Prokinetic Agents for Lower Gastrointestinal Motility Disorders

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Prokinetic agents are currently being investigated as potential therapies for motility disorders of the lower gastrointestinal tract. Cholinergic agonists such as bethanechol are known to improve postoperative ileus but are limited because of side effects. Dopamine antagonists such as domperidone appear to have maximal prokinetic effect in the proximal gastrointestinal tract and are effective for such conditions as gastroparesis and gastroesophageal reflux, but they appear to have little physiologic effect in the colon or in colonic motility disorders. Naloxone, an opioid antagonist, appears to hold promise in patients with irritable bowel syndrome, small intestinal pseudo-obstruction, and constipation. Erythromycin exerts its prokinetic effect by acting as a motilin agonist; it has been used in the treatment of diabetic gastroparesis and appears to improve symptoms of colonic pseudo-obstruction and postoperative ileus. Metoclopramide, a combined cholinergic agonist and dopamine antagonist, is currently used exclusively for proximal motility dysfunction. Cisapride appears to hold the most promise for patients with colonic motility disorders. In patients with postoperative ileus, cisapride is associated with an increased return of bowel function compared with placebo. In patients with chronic constipation, cisapride increases stool frequency and decreases laxative abuse in both adults and children. Hopefully, as an understanding of gastrointestinal motility increases, effective prokinetic agents will be developed that will improve symptoms of patients with large bowel motility disorders and may also help to predict those patients who benefit from surgical management for constipation. [Key words: Prokinetic agents; Constipation; Ileus; Pseudo-obstruction]

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Pharmaceutical agents that promote transit throughout the gastrointestinal tract are referred to as prokinetic agents (Table 1). These agents act through various mechanisms to enhance motility of the gut. Prokinetic agents are currently being employed for a variety of disorders including those that affect the proximal gastrointestinal tract, such as gastroesophageal reflux, diabetic gastroparesis, irritable bowel syndrome, and bile reflux gastritis.[1–4] The mechanisms of action of these agents are incompletely understood. However, it is speculated that these agents enhance intestinal function by either promoting the effect of a motility agonist or antagonizing the effect of an inhibitory transmitter.[5,6]

The spectrum of clinical disorders of the colon and rectum that prokinetic agents may be useful in treating has been incompletely examined. Large bowel motility disorders that may respond to prokinetic agents include postoperative ileus, nonmechanical pseudo-obstruction of the colon, and chronic lower gastrointestinal motility disorders associated with systemic disease and constipation (*i.e.*, diabetes mellitus, systemic sclerosis, *etc.*) (Table 2). The following text provides a current review of the most commonly used prokinetic agents in gastrointestinal disease and discusses their use in motility disorders of both the small and large intestine.

REGULATION OF COLONIC MOTILITY

Colonic motility is modulated by the extrinsic and intrinsic nervous system and by the endocrine system. The extrinsic nervous system is composed of the autonomic nervous system and is subdivided into the sympathetic and parasympathetic divisions. The sympathetic supply to the right colon originates from the lower six thoracic segments, while the sympathetic supply to the left colon and upper rectum originates from the first three lumbar segments.[7] Sympathetic stimulation is mediated by adrenergic fibers and inhibits muscular contraction of the gut wall. Parasympathetic innervation of the

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Table 1.
Prokinetic Agents

Agent	Mechanism of Action
Cholinergic agonists	
Bethanecol	Acetylcholine modulation
Benzamides	
Metoclopramide	Dopamine antagonist/cholinergic agonist
Cisapride	Cholinergic agonist/dopamine antagonist
Renzapride	Cholinergic agonist/serotonin modulation
Zacopride	Cholinergic agonist/serotonin modulation
Dopamine antagonists	
Domperidone	Dopamine antagonist
Macrolide antibiotics	
Erythromycin	Motilin agonist
Opiate antagonists	
Naloxone	Mu-receptor antagonist
Nalmetere	
Somastostatin analogs	
Octreotide	Inhibition of gut hormone release

Table 2.
Motility Disorders of the Large Intestine in Which Prokinetic Agents May Have a Role

Irritable bowel syndrome
Acute colonic pseudo-obstruction (Ogilvie's syndrome)
Chronic intestinal pseudo-obstruction
Idiopathic constipation
Chronic constipation associated with:
Dementia
Disorders of basal ganglia
Multiple sclerosis
Autonomic neuropathy (*i.e.*, diabetes mellitus)
Spinal cord injury
Hirschsprung's disease
Chagas' disease
Myopathic pseudo-obstruction
Idiopathic megarectum/megacolon

right colon is carried by the vagus nerve, and parasympathetic innervation of the left colon and rectum arises from the sacral parasympathetic centers S2 to S5.[8,9] Parasympathetic stimulation, mediated by acetylcholine, results in an increase in contractility and motility of the colon.[10] The interaction of the opposing nervous systems is complex, and cholinergic and adrenergic fibers may stimulate and inhibit a response mediating opposing effects simultaneously on different segments of the colon.

The intrinsic nervous system of the colon consists of an organized network of sensory and motor neurons connected by highly specialized interneurons. The cell bodies of these neurons are found in the submucosal ganglia (Meissner's plexus) and the myenteric ganglia (Auerbach's plexus).[11] The neurons of the submucosal ganglia act as sensory neurons that monitor changes in intraluminal contents as well as wall tension within the colon. The sensory neuron then excites a motor neuron, resulting in release of a neurotransmitter that participates in generating specific motility patterns.[12,13] These neurotransmitters have been traditionally classified as cholinergic agonists that contain acetylcholine but may also contain dopamine, serotonin, vasoactive intestinal polypeptide (VIP), or substance P.[11,14]

Circulating humoral agents may also participate in regulating the motility of the colon. Gastrointestinal hormones released after meals or from rectal stimulation may regulate colonic motility.[15] Cholecystokinin, gastrin, and motilin have been demonstrated to stimulate colonic contractions.[16–18] Peptide tyrosine tyrosine (PYY) and secretin inhibit colonic motility.[19,20] Steroid hormones *in vitro* also participate in the regulation of colonic transit.[21] The release of these hormones may depend upon the specific type of fecal content within the colon.

