

Review Article

The Pharmacology of Prokinetic Agents and Their Role in the Treatment of Gastrointestinal Disorders

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INTRODUCTION

Normal peristalsis of the gut requires complex, coordinated neural and motor activity. Abnormalities can occur at a number of different levels, and can be caused by numerous etiologies. This review summarizes current as well as new agents that show promise in the treatment of gastrointestinal motility disorders. For these conditions, the most common medications used in the US are erythromycin, metoclopramide, and neostigmine (in acute intestinal pseudo-obstruction). A new prokinetic agent, tegaserod, has been recently approved, while other serotonin agonist agents (prucalopride, YM-31636, SK-951, ML 10302) are currently undergoing clinical studies. Other prokinetics, such as domperidone, are not yet approved in the US, although are used in other countries.

DELAYED GASTRIC EMPTYING OR GASTROESOPHAGEAL REFLUX

Motor dysfunctions at the gastric or duodenal level can result in gastric stasis. Symptoms typically associated with delayed gastric emptying include nausea, vomiting, early or easy satiety, bloating, and weight loss. Reflux is characterized by impaired esophageal acid clearance, incompetence of the antireflux barrier and delayed gastric emptying. Prokinetic drugs have been used in addition to proton pump inhibitors for suppression of significant symptoms.

Metoclopramide

Pharmacologic Category : Gastrointestinal Agent. Prokinetic	
Use	Symptomatic treatment of diabetic gastric stasis Gastroesophageal reflux Facilitation of intubation of the small intestine Prevention and/or treatment of nausea and vomiting associated with chemotherapy, radiation therapy, or post-surgery (1)
Mechanism of Action	Blocks dopamine receptors in chemoreceptor trigger zone of the CNS (2) Enhances the response to acetylcholine of tissue in the upper GI tract, causing enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions.
Contraindications	Hypersensitivity to metoclopramide, or any component of the formulation GI obstruction, perforation or hemorrhage pheochromocytoma, seizure disorder(3)
Adverse Reactions	Adverse reactions are more common/severe in dosages used for prophylaxis of chemotherapy-induced emesis. >10%: Central nervous system: Restlessness, drowsiness, extrapyramidal reactions (high-dose, up to 34%) - may be more severe in the

