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NAUSEA & VOMITING

Submitted to:

Dr.fiaz-ud-din

Sidra Batool

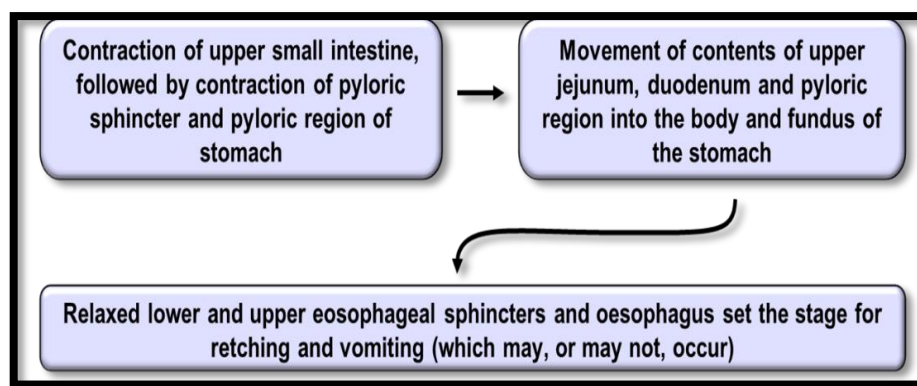
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PHARMACOLOGY-II

NAUSEA: *(derived from Greek “nautia”-Sea sickness*

- Nausea is an unpleasant subjective, diffuse sensation of unease and discomfort, often perceived as an urge to vomit. Acute nausea interferes with mental and physical activity, often relieved by vomiting.
- **Accompanying symptom:**
 - Cold sweat, pallor, salivation.
 - Relaxation of the stomach and lower oesophagus resulting in tension in gastric and oesophageal muscles triggering afferent nerve impulses.
 - Loss of gastric tone
 - Reflux of intestinal contents into stomach.

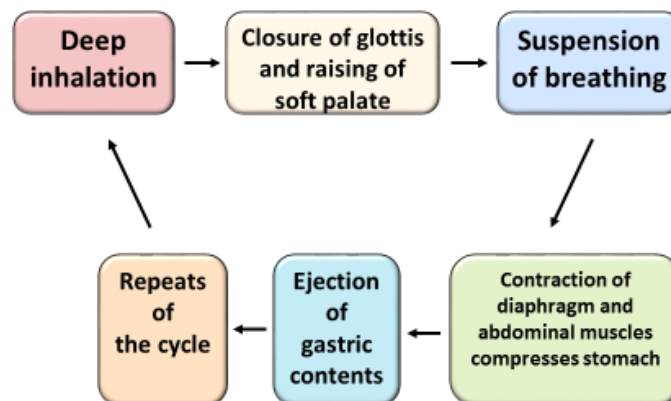
ACT OF NAUSEA:



Vomiting: *(derived from Latin “vomere” to discharge”*

- Vomiting is the forceful expulsion of the contents of the stomach and upper intestinal tract through the mouth.
- Vomiting is the means by which the upper gastrointestinal tract rids itself of its contents when almost any part of the upper tract becomes excessively irritated, over-distended, or even over-excitabile. The major force for expulsion comes from contraction of the respiratory muscles i.e. the diaphragm and the abdominal muscles.

Act of vomiting:



Vomiting is a complex process that consists of :

- *pre-ejection phase*
- *retching*

- and *ejection*

PRE-EJECTION PHASE:

Vomiting is usually preceded by multiple autonomic phenomena including profuse salivation, shivering, sweating, pallor, rapid heart rate and vasomotor changes. During prolonged episodes, marked behavioral changes including lethargy, depression may occur.

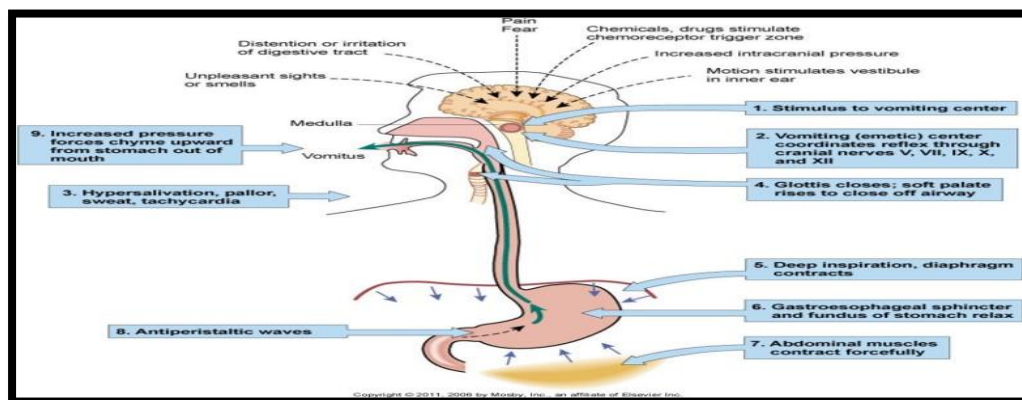
ANTIPERISTALSIS, THE PRELUDE TO VOMITING