Prokinetic agents act by enhancing the release of an excitatory neurotransmitter, inhibiting the inhibitory effect of a biologically active substance, or stimulating the release of a gastrointestinal hormone. The mechanism of action and the clinical utility of different classes of prokinetic substances, with reference to their specific effect on the extrinsic and intrinsic nervous system and gastrointestinal hormones, are unclear.

CLASSIFICATION OF PROKINETIC AGENTS

Cholinergic Agonists

Acetylcholine acts upon muscarinic cholinergic receptors to increase tone, amplitude of contractions, and peristaltic activity of the bowel.[22] Two different types of muscarinic receptors (M1 and M2) have been identified. M1 receptors are located in ganglia, while M2 receptors are found on effector cells such as smooth muscle. Bethanechol is an M2 cholinergic agonist interacting with gastrointestinal M2 receptors of smooth muscle cells throughout the gastrointestinal tract.[23]

The effect of cholinergic stimulation has been investigated in various species. Parasympathetic stimulation stimulates intestinal contractile activity in the cat. Destruction of the parasympathetic nerves decreases phasic and tonic contractile activity throughout the colon.[24] Colonic motility has been examined in both the proximal and distal colon of rabbits.[25] Atropine inhibited spike and contractile activity on both sides of the colon. The alpha-adrenergic agonist phenylephrine and antagonist phentolamine had no effect on colonic motility. However, isoproterenol inhibited the colonic smooth muscle spike and contractile activity that was blocked by propranolol. The cholinergic agent trimethaphan increased the spike and contractile activity that was inhibited by atropine. This study suggests that tonic cholinergic stimulation exists in the proximal and distal colon and that circulating catecholamines have minimal effect on colonic motility.[25] The effect of bethanechol and atropine on colonic motility is currently being investigated in our laboratory in an isolated colon preparation.

Cholinergic agonists have been proposed as prokinetic agents in an effort to promote cholinergic tone in humans. Bethanechol is known to increase both lower esophageal sphincter pressure and the amplitude of esophageal contractions.[26] Clinical trials involving bethanechol in the treatment of gastroesophageal reflux disease have demonstrated both symptomatic and endoscopic improvement in esophagitis.[27,28] Bethanechol has little effect on improving the symptoms of delayed gastric emptying or accelerating small bowel transit.[29] In humans, however, bethanechol has been reported to improve postoperative ileus but is limited by its other cholinergic side effects.[30] Carbachol, a cholinergic agonist, improves gut transit in a rat model of postoperative ileus.[31] No study to date has demonstrated that the administration of exogenous cholinergic agents has a role in the treatment of intestinal pseudo-obstruction or chronic constipation.

Benzamides

Substituted benzamides are derivatives of *p*-aminobenzoic acid. These agents resemble procainamide in structure but lack both its antiarrhythmic and local anesthetic properties. The two prototypic benzamides most commonly used today are metoclopramide (Reglan®; A. H. Robins Co., Richmond, VA) and cisapride. Zacopride and renzapride are newer substituted benzamide prokinetic agents currently undergoing clinical trials.

Metoclopramide. Metoclopramide was introduced in Europe over 25 years ago for the treatment of nausea and vomiting during pregnancy.[32] Besides its potent antiemetic activity, metoclopramide also has a rapid stimulatory effect on the motility of the gastrointestinal tract. The effect of metoclopramide on gastrointestinal smooth muscle remains poorly understood. It is felt that metoclopramide has both a central and peripheral antidopamine effect as well as a direct and indirect stimulatory effect on cholinergic receptors.[33] Metoclopramide inhibits the inhibitory effect of the neurotransmitter dopamine.[34] Dopaminergic receptors have been identified throughout the gastrointestinal tract, particularly in the stomach, pancreas, renal and mesenteric vasculature, and distal gut. It has been suggested that the prokinetic effect of metoclopramide may be due to the blockade of dopamine receptors which inhibit the release of acetylcholine. This inhibition of dopamine and augmentation of acetylcholine release are thought to sensitize the muscarinic receptors of the gastrointestinal smooth muscle, allowing for coordinated intestinal motor function.[35,36]

Numerous studies have established that metoclopramide rapidly influences the motility of the gastrointestinal tract. Metoclopramide increases lower esophageal sphincter pressure and increases the amplitude of esophageal muscle contractions.[37] Metoclopramide also increases the amplitude and frequency of gastric contractions, resulting in accelerated gastric emptying.[38] The effects of metoclopramide on the small intestine are similar to those on the esophagus and stomach in that it stimulates contraction of the small bowel and decreases transit time.[39] Metoclopramide has been demonstrated to produce a dose-related stimulatory effect on colonic myoelectric activity in patients with diabetes and in healthy controls.[40] On the other hand, *in vitro* metoclopramide induces contraction of circular, but not longitudinal, strips of human colonic smooth muscle.[41]

The antiemetic effect of metoclopramide is most commonly used during pregnancy and in the treatment of nausea and vomiting secondary to antineoplastic drugs. This antiemetic effect is due to depression of the chemoreceptor trigger zone in the brainstem.[4] Metoclopramide is an effective agent in the treatment of gastroesophageal reflux;

it has been shown to be more effective than placebo in several controlled prospective trials.[42,43] In patients with gastroparesis due to autonomic neuropathies such as diabetes, metoclopramide has been shown to be effective in accelerating the rate of gastric emptying and eliminating the symptoms of gastroparesis.[44] Previous uncontrolled studies indicated that metoclopramide is effective in the treatment of postoperative ileus.[39] Subsequent controlled studies demonstrated that, in patients undergoing laparotomy with or without intestinal resection, metoclopramide-treated patients had less nausea and vomiting, but no statistical improvement was noted in either passage of flatus or tolerance of liquids.[45,46]

A dose-dependent stimulatory effect has been demonstrated for metoclopramide on rectosigmoid colonic myoelectric activity; however, the utility of metoclopramide in colonic motility disorders is limited. A single case report on the use of metoclopramide in chronic idiopathic pseudo-obstruction in a double-blinded fashion was published.[47] Over a four-month period, the patient received either metoclopramide or placebo. No appreciable symptomatic improvement was seen with metoclopramide or placebo. It has been speculated that patients with pseudo-obstruction suffer from an intrinsic myopathy and not neuropathy, and thus any direct effect of metoclopramide on muscle function is negated. No studies examining the role of metoclopramide in the treatment of chronic constipation currently exist.