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Adverse Reactions	<p>Gastrointestinal: Diarrhea (may be dose-limiting)</p> <p><u>Neuromuscular & skeletal:</u> Weakness 1% to 10%:</p> <p><u>Central nervous system:</u> Insomnia, depression</p> <p><u>Dermatologic:</u> Rash</p> <p><u>Endocrine & metabolic:</u> Breast tenderness, prolactin stimulation</p> <p><u>Gastro intestinal:</u> Nausea, xerostomia</p> <p><1%: Methemoglobinemia (5), tachycardia (6), hypertension or hypotension, tardive dyskinesia, fatigue, anxiety, agitation, constipation</p> <p>Symptoms of overdose include drowsiness, ataxia, extrapyramidal reactions, seizures, and methemoglobinemia (in infants)</p>
Overdosage/ Toxicology	<p>Disorientation, muscle hypertonia, irritability, and agitation are common</p> <p>Metoclopramide often causes extrapyramidal symptoms (eg, dystonic reactions) requiring management with diphenhydramine 1 -2 mg/kg (adults) up to a maximum of 50 mg I.M. or I.V. slow push, followed by a maintenance dose for 48-72 hours</p> <p>When these reactions are unresponsive to diphenhydramine, benztropine mesylate I.V. 1-2 mg (adults) may be effective</p> <p>These agents are generally effective within 2-5 minutes.</p> <p>CYP1A2 and 2D6 enzyme substrate</p> <p><u>Decreased effect:</u> Anticholinergic agents antagonize metoclopramide's actions.</p>
Drug Interactions:	<p><u>Increased toxicity:</u> Opiate analgesics may increase CNS depression.</p> <p><u>Gastroesophageal reflux:</u></p> <p><u>Oral:</u> 0.1-0.2 mg/kg/dose up to 4 times/day; efficacy of continuing metoclopramide beyond 12 weeks in reflux has not been determined</p>
Dosage:Children (7):	<p>Total daily dose should not exceed 0.5 mg/kg/day</p> <p><u>Gastrointestinal hypomotility (gastroparesis):</u></p> <p><u>Oral. I.M., I.V.:</u> 0.1 mg/kg/dose up to 4 times/day, not to exceed 0.5 mg/kg/day</p> <p><u>Antiemetic (chemotherapy-induced emesis):</u></p> <p><u>I.V.:</u> 1-2 mg/kg 30 minutes before</p>
Dosage:Children (7):	<p><u>Gastrointestinal hypomotility (gastroparesis):</u></p> <p><u>Oral. I.M., I.V.:</u> 0.1 mg/kg/dose up to 4 times/day, not to exceed 0.5 mg/kg/day</p> <p><u>Antiemetic (chemotherapy-induced emesis):</u></p> <p><u>I.V.:</u> 1-2 mg/kg 30 minutes before chemotherapy and every 2-4 hours</p> <p><u>Facilitate intubation:</u> I.V.: <6 years: 0.1 mg/kg 6-14 years: 2.5-5 mg</p> <p><u>Gastroesophageal reflux:</u></p>
Dosage:Adults (8):	<p><u>Oral:</u> 10-15 mg/dose up to 4 times/day 30 min. before meals or food and at bedtime</p> <p>Single doses of 20 mg are occasionally needed for provoking situations</p> <p>Efficacy of continuing metoclopramide beyond 12 weeks in reflux has not been determined</p> <p><u>Gastrointestinal hypomotility (gastroparesis):</u></p> <p><u>Oral:</u> 10 mg 30 min. before each meal and at bedtime for 2-8 weeks</p> <p><u>I.V. (for severe symptoms):</u> 10 mg over 1-2 min.; 10 days of I.V. therapy may be necessary for best response</p> <p><u>Antiemetic (chemotherapy-induced emesis):</u></p> <p><u>IV.:</u> 1-2 mg/kg 30 minutes before chemotherapy and every 2-4 hours to every 4-6 hours (and usually given with diphenhydramine 25-50 mg I.V./oral)</p> <p><u>Postoperative nausea and vomiting:</u></p> <p><u>I.M.:</u> 10 mg near end of surgery; 20mg doses may be used</p> <p><u>Facilitate intubation:</u> IV.: 10 mg</p> <p><u>Gastroesophageal reflux:</u></p> <p><u>Oral:</u> 5 mg 4 times/day (30 min. before meals and at bedtime) Increase dose to 10 mg 4 times/day if no response at lower dose</p>
Dosage:Elderly:	<p><u>Gastrointestinal hypomotility (gastroparesis):</u></p> <p><u>Oral:</u> Initial: 5 mg 30 min. before meals and at bedtime for 2-8 weeks Increase if necessary to 10 mg doses</p> <p><u>I.V.:</u> Initiate at 5 mg over 1-2 min.; increase to 10 mg if necessary</p> <p><u>Postoperative nausea and vomiting (I):</u> I.M.: 5 mg near end of surgery; may repeat dose if necessary</p>

<u>Dosage:Elderly:</u>	I.V.: Initiate at 5 mg over 1-2 min.; increase to 10 mg if necessary <u>Postoperative nausea and vomiting (I):</u> I.M.: 5 mg near end of surgery; may repeat dose if necessary
<u>Monitoring parameters:</u>	Perform a periodic renal function test Monitor for dystonic reactions Monitor for signs of hypoglycemia in patients using insulin and those being treated for gastroparesis Monitor for agitation and irritable confusion
<u>Test Interaction:</u>	Increases aminotransferase [ALT (SGPT)/AST (S G O T)] (S) , i n c r e a s e s amylase

