UPPER GI TRACT

PART I

CHAPTER 1

Prokinetic agents and antiemetics

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Prokinetics

Introduction

Prokinetic agents enhance coordinated gastrointestinal motility by increasing the frequency and/or the amplitude of contractions without disrupting normal physiological pattern and rhythm of motility.

Acetylcholine is the principle immediate mediator of muscle contractility in the GI tract. However, most clinically useful prokinetic agents act "upstream" of acetylcholine, at receptor sites on the motor neuron itself, or even more indirectly, on neurons that are one or two orders above. Acetylcholine itself is not pharmacologically utilized because it lacks selectivity. It acts on both nicotinic and muscarinic receptors and is rapidly degraded by acetylcholinesterase. Dopamine is present in significant amounts in the GI tract and has an inhibitory effect on motility. It reduces both lower esophageal sphincter basal pressure and intragastric pressure. These effects are mediated by D_2 receptors through suppression of acetylcholine release from myenteric motor neurons. Thus, dopamine receptor antagonists are effective prokinetic agents because of antagonizing the inhibitory effect of dopamine on myenteric motor neurons. Additionally, they act centrally on the chemoreceptor trigger zone (CTZ), thereby relieving nausea and vomiting. Presently, very few prokinetics are available in the market, primarily due to the failure of many of these compounds to demonstrate significant symptom improvement when compared with placebo in pivotal indication trials. In addition, these agents have an unacceptable safety profile. The exact reasons for the former are unknown but are believed to be related to disassociation between severity and/or frequency of symptoms and the severity or even the presence or absence of a motility abnormality.

Pocket Guide to Gastrointestinal Drugs, Edited by M. Michael Wolfe and Robert C. Lowe. Published 2014 by John Wiley & Sons, Ltd.

Metaclopramide (Reglan)

Metaclopramide is indicated for the prophylaxis of chemotherapy-associated nausea and vomiting (second line agent); diabetic gastroparesis; gastroesophageal reflux disease (GERD); prior to endoscopic or radiologic exam, to place a feeding tube beyond the pylorus; and postoperative nausea and vomiting. Metaclopramide is also commonly used, but not FDA approved in, nondiabetic gastroparesis, hyperemesis gravidarum, and dyspepsia.

Mechanism of action

The drug works through several mechanisms. It is a dopamine receptor antagonist, a 5-HT_3 antagonist, and a 5-HT_4 agonist. It also blocks serotonin receptors in the chemoreceptor trigger zone of the central nervous system (CNS). Metaclopramide enhances the response to acetylcholine in the upper GI tract, resulting in coordinated contractions and thus accelerated gastric emptying, as well as increasing lower esophageal sphincter tone.

Pharmacology

Metaclopramide is absorbed rapidly after oral ingestion, metabolized by the liver and is excreted principally in the urine with a t ½ of 4–6 hours. The onset of action after oral administration is 30–60 minutes; after IV administration, 1–3 minutes; and after IM administration, 10–15 minutes. Dosing of metaclopramide for each different indication is listed in Table 1.1. The bioavailability of different medications may be affected due to accelerated gastric emptying. Drugs with narrow therapeutic indices need to be monitored closely when administered concomitantly with metoclopramide. The concomitant administration of CNS depressants, such as anxiolytics, hypnotics or sedatives, as well as alcohol, with metoclopramide can possibly increase sedation. The concomitant administration of metoclopramide with drugs that can cause extrapyramidal reactions is contraindicated. Patients with hepatic impairment do not need dosage adjustment. In addition, patients with mild renal impairment (CrCl ≥40 ml/minute) do not require a dosage adjustment. However, patients with CrCl <40 ml/minute require a dose reduction of 50%.