Side effects of metoclopramide have been reported in up to 20 percent of patients but are usually mild, transient, and reversible. These include drowsiness, lassitude, and at times anxiety. Extrapyramidal side effects are rare. Long-term administration may lead to breast enlargement, nipple tenderness, galactorrhea, and menstrual disorders. Metoclopramide should not be given to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants, sympathomimetics, or phenothiazines or to patients with epilepsy or extrapyramidal syndromes.

Cisapride. Cisapride is a prokinetic agent that appears to function as an indirect cholinergic stimulant, acting through increased release of acetylcholine in the intramural plexuses.[48] This release of acetylcholine may also be mediated by serotonin (5-hydroxytryptamine; 5-HT). Cisapride is an antagonist of 5-HT3 and is an agonist of 5-HT4 receptors, and both mechanisms could potentially contribute to its gastrointestinal prokinetic effect.[49] Unlike metoclopramide, cisapride does not have dopamine-blocking activity, and thus the antidopaminergic effects on the central nervous system are not present. Cisapride also increases levels of endorphins, motilin, and pancreatic polypeptide and decreases the concentration of substance P and cholecystokinin.[50]

Cisapride increases lower esophageal sphincter pressure in normal volunteers and in patients with gastrointestinal reflux.[51–54] In the stomach, it accelerates gastric emptying of both liquids and solids.[55] The effects of cisapride on human small bowel motility patterns were studied by Stacher *et al.*[56] A higher number of Phase II contractions (of which a significant number were propagated aborally) were identified after the administration of various doses of cisapride compared with placebo. Similarly, Coremans and colleagues[57] demonstrated that intravenous cisapride increased small bowel motor activity. In the colon, cisapride stimulates colonic smooth muscle and accelerates colonic transit. In the pig, cisapride stimulated colonic smooth muscle, which appeared to be cholinergically mediated,[58] while, in humans, it is not associated with increased acetylcholine release.[59] Numerous studies have demonstrated that cisapride accelerates the transit of fecal material from the terminal ileum to the anus.[60–63] Furthermore, other studies have shown that cisapride increases the frequency of bowel movements in healthy volunteers.[64,65] In one study, cisapride had a more pronounced effect on colonic transit on the right side of the colon than on the left.[60] To investigate the effects of cisapride on anorectal sphincter function, anorectal manometry was performed in 10 healthy male volunteers after five days on a 20-mg dose of cisapride. Cisapride significantly increased stool frequency and reduced anal resting pressure by 16 percent in 7 of the 10 patients, while all other measurements were not altered.[66] Cisapride also increased rectal sensation and the threshold of the rectoanal inhibitory reflex.[67]

The spectrum of motility disorders of the lower gastrointestinal tract for which cisapride may be clinically useful includes the treatment of irritable bowel syndrome, constipation, postoperative ileus, and colonic pseudo-obstruction. In experimental animals, the effect of cisapride on the development of postoperative adhesions has been investi-

gated.[68, 69] The theoretic premise of using cisapride in this scenario is that increasing postoperative bowel motility will reduce intestinal adhesions. In two studies of a rat model of intestinal adhesions, cisapride resulted in a significant reduction in both the number and extent of adhesions compared with rats receiving saline.[68, 69]

The effects of treatment with cisapride in 69 patients with irritable bowel syndrome were evaluated in a randomized, double-blind, placebo-controlled study. After 12 weeks of 5 mg of cisapride *t.i.d.*, the reduction in severity and frequency scores for abdominal pain, abdominal distention, and flatulence was greater for the cisapride-treated group than for controls.[70] In patients with postoperative ileus, cisapride was examined in a prospective controlled trial of 53 patients who underwent a variety of operative procedures.[71] Cisapride, in a dose of 4 mg intravenously, was associated with an earlier return of bowel sounds and flatus than occurred with placebo. In another study of patients following cholecystectomy, intestinal transit was measured by radiopaque markers in patients who received either cisapride for three days or placebo.[72] The first passage of feces occurred significantly earlier in cisapride-treated patients than in controls, but the first passage of flatus after surgery did not differ between the two groups. The results of treatment with cisapride in both pediatric and adult intestinal pseudo-obstruction have been favorable[73–75]; however, there are no reports evaluating the use of cisapride in the treatment of colonic pseudo-obstruction (Ogilvie's syndrome).

One of the most promising uses of cisapride may be in the treatment of constipation. In three prospective, double-blind, controlled studies, cisapride increased the number of bowel movements compared with controls.[76–78] Muller-Lissner[76] demonstrated that cisapride increased stool frequency of both laxative users and nonusers with idiopathic constipation compared with placebo. However, only in laxative users was the increased frequency of defecation maintained during a four-week period when cisapride was discontinued and only placebo was given. Verheyen *et al.*[78] reported on 48 patients with chronic functional constipation and found that patients who were randomized to 5 or 10 mg of cisapride had an increase in stool frequency, consistency, and ease of defecation and less laxative abuse compared with placebo. In 20 institutionalized female patients with severe chronic functional nonspecific constipation associated with laxative abuse, cisapride doubled stool frequency.[79] Cisapride has been shown to stimulate small intestinal motility and relieve constipation in myelopathy due to cervical spinal stenosis.[80] In children, cisapride has been reported to increase stool frequency, decrease laxative use, and decrease the rectoanal inhibitory reflex threshold and the conscious rectal sensitivity threshold.[81] In spinal cord patients, cisapride improved bowel function in three case reports.[82, 83] Cisapride should continue to be evaluated in all patient populations suffering from chronic constipation. It may have a role in predicting which patients benefit from surgery for constipation. The potential side effects are either gastrointestinal (abdominal cramping, borborygmi, and diarrhea) or central nervous system related (headache and occasional somnolence). No cardiovascular, hematologic, or biochemical alterations have been identified.[84] We are prospectively evaluating the effect of cisapride on refractory constipation in a large population of spinal cord-injured patients.