Cisapride

<u>Pharmacologic Category : Gastrointestinal Agent. Prokinetic</u>	
<u>Use</u>	<u>Treatment of nocturnal symptoms of gastroesophageal reflux disease (GERD) (9)</u> has demonstrated effectiveness for gastroparesis, refractory constipation, and non-ulcer dyspepsia Cisapride enhances the release of acetylcholine at the myenteric plexus. May increase gastrointestinal motility and cardiac rate. Increases lower esophageal sphincter pressure and lower esophageal peristalsis Accelerates gastric emptying of both liquids and solids (10)
<u>Mechanism of Action</u>	Hypersensitivity to cisapride or any component of the formulations, GI hemorrhage, mechanical obstruction, GI perforation, or other situations when GI motility stimulation is dangerous (11)
<u>Contraindications</u>	Serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation (12, 13, 14, 15), have been reported in patients taking cisapride with other drugs that inhibit CYP3A4. Some of these events have been fatal. Cisapride is also contraindicated for patients with prolonged electrocardiographic QT intervals (QTc >450 msec), a history of QTc

<u>Contraindications</u>	these events have been fatal. Cisapride is also contraindicated for patients with prolonged electrocardiographic QT intervals (QTc >450 msec), a history of QTc prolongation, or known family history of congenital long QT syndrome(13). Clinically significant bradycardia, renal failure, history of ventricular arrhythmias, ischemic heart disease, and congestive heart failure; uncorrected electrolyte disorders (hypokalemia, hypomagnesemia) Respiratory failure; and concomitant medications known to prolong the QT interval and increase the risk of arrhythmia, such as certain antiarrhythmics, certain antipsychotics, certain antidepressants, astemizole, bepridil, sparfloxacin, and terodiline. Cisapride should not be used in patients with uncorrected hypokalemia or hypo-magnesemia or who might experience rapid reduction of plasma potassium, such as those administered potassium-wasting diuretics and/ or insulin in acute settings >5%: <u>Central nervous system:</u> Headache
<u>Adverse Reactions</u>	<u>Dermatologic:</u> Rash <u>Gastro intestinal:</u> Diarrhea, GI cramping, dyspepsia, flatulence, nausea, xerostomia <u>Respiratory:</u> Rhinitis <5%: <u>Cardiovascular:</u> Tachycardia <u>Central nervous system:</u> Extrapyrimal effects, somnolence, fatigue, seizures, insomnia, anxiety <u>Hematologic:</u> Thrombocytopenia, increased LFTs, pancytopenia, leukopenia, granulocytopenia, aplastic anemia <u>Respiratory:</u> Sinusitis, coughing, upper respiratory tract infection, increased incidence of viral infection Concomitant oral or intravenous administration of the following drugs with cisapride may lead to elevated cisapride blood:
<u>Drug Interactions:</u>	<u>Antibiotics:</u> Oral or I.V. Ervthromvcin, clarithromvcin, troleandomvcin <u>Antidepressants:</u> Nefazodone <u>Antifungals:</u> Oral or I.V. fluconazole, itraconazole, miconazole, oral ketoconazole <u>Protease inhibitors:</u> Indinavir, ritonavir,

Drug Interactions:	clarithromycin, troleandomycin <u>Antidepressants:</u> Nefazodone <u>Antifungals:</u> Oral or I.V. fluconazole, itraconazole, miconazole, oral ketoconazole <u>Protease inhibitors:</u> Indinavir, ritonavir, amprenavir	
Dosage: Oral	<i>Children</i>	0.15-0.3 mg/kg/dose 3-4 times/day; maximum:10 mg/dose
	Adults:	Initial: 10 mg 4 times/day at least 15 min. before meals and at bedtime In some patients the dosage will need to be increased to 20 mg to obtain a satisfactory result

Warnings/Precautions: Cisapride was voluntarily withdrawn from the U.S. market in July 2000. This decision was based on 341 reports of heart rhythm abnormalities including 80 reports of deaths. The company will continue to make the drug available to patients who meet specific clinical eligibility criteria for a limited-access protocol (contact 1-800-JANSSEN). Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation have been reported in patients taking this drug.

