BioPharma SERVICES INC.

ANTIEMETIC DRUGS

What to Prescribe and When

CAUSES OF VOMITING

Toxins
Drugs & Chemical Toxins
Food/drink poisoning
Metabolic unbalance

Gastrointestinal
Anatomic obstruction
Motility disorder
Inflammation

Psychogenic
Eating Disorders
Anxiety

Central nervous system
Increase Intracranial Pressure
Motion Sickness
Migraines
Epilepsy

Others
Pregnancy
Infection (post-tussive)
& more

ANTIEMETIC DRUG MECHANISM

A – Anticholinergics
Hyoscine, Scopolamine

D – Dopamine Antagonist
Metoclopramide, Droperidol, Haloperidol, Chlorpromazine, etc.

H – Antihistamines
Doxylamine, Cyclizine, Promethazine, etc.

N – Neurokinin Antagonist
Aprepitant, Rolapitant, Fosaprepitant, etc.

S – Serotonin Antagonist
Ondansetron, Granisetron, Palonosetron, etc.

O – Others
Corticosteroids, Benzodiazepines, Cannabinoids

The various classes of antiemetics target different pro-emetic pathways to alleviate nausea and vomiting.

Some target more than one pathway.

SIDE EFFECTS

The mechanism of action of antiemetics contribute to some of their adverse effects

- Constipation
- Sedation (sleepiness)
- Anticholinergic effects
- QT Prolongation
- Extrapyramidal symptoms

The use of antiemetics in clinical trials is often necessary to manage adverse drug effects as well as to improve drug absorption

Vomiting is one of the most common adverse events in clinical trials with oral drug!

2x

of Tmax is the suggested duration when vomiting can critically impact the absorption of the investigational product (IP).

Management of Vomiting in Clinical Trials

- Resolved without intervention
- IP discontinuation
- Antiemetic drugs as needed
- Pre-treatment with antiemetic drugs for IP with a high rate of emesis
- Beware of drug-drug interactions between the IP and antiemetic

ANTIEMETIC DRUGS

in Clinical Trial Drug Development

WHAT AND WHEN?

When considering antiemetics for use in clinical trials, the choice of specific medications depends on several factors.

- Type of emesis (nausea/vomiting)
- Underlying cause
- Study population
- Objectives of the clinical trial

Generally, for studies with PK as the primary endpoint, antiemetic drug usage must be carefully weighed with the benefit-risk

- to protect the subject's safety
- to limit the drug-drug interaction that could alter the PK

DRUG-DRUG INTERACTIONS

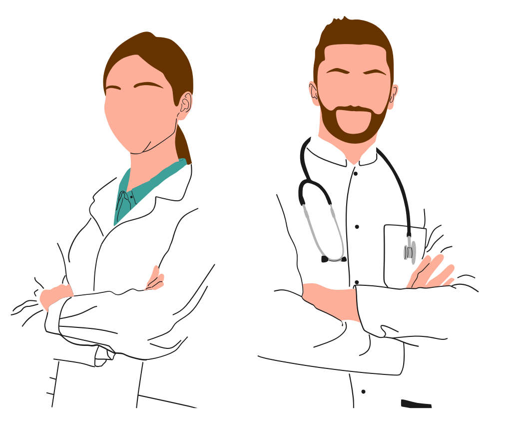
PK interactions can alter both the PK and the PD of the investigational products

- Prolong drug transit time in GI tract (i.e. constipation)
- Competitive inducer/inhibitor/ substrate of P-gp or CYP (e.g ondansetron inhibited CYP1A2 and CYP2D6)
- Competitive elimination at liver and/or kidney

Increase/Decrease IP's absorption, metabolism, elimination.

Increase severity of a known side effect of IP or antiemetics.

Induce a new side-effect.



RECOMMENDATION

*These recommendations are for professional consideration only, based on the literature and in-house experience from clinical trials in healthy volunteers. These recommendations are not intended for personal use.

	Cause of Emesis/ Vomiting	Therapeutic Options
Unrelated to IP	Psychogenic (placebo effect, anxiety)	• No treatment • Antiemetics for moderate to severe: ◦ Antihistamine (dimenhydrinate)
	Gastrointestinal (high-fat meal, glucose solution)	• No treatment • Antiemetics for moderate to severe: ◦ Antihistamine (dimenhydrinate)
	Migraine-related	• No treatment • Antiemetics for moderate to severe: ◦ Dopamine antagonists: Metoclopramide with paracetamol, Metoclopramide or prochlorperazine
Related to IP	Cholinesterase inhibitors (E.g. Donepezil)	• Pre-treatment with antiemetic drugs: lorazepam (if needed) • Discontinue IP • Provide treatment for moderate to severe: ◦ Anticholinergics ◦ Serotonin antagonists: ondasentron
	Chemotherapy-induced medications	• Pre-treatment with antiemetic drugs for drugs with high risk • Discontinue IP Provide treatment for moderate to severe case ◦ Serotonin antagonists ◦ Neurokinin-1 antagonist ◦ Dopamine antagonists ◦ Corticosteroid (dexamethasone) or Benzodiazepines (lorazepam)
	Opioid-induced	• Discontinue TP • Provide treatment for moderate to severe case ◦ Dopamine antagonist (low dose droperidol - US) ◦ Antihistamine (dimenhydrinate) ◦ Serotonin antagonists (ondasentron)
	Opioid antagonist (naltrexone)	• Discontinue IP for moderate to severe • Reduce dose, divide the dose, take with food