Renzapride and Zacopride. As greater attention is directed at the effect of serotonin receptor agonists and antagonists on intestinal motility, newer benzamide prokinetic agents will be developed. The function of serotonin receptors (5-HT3 and 5-HT4) suggests that they have a role in lower gastrointestinal motility. Renzapride and zacopride are selective 5-HT3 antagonists that have 5-HT4 agonist activity. The effects of these new benzamides may prove to be therapeutic for a number of colonic motility disorders including irritable bowel syndrome, pseudo-obstruction, and chronic constipation.[85]

Dopamine Antagonists

The functional significance of dopamine in gastrointestinal motility is uncertain. There are two distinct types of peripheral dopamine receptors: D1 and D2. D1 receptor activation leads to an increase in intracellular levels of cyclic AMP, whereas D2 receptors decrease the formation of cyclic AMP.[86] The role of D1 and D2 receptors in colonic physiology is speculative. As an experimental compound, dopamine decreases the tone and motility of the esophagus, stomach, and small intestine and stimulates pancreatic secretion.[87]

The effect of dopamine on colonic motility appears to be species dependent. In sheep with

chronic cecal fistulas, intravenous dopamine inhibits cecal motility.[88] This result was unaffected by propranolol but was abolished by domperidone, a dopamine antagonist. Two studies have demonstrated that dopamine generates dose-dependent increases in sigmoid contractile activity.[89,90] This motor response of the large intestine to dopamine was significantly reduced by domperidone but not by alpha and beta antagonism. These two studies indicate that dopamine stimulates sigmoid colon activity in contrast to its known inhibitory effect on the upper gastrointestinal tract. The inhibition of dopamine-induced motility by dopamine antagonists suggests the presence of specific dopaminergic receptors in the colon.

Domperidone is a D2 dopamine receptor antagonist[91], and a blocking action of alpha-1 receptors has also been reported. It is a benzimidazole derivative that is structurally related to the butyrophenone tranquilizers such as haloperidol. It was developed as the result of a search for an antiemetic devoid of central nervous system effects. It is readily absorbed from the gastrointestinal tract, with peak plasma concentrations attained at 10 to 30 minutes after oral or intramuscular administration and at one to two hours after rectal administration. Its action is mainly peripheral because it penetrates the blood-brain barrier poorly.[92,93]

In the proximal gastrointestinal tract, the effectiveness of domperidone in the treatment of gastroesophageal reflux disease is less clear than its benefit in the treatment of gastroparesis. Domperidone increases lower esophageal sphincter pressure in healthy human volunteers but not in patients with active reflux disease.[94,95] In the stomach, domperidone increases the duration of antral and duodenal contractions, increases the gastric emptying of liquids and semisolids, and increases pyloric sphincter diameter.[96–98] Motor activity of the small intestine has been reported to increase with a single dose of domperidone.[99] At this time, no study has demonstrated that domperidone increases colonic motility in healthy patients.

Clinically, domperidone appears to be most beneficial in improving the symptoms associated with gastroparesis and gastric stasis.[100,101] Two recent, controlled, clinical trials demonstrated no difference in improvement of symptoms, change in intestinal transit, or frequency of evacuation in patients with irritable bowel disease.[102,103] In irritable bowel patients, domperidone did not induce any change in basal motility, but it did prevent the increase in motor activity produced by the infusion of dopamine.[102] No studies to date have examined the effect of domperidone on patients with colonic pseudo-obstruction or chronic constipation.

Domperidone has minimal effects on the central nervous system because of its poor penetration of the blood-brain barrier. It increases prolactin levels and is thus associated with symptoms similar to metoclopramide (galactorrhea, gynecomastia, and menstrual irregularities).[104] Other side effects include thirst, dry mouth, skin rash, headaches, and diarrhea. Domperidone may induce a hypertensive crisis in patients taking monoamine oxidase inhibitors.

Macrolide Antibiotics

Motilin is a gastrointestinal peptide hormone initially isolated from porcine duodenum.[105] Motilin immunoreactivity has been demonstrated throughout the gastrointestinal tract, from the esophagus to the colon.[106] Motilin release is thought to be mediated by vagal tone and the passage of nutrients through the duodenum.[107] Functionally, motilin, in physiologic doses, stimulates interdigestive but not postprandial activity in the stomach and the entire small intestine.[108] Motilin also stimulates gallbladder contractions.[109]

Erythromycin is a potent stimulator of gastrointestinal motor activity.[110] This prokinetic effect was initially believed to be due to its side effects of nausea, vomiting, and diarrhea. In a search for the mechanism of these side effects, two independent studies reported that intravenous infusion of erythromycin resulted in contractions originating in the stomach and propagating to the ileum.[111,112] The erythromycin-induced contractions were similar to that induced by the infusion of motilin. There was also a significant rise in plasma motilin during erythromycin infusion. Although the mechanism of this phenomenon is unclear, it is felt that erythromycin and other macrolide antibiotics inhibit the binding of motilin to its receptors on gastrointestinal smooth muscle membranes and therefore may act as motilin agonists.[113,114]

Erythromycin causes a dose-dependent contraction of isolated rabbit duodenal muscle strips.[115] Guinea pig smooth muscle strips, on the other hand, do not contract in the presence of erythromycin.[116] In the small intestine, erythromycin stim-

ulated rabbit ileal motility by activation of dihydropyridine-sensitive calcium channels.[117] In dogs, erythromycin induced contractions in the stomach and duodenum that migrated to the terminal ileum and that were inhibited by pentagastrin.[118] Furthermore, erythromycin caused contraction of isolated rabbit colon myocytes by displacing I^{125} bound motilin from colon muscle motilin receptors.[119] In humans, the administration of erythromycin accelerates colonic transit and increases stool frequency in healthy volunteers.[120]

Based on the fact that erythromycin and related compounds act as motilin agonists, it is believed that they may function as prokinetic agents in certain clinical situations where smooth muscle function is impaired.[121] The effect of erythromycin on gastric emptying was reported in 10 patients with insulin diabetes and gastroparesis.[122] After the intravenous administration of 200 mg of erythromycin, the prolonged gastric emptying for both liquids and solids was shortened to normal.

