Drugs Affecting Gastrointestinal Motility

35

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Abstract

Gastrointestinal (GI) motility is an essential function of the gastrointestinal tract, which is regulated by various neurohumoural factors and drugs. The neurohumoural control is mediated by the enteric nervous system (ENS), the autonomic nervous system (ANS), and local and circulating hormones. The principal local hormones that modulate gut motility are ghrelin, cholecystokinin (CCK), motilin, glucagon like peptide-1 (GLP-1), serotonin and dopamine. Also, various drugs can modulate the gastrointestinal motility. Prokinetic drugs stimulate GI motility and smooth muscle relaxants suppress the motility. Dopamine receptor antagonists (like metoclopramide, domperidone), serotonin receptor agonists (like cisapride, mosapride, itopride and prucalopride), macrolide antibiotics (like erythromycin) and sincalide are classified as prokinetic agents. Organic nitrates, phosphodiesterase type 5 inhibitors, calcium channel blockers and botulinum toxin are smooth muscle relaxants that suppress the GI motility.

Keywords

Gastrointestinal motility · Prokinetic drugs · Metoclopramide · Domperidone

35.1 Introduction

- The gastrointestinal (GI) motility is an essential function of the GI tract which is regulated by various neurohumoral factors and drugs.

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Table 35.1 Types of neuronal plexuses constituting the enteric nervous system

Type of plexus	Location	Function
Myenteric (Auerbach) plexus	Between the circular and longitudinal muscle layers	Motor control and co-ordination
Submucosal (Meissner) plexus	In the submucosa	Secretion, fluid transport, and blood flow

Table 35.2 Types of contractions occurring in the gastrointestinal tract (GIT)

Type of contraction of muscles of GIT	Fasting/ fed state	Function of the GI contraction
Migrating motor complex (MMC)	Fasting state	• Aids in expelling any debris in the gut lumen by pushing it caudally • Helps to prevent overgrowth of commensal bacteria in gut lumen
High-frequency propulsive or mixing contractions	Fed state	Helps in mixing and propelling the food in the gut lumen distally

- The neurohumoral control is mediated by the enteric nervous system (ENS), the autonomic nervous system (ANS), and the local and circulating hormones.
- The enteric nervous system—largely contributes to the autonomic nature of GI motility.
- The enteric nervous system is composed of two layers—myenteric (Auerbach) plexus and submucosal (Meissner) plexus (Table 35.1).
- There are two salient types of contractions that occur in the gastrointestinal tract, which are as follows (Table 35.2).
  - Migrating motor complex (MMC)—one MMC cycle has the following four phases.
    Phase I—quiescence.
    Phase II—smooth muscle contractions.
    Phase III—peak contractile activity.
    Phase IV – declining activity toward a renewal of phase I.
  - High-frequency propulsive or mixing contractions.
- The principal local hormones that modulate gut motility are as follows,
  - Ghrelin.
  - Cholecystokinin (CCK).
  - Motilin.
  - Glucagon like peptide-1 (GLP-1).
  - Serotonin.
  - Dopamine.
- Various drugs can also modulate the gastrointestinal motility and can be used for numerous clinical conditions (Box 35.1).
  - Drugs increasing tone of lower esophageal sphincter (LES)—used in Gastro-esophageal reflux disease (GERD).
  - Drugs increasing gastric emptying—used in gastroparesis and postsurgical gastric emptying delay.

- Drugs increasing small-intestinal motility—used in postoperative ileus.
- Drugs increasing colonic transit—used in constipation.

35.2 Regulation of Gastrointestinal Motility by the Enteric Nervous System

- Regulation of GI motility by the enteric nervous system is mediated mainly by the serotonergic neurons (Fig. 35.1).
- Various chemical and mechanical stimuli that can enhance gut motility are as follows:
  - Food boluses.
  - Chemotherapeutic drugs such as cisplatin.
  - Some microbial toxins.
  - Adrenergic, cholinergic, and purinergic receptor agonists.
- Stimuli from the gut lumen causes release of serotonin from the enterochromaffin cells, which activates the $5HT_3$ and $5HT_{1p}$ receptors of primary afferent neurons (PAN) in the submucosa.
- Activation of the $5HT_3$ receptors leads to inhibitory stimuli causing reduction in GI motility.
- Whereas, activation of $5HT_{1p}$ receptors leads to excitatory stimulus, producing enhancement of GI motility.
- Also, activation of presynaptic $5HT_4$ receptors of PAN and blockade of presynaptic D_2 receptors on myenteric motor neurons produces stimulatory action on GI motility.
- Thus, drugs acting on the 5HT and D_2 receptors modulate GI motility.