Adverse effects

Major side effects due to central dopamine antagonism include extrapyramidal reactions, such as acute dystonic attack, pseudo-parkinsonism, akathisia, tardive dyskinesia, and rarely neuroleptic malignant syndrome. Parkinson-like symptoms occur several weeks after the initiation of therapy and usually subside 2–3 months after the discontinuation of

Table 1.1 Dosing and route of administration of metaclopramide (Reglan)

Indications	Adult dosage	Child dosage
Diabetic gastroparesis	Oral: 10 mg 30 minutes before each meal and bedtime for 2–8 weeks Parenteral: IV/IM: 10 mg if oral route is not available	
IV infusion for chemotherapy-induced emesis	1–2 mg/kg administered over 15 minutes, beginning 30 minutes prior to chemotherapy and repeated as needed every 2–3 hrs	1–2 mg/kg administered over 15 minutes, beginning 30 minutes prior to chemotherapy and repeated as needed every 2–3 hrs
Post-operative nausea/ vomiting and nausea vomiting prophylaxis	10 mg IM or IV near end of the surgical procedure, repeat every 4–6 hrs as needed	0.1–0.2 mg/kg IV, repeat every 6–8 hrs as needed
Gastroesophageal reflux disease (GERD)	10–15 mg orally up to 4 times/day. Therapy – recommended no more than 12 weeks	Child/infant: 0.1 mg/kg orally 3–4 times/day Neonates:0.15 mg/kg orally every 6 hrs
Prior to endoscopic or radiologic procedures	10 mg IV	<6 years: 0.1 mg/kg IV single dose; 6–14 years: 2.5.5 mg IV

therapy. Tardive dyskinesia can occur after weeks to years of therapy initiation and may be irreversible. It appears to be more common in elderly patients. Strategies such as titrating to lowest effective dose and drug holidays may decrease these side effects. Patients should be warned to inform their physician if any involuntary movements develop. Rarely, cardiac arrhythmias, hypersensitivity reactions, hyperprolactinimia, impotence and neuroleptic malignant syndrome have all been reported.

Motilin agonists

Motilin, a peptide hormone found in the GI M cells and some enterochromaffin cells, is a powerful contractile agent of the upper

gastrointestinal (GI) tract. Erythromycin and other macrolide antibiotics like azithromycin and clarithromycin mimic the molecular structure of motilin and thus are potent promotility agents. Rapid development of tolerance and side effects, as well as concerns about using antibiotics long term, limits the use of these drugs as prokinetics. Intravenous erythromycin may be used to "restart or kick-start" the stomach during acute episodes of gastroparesis. It has also been used to clear the stomach prior to endoscopy of patients with an upper gastrointestinal bleed.

Pharmacology

The standard dose of erythromycin for gastric stimulation is 3 mg/kg IV or 200–250 mg orally every 8 hours and for azithromycin 250 mg daily. For small intestinal motility, a lower dose of 40 mg IV is more commonly used. However, the drugs are contraindicated in concomitant use with astemizole, dihydroergotamine, ergotamine, pimozide, terfenadine and in patients with known hypersensitivity to motilides. In elderly patients with renal/hepatic impairment, there is an increased risk of hearing loss, hepatotoxicity and QT prolongation. Lastly, erythromycin has been designated as Pregnancy Category B.

Adverse effects

Gastrointestinal toxicity (nausea, anorexia, diarrhea, abnormal liver enzymes and jaundice), bacterial resistance, pseudomembranous colitis and sudden cardiac death due to prolonged QT interval syndrome have all been well documented. Azithromycin has similar effects on GI motility as the other macrolides but was originally thought to lack drug interaction that can lead to prolonged QT interval. However, the FDA recently issued a warning that azithromycin can lead to fatal arrhythmia in certain patients. The extent of the risk is unknown. The macrolides require adjustment in patients with hepatic impairment because of the possibility of accumulation, whereas in patients with renal impairment, no need for dose adjustment is necessary.

Bethanechol

Bethanechol is a prokinetic agent that improves GI motility by acting as a cholinergic agonist, releasing acetylcholine from nerve endings. The drug is less commonly used today as a prokinetic due to its high rate of cholinergic-related adverse events and poor patient tolerability. While not specifically indicated for GI-related disorders, the drug has been used in GERD, primarily in patients who are refractory to proton pump inhibitor (PPI) treatment. The dosing is 25 mg orally four times a day. Bethanechol is contraindicated in patients with asthma and bradycardia.