In the colon, two reports have demonstrated the beneficial effects of both oral and intravenous erythromycin on gastrointestinal motility in colonic pseudo-obstruction.[123, 124] Plasma motilin levels were studied in seven patients with severe, long-standing constipation. When compared with 10 apparently healthy persons with normal bowel function, constipated patients had reduced basal motilin levels and a reduced motilin release after a test meal.[125] A defective motilin release may play a role in the pathogenesis of idiopathic constipation. Since erythromycin is a motilin agonist, it seems a reasonable supposition that chronically constipated patients may benefit from a trial of erythromycin. We are currently evaluating the effect of erythromycin on improvement of bowel function in spinal cord-injured patients.

The most frequent side effects of erythromycin preparations are gastrointestinally related and include abdominal cramping, nausea, vomiting, and diarrhea. Prolonged therapy may cause overgrowth of nonsusceptible bacteria or fungi. Allergic reactions such as urticaria, skin eruptions, and anaphylaxis may occur. Erythromycin may be associated with increased serum theophylline levels and potential theophylline toxicity.

Opiate Antagonists

Opiates have long been known for their effects on gastrointestinal motility. Morphine is known to relax the smooth muscle of the esophagus and decrease gastric emptying and results in spasm of and increased pressure in the biliary tree.[126] In the lower gastrointestinal tract, opiates have powerful effects on the small and large intestine.[127] In the small bowel, there is an initial abrupt increase in contractile activity followed by distention. The overall effect is delayed intestinal transit and increased intestinal absorption.[128]

The effect of morphine and related drugs on the colon is an increase in luminal pressure, segmental contractions, and constipation. The role of opiate receptors in the regulation of colonic transit has been investigated.[129] In a crossover double-blind study of human volunteers, morphine (0.1 mg/kg given subcutaneously every six hours) delayed colonic transit in the proximal colon and decreased the number of bowel movements per 48 hours. The opiate naloxone (0.8 mg given subcutaneously every six hours) accelerated transit in the transverse colon and rectosigmoid but had no effect on the number of bowel movements. The acceleration of transit by naloxone suggests that endogenous opiate peptides may play an inhibitory role in the regulation of human colonic transit.

The actions of opioids either are the result of neural interaction through the inhibition of acetylcholine or VIP or are direct effects on smooth muscle.[130] Furthermore, opiates exert their effect on different opiate receptors (mu, kappa, and delta). The effect of morphine is thought to involve the mu receptor predominantly.[131] The effect of naloxone as a potential prokinetic agent is based on its ability as a potent mu-receptor antagonist.[130, 131] Currently, naloxone is being used to treat pseudo-obstruction, constipation, and irritable bowel syndrome.

In two patients with small intestinal pseudo-obstruction after subtotal colectomy and ileostomy, naloxone decreased small intestinal transit time and decreased ileostomy output.[132] Naloxone has been used in patients with colonic pseudo-obstruction. Kling[133] reported a case of an otherwise healthy man who had a rapid and dramatic resolution of loperamide-induced colonic pseudo-obstruction. The effects of opioid antagonists on constipation have been mixed. Kreek *et al.*[134, 135] have reported that large doses of naloxone are an effective treatment of idiopathic constipation and suggested that constipation may be due to excessive opioid activity. Fotherby and Hunter,[136] on the

other hand, reported that neither naloxone nor an oral preparation, nalmetere, improved the symptoms of constipation or decreased whole gut transit time in nine constipated patients. Oral naloxone has been shown to increase stool weight and frequency in patients with constipation and to alter colonic motility in patients with irritable bowel,[137] but it is expensive and still experimental. The observation that naloxone reverses constipation suggests that an excess release of opioid peptides inhibits motility. These drugs appear to be safe in that they do not cross the blood-brain barrier.

Octreotide

Somatostatin is widely distributed within the nervous system of the gastrointestinal tract. It has diverse physiologic actions on various gastrointestinal functions, including endocrine and exocrine secretion, motility, and visceral blood flow.[138] The long-acting somatostatin analog octreotide acetate has been shown to increase both enteric action potentials and the frequency of migrating myoelectric complexes in healthy dogs and in humans.[139, 140] Octreotide increases lower esophageal sphincter tone and increases esophageal body contraction amplitude and velocity.[141] It has also been effective in patients with dumping syndrome.[142] In patients with scleroderma, octreotide stimulated intestinal motility and inhibited plasma motilin levels, suggesting that the intestinal activity evoked by octreotide is independent of motilin.[143] Finally, in dogs with ileus, octreotide enhanced transit in both the small bowel and colon.[144] This was felt to be due to the hypothesis that octreotide blocked the release of neurotransmitters in the gut wall that are responsible for inhibiting motility (VIP and substance P) in patients with postoperative ileus. These results were similar to the stimulatory effects on rectosigmoid motility seen with octreotide, resulting in enhancement of colonic transit in humans.[145] Future studies on octreotide in large bowel motility disorders are anticipated.

CONCLUSION

Gastrointestinal motility is a complicated and, as yet, incompletely understood phenomenon affected by a wide variety of nervous and humoral factors. As such, we remain novices in our ability to develop prokinetic agents by which to effectively treat such problems as constipation, ileus, irritable bowel syndrome, *etc.* The success of prokinetic agents in managing some disorders of the upper gastrointestinal tract is encouraging, but there is much left to learn. Only by continued laboratory and clinical investigation will improved understanding of colonic physiology result in the development of agents that act selectively on the large bowel and anorectum to promote motility of the distal gut. At this time, second-generation and third-generation benzamides, motilin agonists, and opioid antagonists hold the most promise for effective medical therapy of motility disorders of the lower gastrointestinal tract.