Box 35.1: Classification of Drugs Affecting Gastrointestinal Motility

- Agents stimulating GI motility (Prokinetic agents)
  - Dopamine receptor antagonists: Metoclopramide, domperidone.
  - Serotonin receptor agonists: Cisapride, mosapride, itopride, and prucalopride.
  - Macrolide antibiotics: Erythromycin.
  - Miscellaneous drugs: Sincalide (C-terminal octapeptide of cholecystokinin).
- Agents suppressing GI motility (smooth muscle relaxants)
  - Organic nitrates.
  - Phosphodiesterase type 5 inhibitors.
  - Calcium channel blockers.
  - Botulinum toxin.

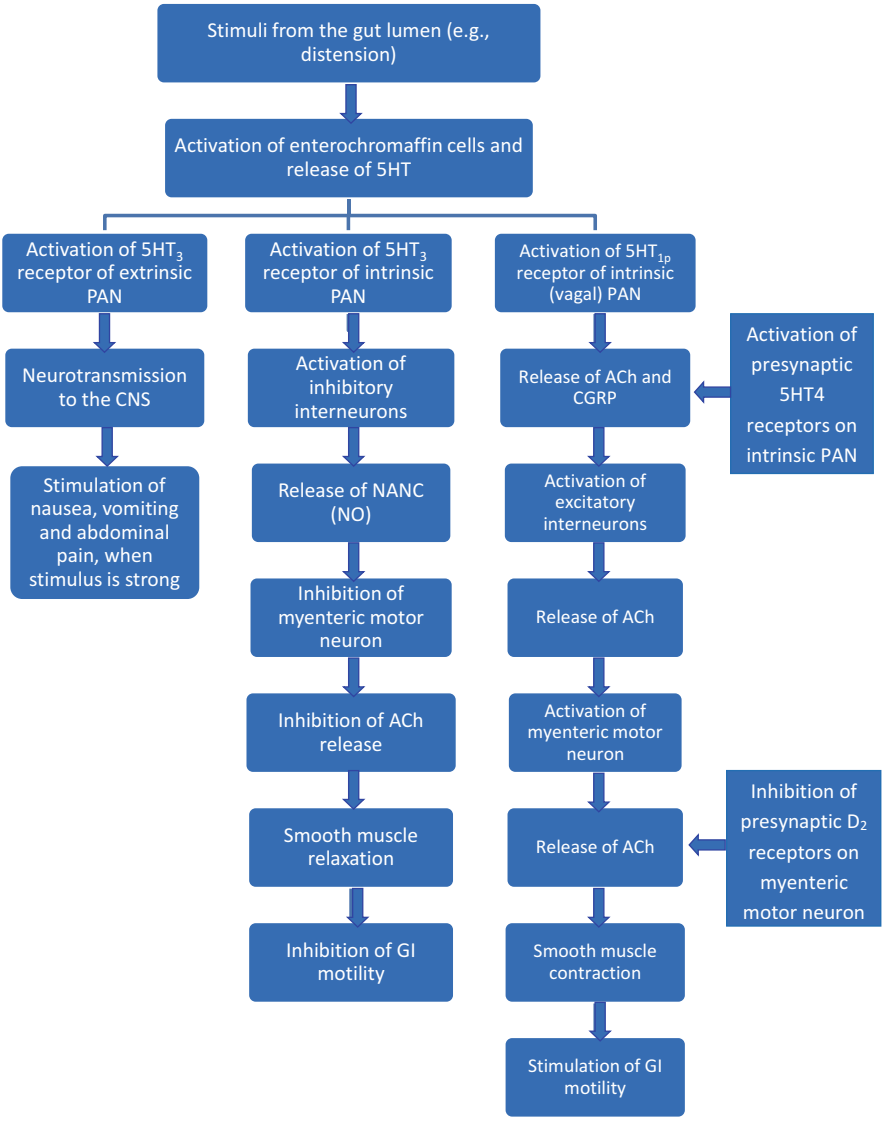

Fig. 35.1 Regulation of gastrointestinal motility. Activation of $5HT_{1p}$ and $5HT_4$ receptors causes stimulation of GI motility. On the contrary, activation of $5HT_3$ and D_2 receptors produces inhibition of GI motility. *5HT* serotonin, *PAN* primary afferent neurons (present in the submucosa), *CNS* central nervous system, *CGRP* calcitonin gene related peptide, *NANC* non-adrenergic non-cholinergic transmitter, *NO* nitric oxide, *ACh* acetylcholine, *GI* gastrointestinal

35.3 Prokinetic Agents

- These drugs hasten the transit of gastrointestinal contents by enhancing coordinated gastrointestinal motility.
- They do not affect the normal physiological pattern of gut motility.
- They increase gut motility by enhancing the release of excitatory neurotransmitters.
- Cholinomimetic agents—do not belong to this class since they cause uncoordinated activation of gut motility with no net propulsive movement.

35.3.1 Dopamine Receptor Antagonists

- Dopamine in the gut—inhibits GI motility (by acting on the D_2 receptors).
- Thus, D2 receptor blockers are used to enhance gut motility (prokinetic drugs).
- Drugs—metoclopramide, domperidone.

Metoclopramide

- Chemistry—belong to class of substituted benzamides.
- Receptor pharmacology—metoclopramide has the following receptor actions:
  - D_2 antagonism.
  - $5HT_4$agonism.
  - Vagal and central $5HT_3$ antagonism.
  - Sensitization of muscarinic receptors on smooth muscle.
- Mechanism of action (for antiemesis and prokinetic action).
  - Central $D_2$and $5HT_3$blockade in chemoreceptor trigger zone (CTZ)–produces antiemesis.