Its adverse effects are primarily related to its cholinergic effects and consequently also include syncope, dizziness, diarrhea, and urgent desire to urinate. Bethanechol is designated as Pregnancy Category C.

Domperidone

The drug is not FDA approved but is available in many countries outside the US, including Mexico and Canada. It is a peripheral dopamine D_2 receptor antagonist. It does not readily cross the blood brain barrier (BBB) and is hence less likely to cause extrapyramidal side effects. It can affect CNS areas that lack this barrier and those areas involved in temperature control, prolactine release and emesis. The drug is used for gastroparesis and GERD. The drug is dosed 10 to 20 mg three times a day.

Antiemetic agents

Introduction

Nausea (Latin *nausea*, from Greek vauoia, nausie, "motion sickness," "feeling sick," queasy" or "wamble") is a sensation of unease and discomfort in the upper abdomen, which often leads to vomiting. Vomiting, an act of forceful expulsion of stomach contents, is a complex process, consisting of coordination between central and peripheral mechanisms. Vomiting is coordinated by a central emesis center in the lateral reticular formation of the mid brainstem that is adjacent to both the chemoreceptor trigger zone (CTZ) in the area postrema (AP) at the base of the forth ventricle and the solitary tract nucleus (STN) of the vagus nerve. The absence of a BBB allows the CTZ to monitor blood and cerebrospinal fluid constantly for toxic substances and to relay information to the emesis center. It also receives input from the vagus nerve via the STN, splanchnic afferents via the spinal cord, the cerebral cortex and the vestibular apparatus. CTZ has high concentration of 5-HT_3, dopamine and opioids receptors, while the STN is rich in enkephalin, histamine, acetylcholine and 5-HT_3 receptors.

Antiemetics are classified according to the predominant receptor on which they are proposed to act. However, the mechanisms of action may overlap among the different antiemetics. Data comparing antiemetics in specific disorders is very limited; hence drug selection in a particular situation is empiric, based on preferred route of administration, safety and personal experience.

Five neurotransmitter receptor sites have been identified that play an important role in the vomiting reflex: muscarinic (M_1), dopamine (D_2), histamine (H_1), serotonin (5-HT_3), and Substance P/Neurokinin Receptor 1. Consequently, antiemetics were primarily developed as

Table 1.2 The different antiemetic classes

Antiemetic class	Medications	Common therapeutic utilization
5-HT_3 antagonist	Ondansetron (Zofran) Granisetron (Kytril) Dolasetron (Anzemet) Palonosetron (Aloxi)	Chemotherapy-induced nausea and vomiting prophylaxis Radiation-induced nausea and vomiting prophylaxis Postoperative nausea and vomiting prophylaxis
D_2 antagonist	Metoclopramide (Reglan) Prochlorperazine (Compazine) Trimethobenzamide (Tigan) Droperidol (Inapsine)	Chemotherapy-induced nausea and vomiting Motion sickness Postoperative nausea and vomiting
H_1 receptor antagonist	Cyclizine (Bonine for children, Marezine) Promethazine (Phenergan) Hydroxyzine (Atarax, Vistaril) Meclizine (Antivert, Bonine, Dramamine, Zentrip, VertiCalm)	Motion sickness Postoperative nausea and vomiting prophylaxis
M_1 antagonist	Hyoscine (Scopolamine)	Motion sickness
NK_1 antagonist	Aprepitant (Emend) Fosaprepitant (Emend Inj)	Chemotherapy-induced nausea and vomiting
Cannabinoids	Dronabino (Marinol) Nabilone (Cesamet)	Chemotherapy-induced nausea and vomiting

inhibitors of these receptors (Tables 1.2, 1.3 and 1.4). This chapter will not cover the serotonin-related products, which are discussed elsewhere in this book.