REFERENCES

1. Bright-Asare P, El Bassoussi M. Cimetidine, metoclopramide or placebo in the treatment of symptomatic gastroesophageal reflux. J Clin Gastroenterol 1980;25:750–5.
2. Muller-Lissner SA, Fraels C, Hartl A. Cisapride offsets dopamine-induced slowing of fasting gastric emptying. Dig Dis Sci 1986;31:807–10.
3. Bailey LD, Stewart WR, McCallum RW. New directions in the irritable bowel syndrome. Gastroenterol Clin North Am 1991;20:335–49.
4. McCallum RW. Review of the current status of prokinetic agents in gastroenterology. Am J Gastroenterol 1985;80:1008–16.
5. Reynolds JC. Prokinetic agents: a key in the future of gastroenterology. Gastroenterol Clin North Am 1989;18:437–57.
6. Reynolds JC, Putnam PE. Prokinetic agents. Gastroenterol Clin North Am 1992;21:567–96.
7. Gray H. Anatomy of the human body. Philadelphia: Lea and Febiger, 1973:1004–36.
8. Goligher J. Surgery of the anus, rectum and colon. London: Bailliere Tindall, 1984:1–47.
9. Telford ED, Stopford JS. The autonomic nerve supply of the distal colon: an anatomical and clinical study. BMJ 1934;1:572–4.
10. Labate JS. The anatomy of the superior hypogastric plexus-"pre-sacral nerve." Surg Gynecol Obstet 1938;67:199–211.
11. Cooke HJ. Neurobiology of the intestinal mucosa. Gastroenterology 1986;90:1057–81.
12. Christensen J. Motility of the colon. In: Johnson LR, ed. Physiology of the gastrointestinal tract. New York: Raven Press, 1981:445–71.
13. Longo WE, Ballantyne GH, Modlin IM. The colon, anorectum and spinal cord patient: a review of the functional alterations of the denervated hindgut. Dis Colon Rectum 1989;32:261–7.

14. Grider JR, Malchlouf GM. Colonic peristaltic reflex: identification of vasoactive intestinal peptide as mediator of descending relaxation. Am J Physiol 1986;251(Gastrointest Liver Physiol 14):G40–5.
15. Snape WJ Jr, Wright SH, Cohen S, Battle WM. The gastrocolonic response: evidence for a neural mechanism—neural versus hormonal mediation. Gastroenterology 1979;77:1235–40.
16. Weisbrodt NW. Gastrointestinal motility. In: Guyton AC, Jacobson ED, Shanbour LL, eds. Gastrointestinal physiology. Baltimore: University Park Press, 1974.
17. Rennie JA, Christofides ND, Bloom SR, Johnson AG. Stimulation of human colonic activity by motilin. Gut 1979;20:916–26.
18. Zara GP, Thompson HH, Pilot MA, Ritchie HD. Effects of erythromycin on gastrointestinal tract motility. J Antimicrob Chemother 1985;16(Suppl A): 175–9.
19. Lundberg JM, Tatemoto K. Localization of peptide YY (PYY) in gastrointestinal endocrine cells and effects on intestinal blood flow and motility. Proc Natl Acad Sci USA 1982;79:4471–5.
20. Kinoso VP, Meshkinpour H, Lorber SH, Gutirrez JG, Chey WY. Motor responses of the sigmoid colon and rectum to exogenous cholecystokinin and secretin. Gastroenterology 1973;65:438–44.
21. Ryan JP, Bhojwani A. Colon transit in rats: effect of ovariectomy, sex steroid hormones and pregnancy. Am J Physiol 1986;251(Gastrointest Liver Physiol 14):G36–50.
22. Burks TF. Actions of drugs on gastrointestinal motility. In: Johnson LR, ed. Physiology of the gastrointestinal tract. Vol. 1. New York: Raven Press, 1987:723–43.
23. Hammer R, Giachetti A. Muscarinic receptors subtypes: M1 and M2. Biochemical and functional characterization. Life Sci 1982;31:2991–8.
24. Gillis RA, Dias Souza J, Hicks KA, *et al.* Inhibitory control of proximal colonic motility by the sympathetic nervous system. Am J Physiol 1987; 253(Gastrointest Liver Physiol 16):G531–9.
25. Snape WJ, Shiff S. Neurohumoral control of colonic motility in the rabbit. Am J Physiol 1983; 245(Gastrointest Liver Physiol 8):G582–8.
26. Cohen S, Green F. Force velocity characteristics of esophageal muscle: effect of acetylcholine and norepinephrine. Am J Physiol 1974;226:1250–5.
27. Miller WN, Ganeshappa KP, Dodds WJ, *et al.* Effects of bethanechol on gastroesophageal reflux. Am J Dig Dis 1977;22:230–4.
28. Thanik DI, Chey WY, Shah AN, *et al.* Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. Ann Intern Med 1980;93: 805–8.
29. McCallum RW, Fink SM, Lerner E, *et al.* Effects of metoclopramide and bethanechol on delayed gastric emptying present in gastroesophageal reflux patients. Gastroenterology 1983;84:1573.
30. Furness JB, Costa M. A dynamic ileus, its pathogenesis and treatment. Med Biol 1974;52:82–9.
31. Ruwart MJ, Klepper MS, Rush BD. Carbachol stimulation of gastrointestinal transit in the postoperative ileus rat. J Surg Res 1979;26:18–26.
32. Besancou JL, Laville C, Thominet M. Le metoclopramide et ses homoloques: introduction a leur etude biologique. C R Acad Sci 1964;258:4384–6.
33. Jacoby HI, Brodie DA. Gastrointestinal actions of metoclopramide: an experimental study. Gastroenterology 1967;52:676.
34. Jenner P, Marsden CD. The substituted benzamides—a novel class of dopamine antagonists. Life Sci 1979;25:479–85.
35. Albibi R, McCallum RW. Metoclopramide: pharmacology and clinical application. Ann Intern Med 1983;98:86–95.
36. Beani L, Bianchi C, Cremer C. Effects of metoclopramide on isolated guinea pig colon. 1. Peripheral sensitization to acetylcholine. Eur J Pharmacol 1970;12:220–31.
37. Wallin L, Boesby S, Madsen T. Effect of metoclopramide on oesophageal peristalsis and gastroesophageal sphincter pressure. Scand J Gastroenterol 1979;14:923–7.
38. Davidson ED, Hersh T, Ilaun C, Brooks WS. Use of metoclopramide in patients with delayed gastric emptying following gastric surgery. Am Surg 1977;43:40–4.
39. James WB, Hume R. Action of metoclopramide on gastric emptying and small bowel transit time. Gut 1968;9:203–5.
40. Battle WM, Snape WJ, Alavi A, *et al.* Colonic dysfunction in diabetes mellitus. Gastroenterology 1980;79:1217–21.
41. Eisner M. Gastrointestinal effects of metoclopramide in man: in vitro experiments with human smooth muscle preparations. BMJ 1968;4:679–80.
42. Fuchs B. Prevention of meal-induced heartburn and regurgitation with metoclopramide in patients with gastroesophageal reflux. Clin Ther 1982;5:179–85.
43. McCallum RW, Fink SM, Winnan GR, *et al.* Metoclopramide in gastroesophageal reflux disease: rationale for its use and results of a double blind trial. Am J Gastroenterol 1984;79:165–72.
44. Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. Gastroenterology 1984;86:1592–610.
45. Pinder RM, Brogden RN, Sawyer PR. Metoclopramide: a review of its pharmacological properties and clinical use. Drugs 1976;12:81–131.

