Pharmaceuticals that alter GI motility
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Financial disclosures
- None

Common pharmaceuticals that alter GI Motility (an incomplete list)
- Analgesics
- Opioids
- NSAIDs
- Anticholinergics
- Antihistamines
- Antispasmodics
- Tricyclic antidepressants
- Antipsychotics
- Antiparkinsonian drugs

Summary of Major MOAs

- Interact with certain receptors:
  - Opiate receptors (mu)
  - Muscarinic receptors (M3)
  - Serotonin (5HT3)
- Decreases neurotransmitter or secondary messenger output (cAMP, IP3)
- Decreases phosphorylation of proteins or changes intracellular Ca2+
- Cause discordant GI motility

Opioids

- codeine
- hydrocodone
- fentanyl
- methadone
- morphine
- tramadol

Opioids – cont.

- mu, kappa, and delta opioid receptors throughout GI tract
- mu-Opioid receptors = primary mediators of analgesic effects in CNS and GI
- Localized in myenteric and submucosal neurons
- Immune cells in lamina propria

Opioids – cont.
- Opiates block adenylate cyclase
- Enzyme that converts ATP → cAMP
- Without cAMP = decreased neuronal activity and neurotransmitter release
- Less ACh, NO, and VIP = abnormal coordination of contractile forces


Opiates – cont.
- Esophagus – “spastic achalasia-like” or GERD
  - Non-peristaltic contractions
  - Incomplete relaxation of LES OR decreased LES sphincter pressure
- Small and large intestine
  - Increased resting contractile tone in circular mm.
  - Decreased tonic inhibition of mm. tone
  - Increased tone in circular mm. layer
  - Increased segmental contraction
  - Decreased propulsive forward peristalsis
  - Stasis of luminal contents

Treatments for opiate-induced constipation (OIC)
- Methylnaltrexone (Relistor) – opiate antagonist
  - does not cross BBB
  - does not block analgesic activity or precipitate withdrawal
- Naloxone – opiate antagonist
  - Oral – 3% bioavailability
  - May reverse systemic effects or induce withdrawal
- Naloxegol – pegylated form of naloxone
  - Effective against refractory OIC
  - Does not reverse analgesic effect
- Targiniq ER – Approved in US for mod-sev pn
  - Long-acting oxycodone + Naloxone
  - No labeled indication for relief or prevention of OIC

Opiate Antagonists

NSAIDs and Acetaminophen
- The impact on motility is unclear, but linked to constipation in many studies
- Possible mechanisms:
  - Inhibited prostaglandin production
  - Interrupted 5-HT production (acetaminophen)
  - Downregulate 5-HT2a receptors


Anticholinergics
- dicyclomine (Bentyl)
- hyoscyamine (Levin, Levbid)
- meperazine (Cantil)
- methscopolamine (Pamine Forte)
- propantheline (Pro Bantin)
- glycopyrrolate/ glycopyronium (Cuvposa, Robanu)

Also....
- Antihistamines
- Antipsychotics
- Tricyclic antidepressants
- Antiparkinsonian
Anticholinergics – cont.

- Action is varied, but all interfere with the action of Acetylcholine
- Acetylcholine binds muscarinic receptors which mediate intestinal smooth muscle contraction
- 5 known muscarinic receptors – M₁-M₅
  - M₁ – mediate intestinal contractility
  - M₂ – mediate heart contractility
- Binding generates inositol triphosphate (IP₃) → Increases intracellular Ca²⁺


5-hydroxytrypamine (5HT₃) Antagonists

- Ondansetron (Zofran)
- Alosetron (Lotronex)
- Granisetron (Granisol)
- Dolasetron (Anzemet)
- Palonosetron (Aloxi)

http://www.slideshare.net/drhidri/serotonin-class

5HT₃ Antagonists

- Serotonin causes proximal contraction with distal relaxation → peristaltic effect
- 5HT₃ → stimulate NO and VIP → Inhibit ACh motor neurons

http://www.d.umn.edu/~/jfitzak/DMED/Lectures/DMED/LowerGI/PhysReview/Serotonin.html
Calcium Channel Blockers
- amiodipine
- diltiazem
- verapamil

Calcium channel blockers
- Inhibit calcium ion influx into gastrointestinal smooth muscle (and vascular smooth muscle and myocardium)
- Have been shown to disturb migrating motor complex cycling


Chemotherapeutic Agents
- Vinca Alkaloids (vincristine, etc.) - inhibits microtubule formation, blocks tubulin polymerization
- Thiopurines (e.g., 6-mercaptopurine)
- Neuropathic effects can lead to bowel obstruction or paralytic ileus
- Thalidomide and analogs - several proposed MOAs
  - Used in refractory multiple myeloma, etc.
  - Can cause constipation
  - Possible mechanism – neuromuscular inertia with resultant hypotonia
- Vandetanib – inhibits tyrosine kinases
  - Used in medullary thyroid cancer and lung cancer
  - Can cause diarrhea or constipation
- Belinostat – histone deacetylase inhibitor
  - Used in multiple myeloma and T cell lymphoma
  - Can cause diarrhea or constipation

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