Patients should have a baseline ECG and an electrolyte panel (magnesium, calcium, potassium) prior to initiating cisapride (see Contraindications). Potential benefits should be weighed against risks prior to administration of cisapride to patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with conditions that could predispose them to the development of serious arrhythmias, such as multiple organ failure, COPD, apnea and advanced cancer.

Domperidone

This medication is not available in the US.

Pharmacologic Category : dopamine antagonist, peripheral	
Use	Symptomatic treatment of upper GI motility disorder in association with diabetic gastroparesis (16) and subacute/chronic

Use	gastroparesis (16) and subacute/chronic gastritis Prevention of GI symptoms associated with use of dopamine-agonist anti-Parkinson agents (17)
Mechanism of Action	Peripheral dopamine receptor blocking Increases esophageal peristalsis and lower esophageal sphincter pressure, increases gastric motility and peristalsis, enhances gastroduodenal coordination Overall, facilitates gastric emptying and decreases small bowel transit time (18,19,20)
Contraindications	GI hemorrhage, mechanical obstruction, perforation; prolactin secreting pituitary tumor (21)
Precautions	Increases prolactin levels (galactorrhea, gynecomastia, amenorrhea, impotence) QTc prolongation tachyarrhythmias, cardiac arrest may be precipitated in hypokalemic patients Liver disease, breast cancer and patients on MAO inhibitors
Adverse Reactions	<u>1 to 10%:</u> <u>CNS:</u> headache (1%); fewer CNS effects compared to metoclopramide <u>Gastrointestinal:</u> xerostomia (2%) <u>Less than 1%:</u> abdominal cramps, constipation, diarrhea, heartburn, dizziness, dysuria, edema, extrapyramidal symptoms, insomnia, nausea, irritability, hot flashes, palpitations, rash, regurgitation, urinary frequency
Overdosage:	CNS effects (extrapyramidal reactions, disorientation) and cardiovascular effects (arrhythmias, hypotension) (21)
Drug Interactions:	Anticholinergics may decrease domperidone effects HIV protease inhibitors, azole antifungals, macrolide may increase plasma levels of domperidone Domperidone may increase the rate of absorption of drugs from small bowel, while slowing absorption of drugs from the stomach

<u>Drug Interactions:</u>	slowing absorption of drugs from the stomach Use with caution in combination with fluoroquinolones, type IA and III antiarrhythmic, and thioridazine because of QT prolongation
<u>Dosage</u>	GI motility disorders (16,17): 10 mg 3-4 times / day, 15-30 min. before meals In severe/resistant cases 20 mg 3-4 times / day Nausea/vomiting associated with dopamine-agonist anti-Parkinson agents: 20 mg 3 -4 times / day

GASTROESOPHAGEAL REFLUX DISEASE

In addition to acid inhibitory agents, and promotility drugs mentioned above, in selected cases cholinergic agonists may be helpful.

Bethanechol

<u>Pharmacologic Category: Cholinergic Agonist</u>	
<u>Use</u>	Gastroesophageal reflux (22, 23) Non-obstructive urinary retention and retention due to neurogenic bladder Treatment and prevention of bladder dysfunction caused by Phenothiazines Diagnosis of flaccid or atonic neurogenic bladder (24)
<u>Mechanism of Action</u>	Stimulates cholinergic receptors in the smooth muscle of the urinary bladder and gastrointestinal tract resulting in increased peristalsis, increased GI and pancreatic secretions, bladder muscle contraction, and increased ureteral peristaltic waves (24)
<u>Contraindications</u>	Mechanical obstruction of the GI or GU tract or when the strength or integrity of the GI or bladder wall is in question (25) Hyperthyroidism, peptic ulcer disease, epilepsy, obstructive pulmonary disease, bradycardia, vasomotor instability,

