ANTI – EMETIC DRUGS

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OVERVIEW OF EMESIS (VOMITING)

- Emesis or vomiting is a physiological response of irritating and potentially harmful substances in the gut or blood stream
- It is usually initiated by a nucleus of cells located in the medulla that is called the vomiting center or emesis center
- This center coordinates a complex series of events involving pharyngeal, gastrointestinal and abdominal wall contractions that lead to expulsion of the gastric contents
- These include orally migrating intestinal contractions (reverse peristalsis), gastric contractions, contractions of the diaphragm and abdominal wall and relaxation of the esophageal sphincter and wall

Overview Cont'd

- These reverse contractions are associated with nausea which is an intensely unpleasant feeling of the imminent need to vomit
- Its worthy noting that nausea can sometimes occur without vomiting
- Sometimes it occurs as a result of excessive vestibular stimulation (motion sickness) or psychological stimuli such as fear, dread or obnoxious sights and odors
- The vomiting center can be activated by afferent fibres arising from the gut, chemoreceptor trigger zone (CTZ), cerebral cortex or vestibular apparatus

Overview Cont'd

- The CTZ is located in the area postrema and responds to blood borne substances including cytotoxic cancer chemotherapy
- These substances activate the CTZ via stimulation of serotonin (5HT3), dopamine (D2) or muscarinic (M1) receptors
- The vestibular apparatus activates the vomiting centre via fibres that project to the cerebellum and release acetylcholine or histamine
- Noxious substances in the gut can activate vagal afferent pathways which projects to the vomiting centre as well as pathways to the nerve tracts that stimulate the CTZ

Scope of anti-emetic drugs

- Most anti-emetic drugs act by blocking dopamine, serotonin, muscarinic or histamine receptors
- The D2 and 5HT-3 receptor antagonists inhibit activation of both the CTZ and the solitary tract nucleus
- Muscarinic receptor antagonists can block the CTZ, solitary tract and vestibular pathways involved in emesis
- Dexamethasone , a glucocorticoid is an effective anti-emetic whose mechanism is not well understood
- Dexamethasone is very effective in preventing delayed nausea and vomiting in persons receiving cancer chemotherapy

Serotonin (5HT3) Receptor antagonists

Examples

First generation

i. Ondasentron

ii. Dolasentron

iii. Granisentron

- First developed for cancer chemotherapy induced nausea and vomiting
- These drugs were found to significantly reduce the number of episodes of emesis in patients treated with cisplatin, the most highly ematogenic anticancer drug

Second generation

i. Polasentron

- Second generation with greater affinity for 5HT3 receptors and much longer half life and duration of action

Mechanism of action and effects of 5HT3 receptor antagonists

- 5HT3 receptor antagonists have structure that resemble the structure of serotonin
- Cancer chemotherapy is associated with nausea and vomiting when serotonin released from enterochromaffin cells of the small intestines activate 5HT3 receptors located on the vagal afferent nerves and activates the vomiting center
- Anticancer drugs also stimulate the CTZ that activates the vomiting center in the medulla
- 5HT3 receptor antagonists therefore, competitively block 5HT3 receptors on the visceral afferent nerves in the GIT, in the solitary nucleus and in the CTZ
- This enables these drugs to prevent both peripheral and central stimulation of the vomiting center

Indications

- Cancer chemotherapy induced emesis except dolasentron
- Prevention and treatment of post operative emesis (Ondasentron, Dolasentron)
- Prevention of nausea and vomiting induced by radiation (Ondasentron, Granisentron)
- First generation 5HT3 antagonists are usually administered just before chemotherapy and continued for 3 to 5 days after chemotherapy course is completed
- However, a single dose Palosentron, a second generation is enough as it can last for up to 7 days it having a half life of 40 hours
- An additive effect is achieved when 5HT3 receptor is combined with Dexamethasone and hence this combination is used for prevention of chemotherapy induced emesis

