Pharmacology Team

Antiemetic drugs

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Introduction

-Vomiting: it's not a disease its indication of certain diseases

Vomiting occur due to stimulation of vomiting center that respond to inputs from:

1. Chemoreceptor trigger zone (CTZ) stimulation
2. Disturbance of vestibular system
3. Higher cortical centers stimulation (CNS)
4. The periphery (Pharynx, GIT) via sensory nerves

-Vomiting sometimes is a life-saving to get rid of toxins in the stomach.

-CRTZ stimulated by Uremia or drugs like: Morphine, Emetine or L-dopa, and periphery stimulated by GI irritation, MI or renal stones.

-Antiemetic drugs should only used when the cause of vomiting is known

-The drug of choice depend on the etiology; post-operative, chemotherapy..etc
Neurotransmitters and receptors involved in vomiting:
1- Histamine (Histaminergic receptors H1)
2- Serotonin (5-HT3)
3- Ach (Muscarinic)
4- Dopamine (D2)
5- Substance P (Neurokinin receptors)
6- Opioid Receptors.
1-5HT3 antagonist:
Ondansetron, Granisetron
B/C they block 5HT3 so it affects VC, CRTZ & GI ➔ most potent one
Oral/IV ➔ long duration
#Effective in nausea & vomiting caused by;
Cytotoxic drugs (Cisplatin), post-operative or post-radiation

2-D2 Antagonist:
A-Prokinetics drugs:

Dom-peridone (orally), Metocloperamide (Orally/I.V.) the latter cross BBB
-Both are Gastroprokinetics; B/C both are 5HT4 agonist
5HT4 ➔ release Ach ➔ GI motility ↑↑
-Effective in vomiting caused by;
Gastroenteritis, uremia, toxins, post-operative, radiation (90%) and drugs
-Which one is better Domperidone or metocloperamide?
Clearly the first is better B/C the second cross BBB causing extrapyramidal S/E "dyskinesia", Galactorrhea, menstruation disorders or sedation.

-So what're the uses of metocloperamide?
   Facilitate endoscopy, Diagnostic radiology of gut ➔ ↓ time required for barium to reach caecum ➔ ↓ No. of films required
   *Clears gastric contents in emergency anaesthesia (I.V.)

B-Antipsychotic drugs" for example Chlorpromazine or Droperidol
due to their potent effect on D2, but 5HT3 blockers replace them due to their S/E such as extrapyramidal symptoms or hypotension "α-1 blocking effect".

3-Neurokinin1 (NK1) blockers:
Apre-pitant; prevent effect of Substance P on NK1 receptors.
Used as adjuvant therapy in chemo induced vomiting
*Usually don't used by doctors.
4-H1 receptors antagonist:
Diphenhydramine, Meclizine, Cyclizine and Promethazine
#Effective against;
*Motion sickness*, Opioid's nausea
Morning sickness in pregnancy
Sever morning sickness in pregnancy $\rightarrow$ **Promethazine**
Not USED IN CHEMOTHERAPY, POST-OPERATIVE OR UREMIA INDUCE VOMITING

5-Muscarinic receptors antagonist:
Hyoscine "Scopolamine", used in:
*Motion sickness*, trans-dermal patches behind external ear
NOT IN CHEMOTHERAPY-INDUCED VOMITING, "like H1 antagonist"

6- "psychoactive drugs:
**Nabilone**, as adjuvant therapy in chemo induced vomiting "like Apre-pitant"
S/E; Hallucination & dysphoria

7-Glucocorticoids
**Dexamethasone, Methyl-predni-solone**
Used alone or in combination with Ondansetron in acute emesis, cytotoxic drugs induce vomiting

S/E:
**Hyperglycemia** "diabetes"
**Hypertension** "Activate aldosterone $\rightarrow$ water retention"
Cataract, Osteoporosis
ICP ↑↑, Infection ↑↑, Appetite ↑↑