Dopamine receptor antagonists

Three classes of dopamine receptor antagonists are currently available. They include phenothiazines: prochlorperazine (Compazine), chlorpromazine (Thorazine); butyrophenones: droperidol (Inaspine), haloperidol (Haldol); and benzamides: metoclopramide (Reglan), Domperidone (Motilium) and trimethobenzamide hydrochloride (Tigan).

Table 1.3 Dosing and indications of antiemetic medications

Indication	Antiemetic class	Medications	Adult dose
Motion sickness	H_1 antagonists	Cyclizine	50 mg q4–6 hr. oral/IM Max 200 mg/24 hr 30 min. before travel
		Hydroxyzine	25–100 mg IM/PO q4–6 hr. Max 600 mg/day 30 min. before travel
		Meclizine	50 mg orally q24 hrs. Start 1 hour before travel
		Promethazine	25 mg orally BID 30 min. before travel
	M_1 antagonists (anticholinergics)	Scopolamine	1 transdermal patch behind ear 4 hours before travel. Replace every 3 days if needed.
Post-operative N/V	H_1 antagonists	Promethazine	12.5–25 mg orally/IM/IV q4–6 hrs Max. 50 mg/dose orally/IM; 25 mg/dose IV
		Cyclizine	50 mg IM/IV q4–6 hrs
	D_2 antagonists	Metoclopramide	10 mg IM or IV near end of surgical procedure Repeat q4–6 hrs as necessary
		Tigan	Adult: 300 mg orally q6–8 hrs 200 mg IM q6–8 hrs
		Compazine	Adult: 5–10 mg orally q6–8 hrs 5-10 mg IM or 2.5–10 mg IV q3–4 hrs 25 mg suppository rectally q12 hrs
		Droperidol	Adult: 0.625–1.25 mg IM/IV q3–4 hrs as needed Max 2.5 mg IM/IV May repeat 1.25 mg based on response, cautiously
	M_1 antagonists (anticholinergics)	Scopolamine	1 transdermal patch behind ear the evening before surgery and 24 hrs after

Table 1.4 Pregnancy class and use in children of antimetic medications

Antiemetic class	Medications	Pregnancy class	Use in children
D_2 antagonist	Metoclopramide (Reglan)	B	Yes
	Prochlorperazine (Compazine)	C	Yes (>2 years)
	Trimethobenzamide (Tigan)	C	No
	Droperidol (Inapsine)	C	Yes (>2 years)
H_1 receptor antagonist	Cyclizine (Bonine for children, Marezine)	B	Yes (>6 years)
	Promethazine (Phenergan)	C	Yes (>2 years)
	Hydroxyzine (Atarax, Vistaril)	C	Yes
	Meclizine (Antivert, Bonine, Dramamine, Zentrip, VertiCalm)	B	Yes (>12 years)
M_1 antagonist	Hyoscine (Scopolamine)	C	Yes
NK_1 antagonist	Aprepitant (Emend)	B	No
	Fosaprepitant (Emend Inj)	B	No
Cannabinoids	Dronabinol (Marinol)	C	No
	Nabilone (Cesamet)	C	No

Phenothiazines

The phenothiazines are the most commonly used antiemetics. These drugs are moderately effective for nausea caused by various GI and non-GI disorders and in mild to moderate, but not highly emetogenic, chemotherapy. Prochlorperazine (Compazine) predominantly blocks D_2 dopamine receptors in the area postrema, but also possesses muscarinic (M_1) and histamine (H_1) antagonist effects. Prochlorperazine is indicated for severe nausea and vomiting. Although not indicated, it is also used in chemotherapy–induced nausea and vomiting. The drug is contraindicated in children under 2 years of age, comatose states, and in patients with hypersensitivity to phenothiazines. The drug should be cautiously used in elderly patients with dementia-related psychosis, adolescents and children with signs suggestive of Reye's syndrome and in those with bone marrow suppression. The

adverse effects include hypotension, hypertension, and prolonged QT interval.