46. Davidson ED, Hersh T, Ilaun C, *et al.* Use of metoclopramide in patients with delayed gastric emptying following gastric surgery. Am Surg 1977; 43:40–4.
47. Lipton AB, Knauer CM. Pseudo-obstruction of the bowel: therapeutic trial of metoclopramide. Dig Dis 1977;22:263–5.
48. Van Neuten JM, Reyntjens A, Schurkes JA. Gastrointestinal motility stimulating properties of the non-antidopaminergic and non-cholinergic compound R 41 619. Gastroenterol Clin Biol 1983;7:706.
49. Boeckxstaens GE, Pelckmans PA, Rampart M, *et al.* Pharmacological characterization of 5-hydroxytryptamine receptors in the canine terminal ileum and ileocolonic junction. J Pharmacol Exp Ther 1990;254:652–7.
50. Koop H, Monnikes H, Koop I, Dionysius J, Schwarz C, Arnold R. Effect of the prokinetic drug cisapride on gastrointestinal hormone release. Scand J Gastroenterol 1986;21:907–13.
51. Corazziari E, Scopinaro F, Bontempo G, *et al.* Effects of R-51619 on distal esophageal motor activity and gastric emptying. Ital J Gastroenterol 1983; 15:185–6.
52. Ceccatelli P, Janssens J, Van trappen G, *et al.* Cisapride restores the decreased lower oesophageal sphincter pressure in reflux patients. Gut 1988; 29:631–5.
53. Janssens J, Ceccatelli P, Van trappen G. Cisapride restores the decreased lower esophageal sphincter pressure in reflux patients. Digestion 1984;34:139.
54. Smout AJ, Bogaa JW, Grade AC, Thije OJ, Akkermans LM, Wittebol P. Effects of cisapride, a new gastrointestinal prokinetic substance on interdigestive and postprandial motor activity of the distal esophagus in man. Gut 1985;26:246–51.
55. Muller-Lissner SA, Fraas C, Hartl A. Cisapride offsets dopamine-induced slowing of fasting gastric emptying. Dig Dis Sci 1986;31:807–10.
56. Stacher G, Sternringer H, Schneider C, *et al.* Effect of cisapride on jejunal motor activity in fasting healthy humans. Gastroenterology 1986;90:1210.
57. Coremans G, Chaussade S, Janssen J, *et al.* Stimulation of propulsive motility patterns by cisapride in the upper gut of man. Dig Dis Sci 1985;30:765.
58. Den Hertog A, Adder JF. The effect of cisapride on smooth muscle cells of guinea pig taenia caeci. Eur J Pharmacol 1986;126:31–5.
59. Burleigh DE, Trout SJ. Evidence against an acetylcholine releasing action of cisapride in the human colon. Br J Clin Pharmacol 1985;20:475–8.
60. Edwards CA, Holden S, Brown C, Read NW. Effect of cisapride on the gastrointestinal transit of a solid meal in normal human subjects. Gut 1987;28:13–6.
61. McCallum RW, Petersen J, Caricle B, *et al.* Scintigraphic evaluation on colon transit in normal subjects: prokinetic effect of cisapride. Clin Res 1986; 34:182A.
62. Krevsky B, Malmud L, Mauer A, Siegel J, Fisher RS. Effects of cisapride on colonic transit in man. Proceedings of the First International Cisapride Investigators' Meeting, p. 156, #43.
63. Lederer E, Ellermann A, Schmidt H, Ernst V, Lux G. Effect of cisapride on sigmoid motility in healthy subjects and in diabetic enteropathy (DE) with constipation. Proceedings of the First International Cisapride Investigators' Meeting, p. 155, #41.
64. Krevsky B, Malud LS, Maurer AH, Somers MB, Siegel JA, Fisher RS. The effect of oral cisapride on colonic transit. Aliment Pharmacol Ther 1987;1: 293–304.
65. Chey Wy, Lee KY, You CH. Effect of cisapride on colonic transit time in dogs and humans. Dig Dis Sci 1984;7:29.
66. Enck P, Arping HG, Engel S, Bielefeldt K, Erckenbrecht JF. Effects of cisapride on anorectal sphincter function. Aliment Pharmacol Ther 1989;3: 539–45.
67. Reboa G, Arnulfo G, Frascia M, DiSomma C, Pitto G, Berti-Riboli E. Colon motility and coloanal reflexes in chronic idiopathic constipation: effects of a novel enterokinetic agent cisapride. Eur J Pharmacol 1984;26:745–8.
68. Sparnon AL, Spitz L. Pharmacological manipulation of postoperative intestinal adhesions. Aust N Z J Surg 1989;59:725–9.
69. Springall RG, Spitz L. The prevention of postoperative adhesions using a gastrointestinal prokinetic agent. J Pediatr Surg 1989;24:530–3.
70. Van Outryve M, Milo R, Toussiant J, Van Eeghem P. Prokinetic treatment of constipation-predominant irritable bowel syndrome: a placebo-controlled study of cisapride. J Clin Gastroenterol 1991;13:49–57.
71. Boghaert A, Haesert G, Mourisse P, Verlinden M. Placebo controlled trial of cisapride in postoperative ileus. Acta Anaesthesiol Belg 1987;38:195–9.
72. Tollesson PO, Cassuto J, Rimback G, Faxen A, Bergman L, Mattson E. Treatment of postoperative ileus with cisapride. Scand J Gastroenterol 1991; 26:477–82.
73. Cohen NP, Booth IW, Parashar K, Corkery JJ. Successful management of idiopathic intestinal pseudo-obstruction with cisapride. J Pediatr Surg 1988;23:229–30.
74. Camilleri M, Brown ML, Malagelada JR. Impaired transit of chyme in chronic intestinal pseudo-obstruction: correction by cisapride. Gastroenterology 1986;91:619–26.
75. Hyman PE, McDiarmid SV, Napolitano J, Abrams

