of emesis. CTZ is the chemoreceptor trigger zone. EC is the emetic centre.

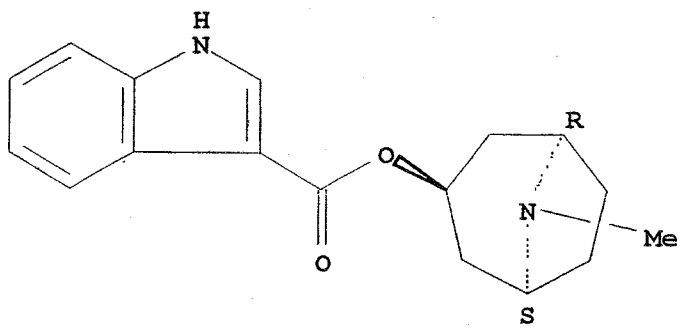
Antagonistes $5HT_3$



Ondansétron



Granisétron



Tropisetron

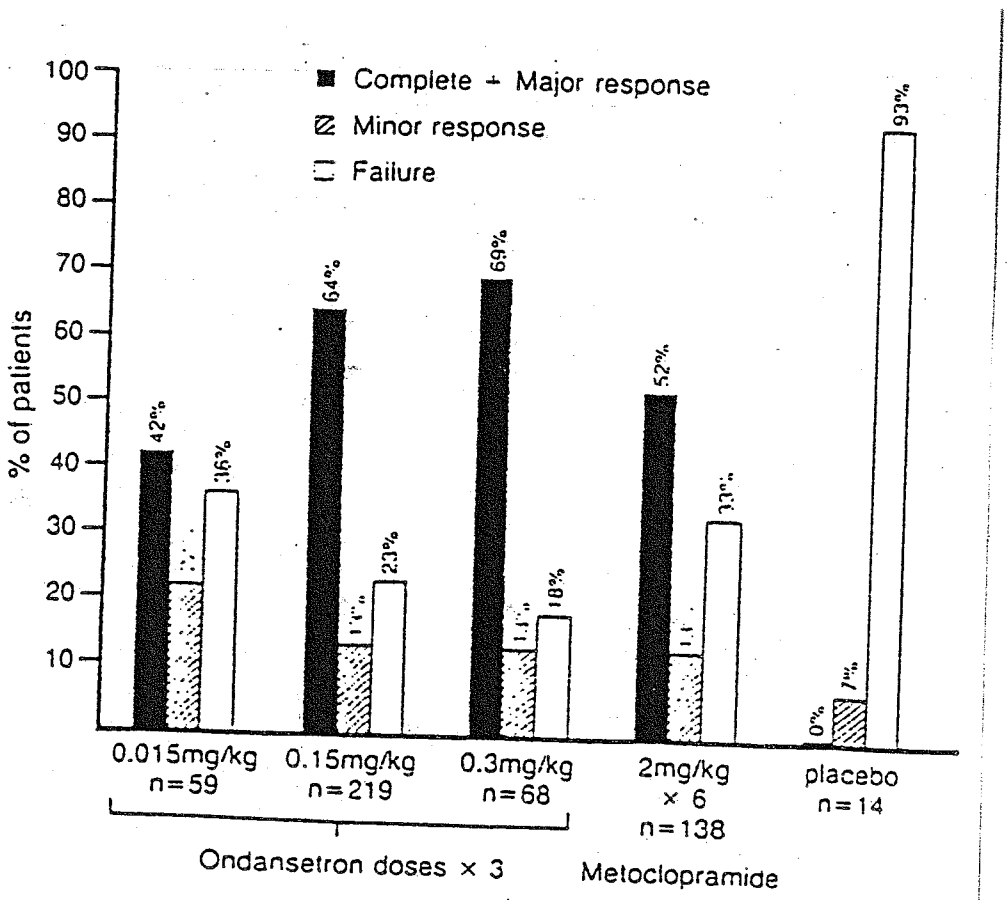


Figure 17. Overall control of cisplatin-induced emesis (USA studies).

▶ EVALUATION OF THERAPEUTIC OUTCOMES

- The etiology of a patient's nausea and vomiting determines the expected outcome of antiemetic therapy. Depending on their ability to tolerate antiemetics, symptomatic relief is often unattainable until definitive therapy can be instituted (i.e., delivery of fetus, GI surgery, correction of metabolic disorders, or removal of emetogenic agents).
- If nausea and vomiting persist despite maximal and frequent dosing of an antiemetic agent, an agent with a different mechanism of action is administered. In addition, the patient should be examined closely to elicit any signs of volume contraction and assess the need for aggressive fluid replacement.
- Individualized therapy is recommended through drug selection and dosage adjustment.
- Monitoring criteria for drug therapy includes the subjective assessment of the severity of nausea as well as objective parameters such as the number of vomiting episodes each day, the volume of vomitus lost, and evaluation of fluid, acid–base balance, and electrolyte status,

ANTIEMETIC USE DURING PREGNANCY

- Agents that have commonly been prescribed during pregnancy include phenothiazines (**prochlorperazine** and **promethazine**), the antihistaminic–anticholinergic agents (**dimenhydrinate, diphenhydramine, meclizine,** and **scopolamine**), **metoclopramide,** and **pyridoxine.**
- The efficacy of antiemetics has been questioned while the importance of other management plans (including emphasis on fluid and electrolyte management, vitamin supplements, and efforts aimed at reducing psychosomatic complaints) has been addressed.
- Presently, **cyclizine** and **meclizine*** are considered the drugs of choice for the treatment of nausea and vomiting during pregnancy.
- Teratogenicity is a major consideration for the use of antiemetic drugs during pregnancy and is the primary factor that dictates the drug of choice. Of the agents commonly used, those that have demonstrated teratogenicity in animals include diphenhydramine, meclizine, prochlorperazine, and thiethylperazine; however, in humans meclizine has not been shown to have these same effects.
- Most authors currently do not recommend metoclopramide because its use during pregnancy requires further study. In addition, serotonin antagonists cannot be recommended in this setting, even though animal studies to date have revealed no harm.

* meclozine en Belgique (2 spécialités).

(Neal)

13 Drugs acting on the gastrointestinal tract: II motility and secretions