Chlorpromazine (Thorazine) is used less often than prochlorperazine. It is a dimethylamine derivative of phenothiazine, whose exact mechanism of action is unknown. It has weak anticholinergic, antihistaminic and antiserotonin activities. The drug is indicated for nausea, vomiting and intractable hiccups. The dosing for nausea and vomiting in the adult is 10–25 mg orally every 4–6 hours and 25 mg IV/IM every 3–4 hours. In the pediatric population, the dose is 0.25 mg/lb orally and 0.125 mg/lb IM. Chlorpromazine is contraindicated in a comatose state, concomitant use of large doses of CNS depressants and in those with hypersensitivity to the drug. Administration in elderly patients with dementia-related psychosis or those with bone marrow suppression should be cautiously done. Adverse effects include akathesia, dizziness, tardive dyskinesia, and constipation. In patients with hepatic impairment, a lower dose should be considered. In contrast, in patients with renal impairment, there is no need for dose adjustment. The drug has been designated Pregnancy Category C.

Butyrophenones

The butyrophenones are used for procedural sedation as preanaesthetic agents and for post-operative nausea and vomiting. They are tranquilizers that potentiate action of opioids and have antiemetic effect when used alone.

The exact mechanism of action of droperidol (Inapsine) is unknown. Its antiemetic effect may be due to binding of GABA receptors in the CTZ. It antagonizes the action of dopamine by binding to D_2 receptors centrally. The drug is indicated for nausea and vomiting associated with surgical or diagnostic procedures and for prophylaxis of nausea/vomiting. The drug is not indicated, but is commonly used, for nausea and vomiting due to other reasons and for chemotherapy-induced vomiting. Droperidol is contraindicated in patients with hypersensitivity to the drug or those with prolonged QT interval. In those patients with other arrythmogenic medications, elderly patients, and in patients with renal or hepatic impairment, the drug should be used with caution. Adverse effects include prolonged QT interval, torsades de pointes, ventricular tachycardia, cardiac arrest, hypertension, and somnolence. In patients with hepatic impairment, lower doses may be required. Similarly, in patients with renal impairment, lower doses are required.

Benzamides

The benzamides include metoclopramide and domperidone, which are discussed earlier in this chapter.

Trimethobenzamide hydrochloride (Tigan) is a dopamine receptor antagonist that is indicated for nausea due to gastroenteritis and for postoperative nausea and vomiting. The drug is contraindicated in patients with previous hypersensitivity to the drug and in patients in the pediatric age group. Elderly patients may have an increased risk of extrapyramidal and CNS side effects. Adverse effects include hypotension, xerostomia, diarrhea, anticholinergic adverse reactions, and somnolence. A decrease in the total daily dose or frequency of administration should be considered in patients with diminished renal function, defined as a CrCl # 70 ml/minute. In those with hepatic impairment, there is no need for dose adjustment. In pregnant women, fetal risk cannot be ruled out.

Histamine 1 receptor antagonists

The antihistaminics are histamine 1 (H_1) receptor antagonists that are primarily useful for motion sickness and post-operative emesis. Their precise mechanism of action is not known, but may be due to a direct effect on the labyrinthine apparatus, as well as central action on CTZ.

Cyclizine (Marezine) is indicated in adults for nausea and vomiting due to motion sickness and should be taken 30 minutes prior to travel time. It is also indicated in the pediatric population for postoperative vomiting. The dose for those aged 6–12 years is 25 mg every 6–8 hours, not to exceed 75 mg/24 hours. For those older than 12 years, the dose is 50 mg every 4–6 hours, not to exceed 200 mg/24 hours. In patients with postoperative nausea who are between the ages of 6–10 years, the dose is 3 mg/kg/day in three divided doses IM or orally. The drug is contraindicated in patients with known hypersensitivity to the drug. In subjects with asthma, COPD, glaucoma, congestive heart failure (CHF), obstructive uropathy and epilepsy, caution should be taken when using the drug. Adverse effects include drowsiness, dizziness, dry mucous membranes, pancytopenia, arrhythmias, and heat stroke.