	hypotension, or Parkinsonism Contraindicated for IM or IV use due to a likely severe cholinergic reaction
<u>Adverse Reactions</u>	More common with S.C. Administration <u>Cardiovascular:</u> Hypotension, tachycardia, flushed skin <u>Central nervous system:</u> Headache, malaise <u>Gastrointestinal:</u> Abdominal cramps, diarrhea, nausea, vomiting, salivation, eructation <u>Genitourinary:</u> Urinary urgency <u>Ocular:</u> Lacrimation, miosis <u>Respiratory:</u> Asthmatic attacks <u>M i s c e l l a n e o u s :</u>
<u>Overdosage/ Toxicology:</u>	Diaphoresis Symptoms of overdose (25) include nausea, vomiting, abdominal cramps, diarrhea, involuntary defecation, flushed skin, hypotension, and bronchospasm Treat symptomatically with atropine for severe muscarinic symptoms or epinephrine to reverse severe cardiovascular or pulmonary sequelae
<u>Drug Interactions:</u>	<u>Decreased effect:</u> Procainamide, quinidine <u>Increased toxicity:</u> Bethanechol and ganglionic blockers -> critical fall in blood pressure Cholinergic drugs or anticholinesterase agents.
<u>Dosage: Children (26, 27)</u>	Oral (administered 1 hour before meals or 2 hours after meals) <u>Abdominal distention or urinary retention:</u> 0.6 mg/kg/day divided 3-4 times/day <u>Gastroesophageal reflux:</u> 0.1-0.2 mg/ kg/ dose given 30 min. to 1 hour before each meal to a maximum of 4 times/day <u>S.C.:</u> 0.15-0.2 mg/kg/day divided 3-4 times/ day
<u>Dosage: Adults (28)</u>	Oral: 10-50 mg 2-4 times/day

ACUTE COLONIC INTESTINAL PSEUDOObSTRUCTION (OGILVIE'S SYNDROME)

Is a disorder characterized by dilatation of the cecum and right hemicolon (occasionally extending to the rectum) in the absence of a mechanical obstruction. Active intervention is indicated for deteriorating patients; most patients will respond to neostigmine, administered during close cardiovascular monitoring. Patients who have contraindications or are not responding should be decompressed with a colonoscopy.

Neostigmine

	Pharmacologic Category: Acetylcholinesterase Inhibitor
<u>Use</u>	Acute intestinal pseudo-obstruction(26) Diagnosis and treatment of my asthenia gravis Prevention and treatment of postoperative bladder distention and urinary retention Reversal of the effects of non-depolarizing neuromuscular-blocking agents after surgery (27)
<u>Mechanism of Action</u>	Inhibits destruction of acetylcholine by acetylcholinesterase, which facilitates transmission of impulses across myoneural junction
<u>Contraindications</u>	Hypersensitivity to neostigmine, bromides, or components of the formulation GI or GU obstruction
<u>Warnings / Precautions:</u>	Does not antagonize and may prolong the phase I block of depolarizing muscle relaxants (eg, succinylcholine) Use with caution in patients with epilepsy, asthma, bradycardia, hyperthyroidism, cardiac arrhythmias, or peptic ulcer Adequate facilities should be available for cardiopulmonary resuscitation when testing and adjusting dose for myasthenia gravis Have atropine and epinephrine ready to treat hypersensitivity reactions

	but this must be distinguished from myasthenic crisis Anticholinesterase insensitivity can develop for brief or prolonged periods
<u>Adverse Reactions</u>	<u>Frequency not defined</u> <u>Cardiovascular:</u> Arrhythmias (especially bradycardia), hypotension, decreased carbon monoxide, tachycardia, AV block, nodal rhythm, nonspecific EKG changes, cardiac arrest, syncope, flushing <u>Central nervous system:</u> Convulsions, dysarthria, dysphonia, dizziness, loss of consciousness, drowsiness, headache <u>Dermatologic:</u> Skin rash, thrombophlebitis (I.V.), Urticaria <u>Gastrointestinal:</u> Hyperperistalsis, nausea, vomiting, salivation, diarrhea, stomach cramps, dysphagia, flatulence <u>Genitourinary:</u> Urinary urgency <u>Neuromuscular & skeletal:</u> Weakness, fasciculations, muscle cramps, spasms, arthralgias <u>Ocular:</u> Small pupils, lacrimation <u>Respiratory:</u> Increased bronchial secretions, laryngospasm, bronchiolar constriction, respiratory muscle paralysis, dyspnea, respiratory depression, respiratory arrest, bronchospasm <u>Miscellaneous:</u> Diaphoresis (increased), anaphylaxis, allergic reactions
<u>Overdosage/ Toxicolog:</u>	Symptoms of overdose include muscle weakness, blurred vision, excessive sweating, tearing and salivation, nausea, vomiting, diarrhea, hypertension, bradycardia, muscle weakness, and paralysis Atropine sulfate injection should be readily available as an antagonist for the effects of neostigmine (26,29,30)
<u>Drug Interactions:</u>	<u>Anticholinergics:</u> Effects may be reduced with cholinesterase inhibitors Atropine antagonizes the muscarinic effects of cholinesterase inhibitors (31) <u>Beta-blockers without ISA:</u> Activity may increase risk of bradycardia