Side effects

- Generally 5HT3 receptor antagonists are tolerated
- Dolasentron high doses when administered through I.V were found to cause prolonged QT interval and potentially fatal torsade de pointes (Only lower oral doses are currently used)
- Most common side effects are headache, constipation and diarrhoea
- Less common reactions include hypertension and elevated liver enzyme levels
- Anaphylactoid reactions consisting of bronchospasms, angioedema, hypotension and urticaria were also reported in the use of ondasentron

Dopamine D2 receptor Antagonists

Examples

i. Metoclopramide

ii. Domperidone

- **Phenothiazine drugs**

iii. Proclorperazine

iv. Perphenazine

V. Promethazine

- Phenothiazines have anti emetic, antipsychotic, antihistamine and sedative properties

Mechanism of action of D2 receptor antagonists

- Act primarily on the CTZ to inhibit stimulation of the vomiting centre
- May also inhibit the afferent impulses from the gut by antagonizing receptors in the solitary tract nucleus

Indications of D2 receptor antagonists

- Phenothiazines are used in treating emesis caused by a wide range of medical conditions

- Phenothiazine are not as effective as other drugs in treating chemotherapy induced emesis

Side effects of D2 receptor antagonists

- Drowsiness
- Dizziness
- Diarrhea
- Nausea and Vomiting
- Breast enlargement and discharge
- Decreased sexual ability
- Frequent urination and inability to control urination

D4 FNB

Neurokinin 1 receptor antagonists

Example

- Aprepitant

Mechanism of Action

- Substance P is a peptide of the tachykinin family that acts as a neurotransmitter in the gut and brain
- Substance P is released from vagal afferent fibers in the solitary tract where it activates NK1 receptors and thereby producing emesis
- Aprepitant is a non peptide NK1 receptor antagonist and hence its anti-emetic effect

Indications of Neurokinin 1 Receptor antagonists

- Used in combination with 5HT3 receptor antagonists like ondasentron and dexamethasone to prevent acute and delayed nausea and vomiting in cancer chemotherapy

Interaction

- Drugs that inhibit CYP 450 3A4 enzymes can elevate plasma concentration of aprepitant

Other Anti-emetics

Dronabinol

- An oral formulation of tetrahydrocannabinol (Cannabis derivative)
- The drug is known to work on the vomiting centre in the medulla
- Approved for use in chemotherapy induced emesis when conventional anti-emetic drugs have failed
- As anti-emetic drug, it is less effective than 5HT3 but is as effective as phenothiazine
- Dronabinol is also indicated as an appetite stimulant for anorexic patients with acquired immune deficiency syndrome (AIDS)

Scopolamine

- Muscarinic receptor antagonist similar to atropine and is primarily used to control motion sickness
- It is available as a patch to extended release of the drug where it releases over 72 hours

Hyper emesis gravindarum

- This is uncontrolled vomiting during pregnancy that results in dehydration, weight loss and ketosis
- Diagnosis is clinical and by measuring of urine ketone, electrolytes and kidney function
- Hyperemesis gravindarum is suspected based on the symptoms e.g onset, duration, frequency of vomiting, exacerbating and relieving factors
- Care should be taken to avoid misdiagnosis of hyperemesis gravidarum and therefore, other disorders that can cause vomiting must be ruled out
- Examples of conditions that should be ruled out are gastroenteritis, hepatitis, appendicitis, cholecystitis, PUD, intestinal obstruction, hyperthyroidism

Treatment of hyperemesis gravidarum

1. Temporary suspension of oral intake followed by gradual resumption

- At first patients are given by mouth with initial treatment being IV fluid resuscitation beginning with Ringers lactate
- If Dextrose is given the thiamine IV should first be given to prevent Wernicke encephalopathy
- Thiamine should then be continued for up to 3 days

2. **Electrolyte and vitamins**

- Fluids, multivitamins and electrolytes such as potassium, magnesium and phosphorus are replaced as needed

3. **Anti-emetics**

- These drugs are used where vomiting persists even after initial fluid and electrolyte replacement

Drugs used in hyperemesis gravidarum

The following drugs are effective and safe for use in treatment of hyperemesis gravidarum;

- Low dose of pyridoxine (vitamin B6)
- Doxylamine succinate
- Promethazine
- Metoclopramide
- Ondasentron
- Prochlorperazine

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