Hydroxyzine (Atarax, Vistaril) is indicated for motion sickness. In patients with renal impairment (CrCl <50), the dose should be decreased by 50%, while in those with hepatic impairment, the frequency of administration should be decreased. Another member of the antihistaminics family is promethazine (Phenergan). The drug is indicated for nausea/vomiting and for motion sickness. Dose adjustments have not been defined in patients with renal or hepatic impairment.

Meclizine (Antivert, Bonine, Dramamine, Zentrip), another H_1 antagonist, is used for non-GI related indications, but also for motion sickness.

Anticholinergic agents

Scopolamine is a belladonna alkaloid that possesses anticholinergic properties. It functions as an M_1-muscarinic antagonist by blocking cholinergic transmission from the vestibular nuclei. The drug is indicated for motion sickness and postoperative nausea and vomiting (1.5 mg transdermal patch). Scopolamine is contraindicated in COPD, liver impairment and in patients with tachyarrythmia. Adverse effects include xerostomia, blurred vision, and somnolence.

Neurokinin receptor antagonists

Aprepitant (Emend) and fosaprepitant (Emend Injection) are selective high affinity antagonists of human substance P/neurokinin 1 (NK_1). In animal models, they appear to work at the cerebral cortex and dorsal raphae. By inhibiting the substance P/neurokinin 1 receptor, they prevent acute and delayed vomiting. They are indicated for chemotherapy-associated nausea and vomiting due to highly and moderately emetogenic chemotherapy, nausea and vomiting prophylaxis and post-operative nausea and vomiting prophylaxis.

Aprepitant (Emend) is dosed for chemotherapy-induced nausea and vomiting prophylaxis at 125 mg orally 1 hour prior to chemotherapy on day 1 followed by 80 mg orally daily in the morning on days 2 and 3 (used in combination with corticosteroids/5-HT_3 antagonist as per treatment protocol). In postoperative nausea-vomiting prophylaxis, the drug is dosed at 40 mg orally once, 3 hours prior to anesthesia.

Fosaprepitant (Emend Injection) is dosed for chemotherapy-induced nausea and vomiting as a single-dose regimen, a single dose of 150 mg IV started 30 minutes prior to chemotherapy on day 1 or as a three-day regimen. An alternate regimen includes a single dose of fosaprepitant 115 mg IV, followed by aprepitant 80 mg orally for 2 days, which is started 30 minutes prior to chemotherapy. The drug is contraindicated in patients with hypersensitivity to the medication and those with severe liver impairment. Adverse effects may include neutropenia, bradycardia, and Stevens Johnson syndrome. In hepatic impairment, there is no dose adjustment for Child-Pugh A and B. However, it is not yet defined for C. There is no need for dose adjustment in renal impairment.

Cannabinoids

The exact mechanism of action of cannabinoids is not known, although they bind to cannabinoid receptors in the neural tissues. Dronabinol is indicated in chemotherapy-induced nausea and vomiting prophylaxis. The drug is dosed in adults at 5 mg/m^2 orally 1–3 hours before chemotherapy and 5 mg/m^2 orally every 2–4 hours after chemotherapy for total of 4–6 doses/day. The dose may be increased by 2.5 mg/m^2 to a

maximum of 15 mg/m^2/dose. Nabilone7 is dosed in the adult at 1–2 mg orally 2–3 times a day, 1–3 hours prior to chemotherapy. The drug may be given the night before chemotherapy (1–2 mg). The maximum is 6 mg a day. Both drugs are not recommended to patients below age 18. They are contraindicated in those with hypersensitivity to dronabinol, cannabinoids and sesame oil. They should be used cautiously in patients with a history of alcohol abuse, seizure disorder and psychiatric illness. Adverse effects include tachyarrythmia, abdominal pain, amnesia and ataxia. No need for dose adjustments in patients with either hepatic or renal impairment.

Recommended reading

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