Drug Interactions:	<p><u>Cholinergic agonists:</u> Effects may be increased with cholinesterase inhibitors</p> <p><u>Corticosteroids:</u> May see increased muscle weakness and decreased response to anticholinesterases shortly after onset of corticosteroid therapy in the treatment of myasthenia gravis</p> <p>Deterioration in muscle strength, including severe muscular depression, has been documented in patients with myasthenia gravis while receiving corticosteroids and anticholinesterases</p> <p><u>Digoxin:</u> Increased risk of bradycardia with concurrent use</p> <p><u>Neuromuscular blockers:</u> Depolarizing neuromuscular blocking agents effects may be increased with cholinesterase inhibitors</p> <p>Nondepolarizing agents are antagonized by cholinesterase inhibitors (29)</p>
Dosage:	Acute intestinal pseudoobstruction - 2 mg administered undiluted by slow I.V. injection over several minutes (26, 29, 30)

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits in the absence of any organic disorder. Prokinetic drugs should be considered only for short-term use in constipation predominant IBS.

Tegaserod

	<u>Pharmacologic Category:</u> Aminoguanidine indole derivative of serotonin that acts as selective partial agonist of 5-HT ₄ receptor (32)
Use	Constipation predominant irritable bowel syndrome (33)
Mechanism of Action	Activates 5-HT ₄ receptors located on neurons of the gastrointestinal tract, increasing the gastrointestinal motility May reduce visceral sensitivity in experimental animal models (34)

Pharmacokinetics	It is absorbed rapidly after oral administration, and is metabolized mainly pre-systemically when absorbed, intact tegaserod is excreted as N-glucuronides via bile (32)
Contraindications	Severe renal impairment, hepatic impairment (moderate or severe), history of bowel obstruction abdominal adhesions, symptomatic gallbladder, sphincter of Oddi dysfunction
Adverse Reactions	<p>Most common reported is diarrhea (9% vs. 4% compared to placebo) (35)</p> <p>In a majority of cases, a single episode, mainly within the first week of treatment</p> <p>Abdominal pain, flatulence, and headaches had a rate comparable to placebo</p> <p>Abdominal surgeries were increased in patients treated with tegaserod (0.3 vs. 0.2 percent), primarily cholecystectomy</p> <p>Tegaserod was not found to be carcinogenic, teratogenic or toxic to the fetus in animal studies (36)</p>
Drug Interactions:	<p>No clinically relevant or adverse drug - drug interactions have been reported</p> <p>No dose adjustments are required for concomitant administration of drugs that are metabolized via CYP1A2 (theophylline) or digoxin</p>
Dosage:	<p>6 mg orally BID with or without food</p> <p>May start with a single dose of medication and titrate up to BID</p> <p>Treatment has been approved for 4 to 6 weeks with another 4 to 6 weeks in responsive patients (37)</p>

CONCLUSIONS

Several prokinetic agents have been of value in treating GI disorders. Research into specific receptors, agonists and antagonists in the GI tract have led to the development of new agents with more specificity and fewer side effects. It is likely that in the future more of these tailored drugs will become available for the treatment of motility disorders.

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