NOTE :most of antiemetic drugs are antagonist except Cannabinoids
<table>
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<tr>
<th>Classification of Antiemetic Drugs</th>
<th>Drugs</th>
<th>MAO</th>
<th>Uses</th>
<th>Side effects</th>
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<tr>
<td>5-HT3 antagonists</td>
<td>Ondansetron, Granisetron</td>
<td>Block 5-HT3 receptor in vomiting center, CTZ and 5HT3 receptors on intestinal vagal afferents.</td>
<td>First choice for prevention of: 1-Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin. 2-Post-radiation NV &amp; Post-operative NV 3-Their effects is increased by combination with corticosteroids and NK1 antagonists</td>
<td>1-Well tolerated 2-mild headache, dizziness and constipation 3-minor ECG abnormalities (QT prolongation)</td>
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<tr>
<td>D₂ receptor antagonists</td>
<td>1-Prokinetics drugs - metoclopramide, domperidone</td>
<td>Both are prokinetic agents due to their 5 HT4 agonistic activity</td>
<td>1-used in GERD (gastroesophageal reflux disease), gastroparesis 2-Used as antiemetics (blocking D2 receptors) 3- Metoclopramide crosses BBB but domperidone cannot (both have antiemetic effects as CTZ is outside BBB).</td>
<td>Side effects (only for metoclopramide): 1-Dyskinesia (extra-pyramidal side effects), 2-Galactorrhea, menstrual disorders, impotence. 3-Sedation, postural hypotension.</td>
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<td>2-Neuroleptics (antipsychotics): - Chlorpromazine(CPZ), - droperidol</td>
<td></td>
<td>postoperative vomiting and chemotherapy-induced nausea &amp; vomiting.</td>
<td>1-extrapyramidal symptoms 2-sedation, postural hypotension</td>
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<tr>
<td><strong>Group</strong></td>
<td><strong>Agent</strong></td>
<td><strong>Action</strong></td>
<td><strong>Uses</strong></td>
<td><strong>Side Effects</strong></td>
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<td><strong>NK₁ antagonists</strong></td>
<td>Aprepitant</td>
<td>&quot;Orally&quot;</td>
<td>Is a substance P antagonists that acts by blocking neurokinin 1 receptor</td>
<td>1-Used in prevention of acute and delayed chemotherapy-induced nausea and vomiting and for prevention of postoperative nausea and vomiting. 2-Usually combined with 5-HT₃ antagonists and corticosteroids.</td>
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<td><strong>H₁-receptor antagonists</strong></td>
<td>1- Diphenhydramine 2-Meclizine - Cyclizine 3- Promethazine</td>
<td></td>
<td>Promethazine severe morning sickness of pregnancy <em>(if only essential)</em></td>
<td>prominent sedation, hypotension, anticholinergic effects (dry mouth, dilated pupils, urinary retention, constipation).</td>
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<tr>
<td><strong>Muscarinic receptor antagonists</strong></td>
<td>Hyoscine (scopolamine)</td>
<td>&quot;Orally, injection, patches&quot;</td>
<td>1-Used as transdermal patches in motion sickness (applied behind the external ear). 2-Not in chemotherapy-induced vomiting</td>
<td>tachycardia, blurred vision, dry mouth, constipation, urinary retention (atropine-like actions).</td>
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<td><strong>Cannabinoids</strong></td>
<td>1-Nabilone 2-dronabinol</td>
<td>act at central cannabinoid receptors</td>
<td>1-Used in vomiting due to cytotoxic anticancer drugs (adjuvant therapy). 2-Not commonly used.</td>
<td>euphoria, dysphoria, sedation, hallucination.</td>
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<td><strong>Glucocorticoids</strong></td>
<td>1-Dexamethasone 2-methylprednisolone</td>
<td>.</td>
<td>1-chemotherapy-induced vomiting 2-combined with 5-HT₃ antagonists or NK1 receptor antagonists</td>
<td>-Hyperglycemia, Hypertension -Cataract, Osteoporosis -Increased intraocular pressure -Increased susceptibility to infection -Increased appetite &amp; obesity</td>
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Summary

**Motion sickness**
- Muscarinic antagonists
- Antihistaminics

**Vomiting with pregnancy (morning sickness)**
avoid all drugs in the first trimester
Pyridoxine (B6)
Promethazine (late pregnancy).

**Drug-induced vomiting (CTZ)**
Dopamine antagonists

**Post operative nausea & vomiting**
Dopamine antagonists
5-HT₃ antagonists
NK1 antagonists

**Vomiting due to cytotoxic drugs**
5-HT₃ antagonists
NK1 antagonists
D₂- antagonists
Glucocorticoids
Cannabinoids
Questions

1- A 53 year old female patient receiving chemotherapy for the treatment of ovarian cancer. Currently, she is suffering from severe vomiting. which one of the following would be most effective to counteract her emesis?

A-Chlorpromazine
B-Hyoscine
C-Ondansetron
D-Promethazine

2- A patient on an antiemetic drug therapy. She suddenly developed extrapyramidal symptoms and galactorrhea. Which one of the following drug is responsible for these side effects?

A- Hyoscine
B- Metocopramide
C- Nablione
D- Ondansetron

Answers:
1-C
2-B