- Vomiting is usually preceded by multiple autonomic phenomena including profuse salivation, shivering, sweating, pallor, rapid heart rate and vasomotor changes.
- During prolonged episodes, marked behavioral changes including lethargy, depression may occur.
- In the early stages of excessive gastrointestinal irritation or over-distention, antiperistalsis begins to occur, often many minutes before vomiting appears.
- This process can actually push a large share of the lower small intestine contents all the way back to the duodenum and stomach within 3 to 5 minutes.
- Then, as these upper portions of the gastrointestinal tract, especially the duodenum, become overly distended, this distention becomes the exciting factor that initiates the actual vomiting act
- At the onset of vomiting, strong intrinsic contractions occur in both the duodenum and the stomach, along with partial relaxation of the esophageal-stomach sphincter LES, thus allowing vomitus to begin moving from the stomach into the esophagus.
- From here, a specific vomiting act involving the abdominal muscles takes over and expels the vomitus to the exterior.

RETCHING:

follows nausea. Muscular activity of the abdomen, and the thorax often voluntary leading to forced inspiration against a closed mouth and glottis without oral discharge of gastric contents (“dry heaves”).

It can occur without vomiting but normally it generates the pressure gradient that leads to vomiting.



PROCEDURE OF VOMITING:

The process of vomiting involves several phases and steps. These include:

- ▶ Stimulation of the CTZ leading to activation of the motor, parasympathetic and sympathetic nervous system
- ▶ Stimulation of the parasympathetic nervous system leading to increased salivation
- ▶ Deep breathing preceding the actual vomiting to protect the lungs from aspiration
- ▶ Heaving or retching before the actual vomiting

- ▶ Relaxation of the pyloric sphincter that guards the lower end of the stomach to bring up content from the gut
- ▶ The pressure within the abdomen rises and the pressure within the chest or thorax is lowered. The abdominal muscles contract to expel the contents of the stomach
- ▶ Activation of the sympathetic nervous system leads to sweating, palpitation and rapid heart rate.

Neuronal Pathways, transmitters and receptors involved in N & V

MECHANO AND CHEMORECEPTORS:

- Abdominal stimulation by irritants or toxins can activate nausea and vomiting through mechanoreceptors or chemoreceptors.
- These receptors have been found in the stomach, jejunum and ileum and are involved with detection of emetic stimuli in the gastrointestinal tract.
- Mechanoreceptors are activated by both contraction and distension of the gut
- Distension of the gastric antrum or proximal small intestine may induce nausea and vomiting by stimulation of these afferents
- Chemoreceptors monitor several features of the intraluminal environment. They respond to acid, alkali, hypertonic solutions, temperature and irritants (e.g. copper sulphate).

CONTROL OF VOMITING REFLEX:

- The complex act of vomiting is coordinated by a **vomiting center** in the lateral reticular formation deep in the medulla.
- Neural input to this center from receptors in many different regions of the body can initiate the vomiting reflex.

Vomiting centre:

- It is final common pathway for efferent responses that produce emesis
- consists of various scattered groups of neurons
- inputs include: vagal sensory pathways from the pharynx, gastro-intestinal tract and, higher centres of the cortex, the vestibular nucleus, intracranial pressure and the chemoreceptor trigger zone.
- When activated induces vomiting via stimulation of the salivary and respiratory centres and the pharyngeal, gastrointestinal and abdominal muscles.

Chemoreceptor Trigger Centre (CTZ)

- CTZ receives inputs from blood-borne drugs or hormones, and communicates with other structures in the vomiting center to initiate vomiting.
- The AP is located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle.
- The AP lacks a specific blood-brain diffusion barrier to large polar molecules (i.e., a "blood-brain barrier") and is thus anatomically positioned to detect emetic toxins in the blood as well as in the CSF.
- CTZ being a purely sensory relay station, is incapable of initiating vomiting in the absence of vomiting centre, while direct stimulation of the latter evokes vomiting irrespective of the CTZ.

Visceral afferent pathway

- Poisonous compounds, cytotoxic drugs, radiation, mechanical distension and g.i. irritants release Serotonin 5-HT from enterochromaffin cells → acts on 5-HT₃ receptors

present on extrinsic primary afferent neurons (PAN) of the enteric nervous system (ENS).