  - D_2 blockade,$5HT_4$agonismand vagal $5HT_3$ antagonism in gut—stimulates GI motility by enhancing acetylcholine release.
- Pharmacological actions.
  - Gastrointestinal tract.
    Predominant action on the upper part of GIT.
    Increases lower esophageal sphincter tone.
    Increases antral and small intestinal contractions.
    No effect on the motility of large bowel.
  - Central nervous system—blocks the D_2 receptors in chemoreceptor trigger zone and has antiemetic activity.
- Pharmacokinetics.
  - Administered by oral, intravenous, and intramuscular routes.
  - Metabolized in liver (sulfation and glucuronide conjugation).
  - Crosses the blood–brain barrier.
  - Excreted in urine.
- Therapeutic uses.
  - Antiemetic—used in chemotherapy/radiation-induced, postoperative, drug induced, and disease-induced (e.g., migraine) emesis.

  - Gastrokinetic—to increase gastric emptying in the following conditions.
    Postvagotomy or diabetic gastroparesis.
    Facilitate duodenal intubation.
    When emergency general anesthesia is indicated but patient has consumed food less than 4 h before.
  - Dyspepsia—produces symptomatic relief.
  - Gastroesophageal reflux disease—less effective than proton pump inhibitors or H_2 blockers.
- Therapeutic dose.
  - Oral/intramuscular—10 mg three times daily.
  - Intravenous infusion (for chemotherapy-induced emesis) —1–2 mg/kg given over at least 15 min, starting 30 min before the chemotherapy is given and repeated as needed every 2 h for two doses, then every 3 h for three doses.
- Adverse effects.
  - Restlessness, drowsiness, insomnia, anxiety, and agitation.
  - Extrapyramidal reactions, especially muscle dystonia, akathisia, Parkinsonian features (reversible on discontinuation of the drug)—common in children and at higher doses of the drug.
  - Tardive dyskinesia (irreversible sometimes).
  - Galactorrhea, gynecomastia, impotence, and menstrual disorders—due to blockade of inhibitory effect of dopamine on prolactin secretion.
  - Methemoglobinemia—rarely seen in premature and full-term neonates.
- It should be avoided in cases of gastrointestinal obstruction, perforation or hemorrhage.
- Recommended duration of use—less than 12 weeks (due to risk of side effects).