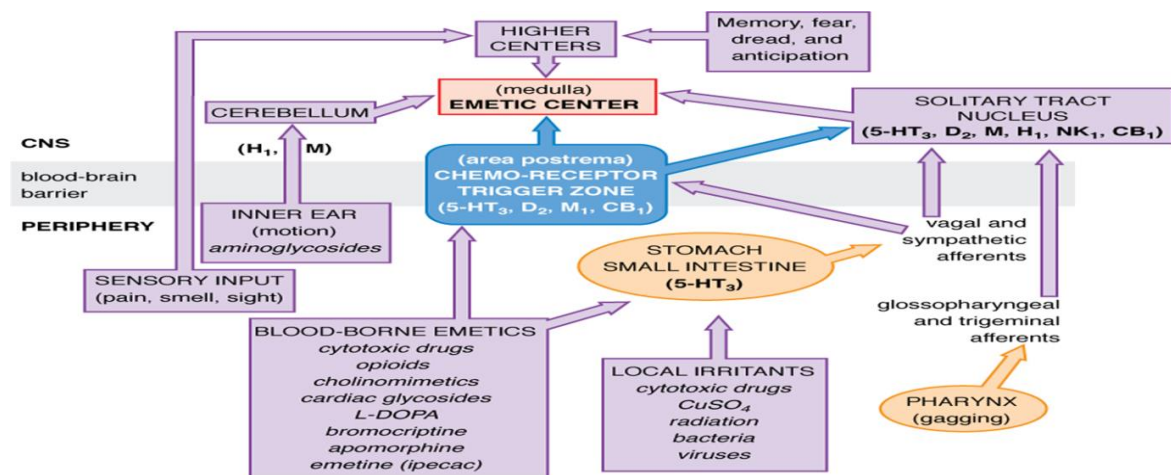
- These neurons connect with vagal and spinal visceral afferents to send impulses to nucleus tractus solitarius NTS and CTZ. Released in large quantity, 5-HT may also spill into circulation and reach CTZ via the vascular route.
- 5-HT may as well be released from platelets by inflammatory mediators.

Vestibular system of vomiting:

- Inputs from the vestibular system of the inner ear. These travel via the eighth cranial nerve or the vestibulocochlear nerve and are involved in motion sickness causing nausea and vomiting. These contain abundance of H₁-type receptor.
- The tenth cranial nerve or the vagus nerve carries signals to the CTZ when the back of the throat or pharynx is irritated or stimulated. This is called the gag reflex.
- The nervous system around the gut or the enteric nervous system also transmits signals to the brain via the vagus nerve. It is via this system that radiation therapy, chemotherapy and gastroenteritis activate the 5-HT₃ receptors leading to vomiting.

Efferent pathway

- From the vomiting center, the impulses are distributed over the efferent fibers, some passing down over the primary motor neurons of the spinal cord that supplies the **abdominal muscles** and gives rise to the motor neurosis of the abdominal walls
- Some passing over the phrenic nerves, causing a contraction of the **diaphragm**, and others to the dorsal motor nucleus of the vagus, which supplies the stomach causing a contraction of the **stomach wall**.
- These impulses reach the fauces, glottis and the esophagus by way of the efferent visceral fiber of the vagus.



NEUROTRANSMITTER & RECEPTORS:

The receptors implicated in the control of nausea and vomiting include

- cholinergic (M receptor)
- histamine (H-1 receptor)
- substance P (NK-1 receptor)
- dopamine (D2 receptor)
- serotonin (5-HT₃ receptor)
- cannabinoid (CB1 receptor)
- opioid (μ receptors).

CAUSES:

- 1) Tactile (touch) stimulation of the back of the throat.
- 2) Irritation or distension of the stomach and duodenum.
- 3) Elevated intracranial pressure (e.g. caused by cerebral hemorrhage).
- 4) Rotation or acceleration of the head producing dizziness, such as in motion sickness.
- 5) Stimulation of chemoreceptors in Specialized chemoreceptor trigger zone in the area postrema.
- 6) Psychogenic vomiting induced by emotional factors (sights and odors and anxiety)
- 7) Intense pain
- 8) Metabolic disturbances or intoxication
- 9) Cytotoxic drugs and Analgesics

Complications of vomiting

- Chronic vomiting can result in *under-nutrition*, weight loss, and metabolic abnormalities.
- *Cutaneous*: (vomiting, can result in facial petechiae and purpura, especially around the eyes)
- *Oropharyngeal*: (dental enamel loss, sore throat)
- *Esophagitis*/ esophageal hematoma
- Vomiting can also cause *mucosal damage* such as Mallory-Weiss tears, or rupture the esophagus (eg, Boerhaave syndrome).
- *Metabolic*: electrolyte depletion and acid-base imbalance
- *Renal*: pre-renal azotemia and acute tubular necrosis ATN can be caused by hypovolemic state; hypokalemic nephropathy
- *Metabolic alkalosis*
- Large losses of secreted fluids and acid result in reduction of plasma volume that leads to dehydration and circulatory problems and loss of acid from stomach leads to metabolic alkalosis.
- retention of HCO_3^-
- loss of gastric H^+ ions
- volume depletion
- *Hypokalemia*
- renal K^+ losses
- GI K^+ loss
- *Hypochloremia*
- gastric chloride Cl^- losses
- Patients with uremia or Addison's disease may have normal or even high serum K^+ despite vomiting