Domperidone

- Chemistry—benzamide derivative.
- Receptor pharmacology—it is a peripheral D_2 receptor blocker.
- Mechanism of action (for antiemesis and prokinetic action).
  - Central D_2 blockade in CTZ (since CTZ not protected by blood–brain barrier)—produces antiemesis.
  - D_2 blockade in gut—stimulates GI motility by enhancing acetylcholine release (prokinetic activity).
- It does not have any action on lower GI motility.
- Pharmacokinetics
  - Given orally.
  - Metabolized in liver.
  - Does not cross the blood–brain barrier.
  - Excreted in feces and urine.
- Therapeutic uses—similar to metoclopramide except its efficacy is less as gastrokinetic and in chemotherapy-induced emesis.
- Therapeutic dose (oral)—10–40 mg three times daily.
- Adverse effects

  - Cardiac side effects (QT prolongation), ventricular arrhythmias, including sudden cardiac death (especially in elderly patients and doses >30 mg/day).
  - Galactorrhea, gynecomastia, impotence, and menstrual disorders—due to blockade of inhibitory effect of dopamine on prolactin secretion.
  - It does not produce extrapyramidal side effects since it cannot penetrate the blood–brain barrier.
- Contraindications
  - Patients with liver or cardiac diseases.
  - Along with QT-prolonging drugs (e.g., clarithromycin, citalopram or amiodarone) or CYP3A4 inhibitors (e.g., diltiazem or verapamil).

35.3.2 Serotonin Receptor Agonists

- Serotonin(5HT) plays a very important role in gastric motility.
- GI tract—has >90% of the total 5HT in the body.
- Various serotonin receptors like $5HT_{1p}$, $5HT_{3,}$ and $5HT_4$ receptors are involved in regulation of GI motility.
- Re-uptake of the released serotonin by the neurons and epithelium of the gut is mediated by the serotonin transporter(SERT), which can be blocked by selective serotonin re-uptake inhibitors (SSRIs), thus causing diarrhea as an adverse effect.
- Drugs—Cisapride, Mosapride, Itopride, and Prucalopride.

Cisapride
- Chemistry—benzamide derivative.
- Receptor pharmacology—$5HT_4$ agonist, weak $5HT_3$ antagonist.
- Mechanism of action
  - Activation of $5HT_4$ presynaptic receptors in the PAN causes release of acetylcholine and activation of myenteric neurons, which causes smooth muscle contraction and produces prokinetic effect.
  - Weak $5HT_3$ antagonism suppresses the inhibitory transmission in the myenteric neurons and thus promotes smooth muscle contraction, potentiating the prokinetic action.
- Pharmacological actions
  - Improves the tone of lower esophageal sphincter.
  - Increases esophageal peristalsis.
  - Accelerates gastric emptying.
  - Increases colonic motility and secretion (unlike metoclopramide and domperidone).
  - Mild antiemetic activity.
- Pharmacokinetics—given orally, metabolized in liver by CYP3A4.

- Therapeutic uses—It is not commonly used because of its propensity to cause ventricular arrhythmias. However, it can be used in the following conditions where other standard therapies have failed:
  - Gastroesophageal reflux disease.
  - Gastroparesis.
  - Intestinal pseudo-obstruction.
  - Refractory severe chronic constipation.
- Therapeutic dose (oral)—5–10 mg four times a day before meals.
- Adverse effects—QT prolongation leading to ventricular fibrillation and torsades de pointes due to blockade of delayed rectifier K^+ channels.
- Contraindications.
  - Patients taking CYP3A4 inhibitors (e.g., azole antifungals, macrolide antibiotics, antidepressants, HIV protease inhibitors).
  - Patients with history of prolonged QT interval, ventricular arrhythmias, ischemic heart disease, congestive heart failure.
  - Patients with history of renal failure, respiratory failure, uncorrected electrolyte abnormalities.

Mosapride
- Mechanism of action and pharmacology—similar to cisapride.
- No antiemetic action (unlike cisapride with mild antiemetic activity).
- Therapeutic uses—used in the following refractory cases.
  - Gastroesophageal reflux disease.
  - Non-ulcer dyspepsia.
  - Gastroparesis.
  - Chronic constipation.
- Therapeutic dose (oral)—5 mg three times a day.
- Adverse effects—Prolongs QT interval.
- Metabolized by CYP3A4 enzyme and concomitant administration with enzyme inhibitors increases the risk of QT prolongation.

Itopride
- Chemistry—substituted benzamide.
- Receptor pharmacology—D_2 antagonism, acetylcholine potentiating action(due to anticholinesterase activity) and weak $5HT_4$agonism.
- Adverse effects—diarrhea, abdominal pain, headache, galactorrhoea, and gynecomastia.
- Does not cause QT prolongation (due to low affinity for cardiac 5HT4 receptors responsible for QT prolongation).
- Metabolized by flavin monooxygenases and thus devoid of drug interactions with CYP3A4 inhibitors.

Prucalopride
- Receptor pharmacology—$5HT_4$ receptor agonist.

- Mechanism of action—Activation of presynaptic $5HT_4$ receptors facilitates cholinergic neurotransmission and causes smooth muscle contraction.
- Pharmacological action
  - Does not affect gastric emptying.
  - Increases oral-cecal transit and colonic transit.
- Therapeutic use—severe chronic constipation.
- Therapeutic dose (oral)—1–4 mg once a day.
- Adverse effects—Nausea, diarrhea, abdominal pain, and headaches.

35.3.3 Motilin and Macrolide Antibiotics

- Motilin—peptide hormone secreted by enteroendocrine M cells and by some enterochromaffin cells of the upper small intestine.
- Main role of motilin—acts on motilin receptors and produces contraction of the upper GI tract.
- Motilin receptors—G protein coupled receptors found on smooth muscle cells and enteric neurons.
- Erythromycin (a macrolide antibiotic)—has prokinetic activity due to the following mechanisms.
  - At higher doses (250–500 mg)—mimics the effect of motilin.
  - At lower doses (40–80 mg)—facilitates cholinergic transmission.
- Pharmacological actions
  - Increases lower esophageal pressure.
  - Stimulates gastric and small-intestinal contractility.
  - No effect on colonic motility.
- Pharmacokinetics
  - Given orally.
  - Metabolized in liver by CYP3A4.
  - Excreted in the feces.
- Therapeutic uses—diabetic gastroparesis, clear the stomach of undigestible residue such as bezoars.
- Therapeutic doses
  - For gastric stimulation—1.5–3 mg/kg intravenous infusion every 6 h in a hospital setting or 125 mg orally every 12 h.
  - For small bowel stimulation—3 mg/kg IV every 8 h.
- Adverse effects
  - Gastrointestinal toxicity.
  - Ototoxicity.
  - Pseudomembranous colitis and the induction of resistant strains of bacteria.
  - QT prolongation, and sudden death (especially in patients taking CYP3A4enzyme inhibitors).
- Erythromycin is not used commonly as a prokinetic because of the following reasons

- Development of tolerance to its prokinetic action(usually within 28 days)—due to down regulation of the motilin receptor.
- Antibiotic effects leading to pseudomembranous colitis or induction of resistant strains of bacteria.

35.3.4 Miscellaneous Agents for Stimulating GI Motility

- The hormone cholecystokinin (CCK)—released from the intestine in response to meals.
- Pharmacological actions of CCK are as follows:
  - Delays gastric emptying.
  - Contraction of the gallbladder.
  - Stimulation of pancreatic enzyme secretion.
  - Increases intestinal motility.
  - Promotes satiety.
- Sincalide—C-terminal octapeptide of CCK.
- Sincalide (intravenous injection or infusion)—uses are as follows:
  - Stimulating the gallbladder or pancreas.
  - Accelerating barium transit through the small intestine for diagnostic testing of these organs.

35.4 Agents Suppressing GI Motility

- Smooth muscle relaxants—produce temporary relief in motility disorders like achalasia.
- Smooth muscle relaxant agents—organic nitrates, phosphodiesterase type 5 inhibitors, calcium channel blockers, and botulinum toxin.
- Botulinum toxin (onabotulinumtoxin A)—used in achalasia, gastroparesis, sphincter of Oddi dysfunction, and anal fissures.

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