CE, Tomomasa T. Antroduodenal motility in children with chronic intestinal pseudo-obstruction. J Pediatr 1988;112:899–905.
76. Muller-Lissner SA. Treatment of chronic constipation with cisapride and placebo. Gut 1987;28: 1033–8.
77. Hernandez G, Troncoso G, Palencia C, Maldonado S. Double-blind dose response study of cisapride in the treatment of chronic functional constipation. Adv Ther 1988;5:121–7.
78. Verheyen K, Vervaeke M, Demyttenaere P, Van Mierlo FJ. Double-blind comparison of two cisapride dosage regimens with placebo in the treatment of functional constipation. Curr Ther Res 1987;41:978–85.
79. Creytens G, Verlinden M, Reyntjens A. Double blind study of cisapride in the treatment of chronic functional, nonspastic constipation. Proceedings of the First International Cisapride Investigators' Meeting, #47.
80. Hellstrom PM, Aly A, Johansson C. Cisapride stimulates small intestinal motility and relieves constipation in myelopathy due to cervical spinal stenosis: case report. Paraplegia 1990;28:261–4.
81. Staiano A, Cucchiara S, Andreotti MR, Minella R, Manzi G. Effect of cisapride on chronic idiopathic constipation in children. Dig Dis Sci 1991;36: 733–6.
82. deGroot GH, dePagter GF. Effects of cisapride on constipation due to a neurological lesion. Paraplegia 1988;26:159–61.
83. Etienne M, Verlinden M, Brassinne A. Treatment with cisapride of the gastrointestinal and urological sequelae of spinal cord transection: case report. Paraplegia 1988;26:162–4.
84. Reyntjens A, Verlinden M, Schrermans V. Safety profile of cisapride. In: Johnson, Lux, eds. Progress in the treatment of gastrointestinal motility disorders: the role of cisapride. Amsterdam: Excerpta Medica, 1988:30–6.
85. Talley NJ. Review article: 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical applications. Aliment Pharmacol Ther 1992;6:273–89.
86. Bertaccini G, Coruzzi G. Receptors in the gastrointestinal tract. Pharmacol Res Commun 1987;19: 87–118.
87. Willems JL, Bylaert WA, Lefebvre RA, Bogaert MG. Neuronal dopamine receptors on autonomic ganglia and sympathetic nerves and dopamine receptors in the gastrointestinal system. Pharmacol Rev 1985;327:165–216.
88. Zieba D, Wegrzyn T, Cebrat E, Leroch Z. Effect of dopamine on cecum motility in sheep. Pol Arch Weter 1991;31:109–14.
89. Wiley J, Owyang C. Dopaminergic modulation of rectosigmoid motility: action of domperidone. J Pharmacol Exp Ther 1987;242:548–51.
90. Lanfranchi GA, Marzio L, Cortini C, Osset EM. Motor effect of dopamine on human sigmoid colon: evidence for specific receptors. Dig Dis 1978; 23:257–63.
91. Laduron PM, Leysen JE. Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Biochem Pharmacol 1979;28:2161–5.
92. Brogden RN, Carmine AA, Heel RC, *et al.* Domperidone: a review of its pharmacological activity, pharmacokinetics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as an antiemetic. Drugs 1982;24:360–400.
93. Jay GT, Feldman TA. Focus on domperidone: a selective dopamine antagonist for diabetic gastroparesis and idiopathic gastric stasis. Hosp Formul 1991;26:171–83.
94. Bron B, Massih L. Domperidone: a drug with powerful action on the lower esophageal sphincter pressure. Digestion 1980;20:375–8.
95. Schulze-Delrieu K, Summers RW, Fink D. Domperidone in reflux esophagitis and gastric stasis. Lancet 1981;1:159.
96. Platteborse R, Hermans C, Loots W, *et al.* The effect of domperidone on pyloric activity in dog and in man. Postgrad Med J 1979;55(Suppl 1):15–8.
97. Schuurkes JA, Van Nueten JM, Van Daele PG, *et al.* Domperidone improves myogenically transmitted antroduodenal coordination by blocking dopaminergic receptor sites. Scand J Gastroenterol 1984;(Suppl 96):101–10.
98. Albibi R, DuBovic S, Lange RC, *et al.* A dose response study of the effects of domperidone on gastric retention states in man. Am J Gastroenterol 1983;78:679.
99. Baeyens R, Van DeVelde E, DeSchepper A, *et al.* Effects of intravenous and oral domperidone on the motor function of the stomach and small intestine. Postgrad Med J 1979;55(Suppl 1):19–23.
100. Horowitz M, Harding PE, Chatterton BE, *et al.* Acute and chronic effects of domperidone on gastric emptying in diabetes and autonomic neuropathy. Dig Dis Sci 1985;30:1–9.
101. McCallum RW, Ricci D, DuBovic S, *et al.* Effect of domperidone on gastric emptying and symptoms in patients with idiopathic gastric stasis (abstr). Gastroenterology 1984;5.
102. Lanfranchi GA, Bazzocchi G, Fois F, Brignola C, Campieri M, Menni B. Effect of domperidone on colonic motor activity in patients with the irritable bowel syndrome. Eur J Clin Pharmacol 1985;29: 307–10.

103. Cann PA, Read NW, Holdsworth CD. Oral domperidone: double blind comparison with placebo in irritable bowel syndrome. Gut 1983;12:1135–40.
104. Sowers JR, Sharp B, McCallum RW. Effect of domperidone, an extracerebral inhibitor of dopamine receptors, on thyrotropin, prolactin, renin, aldosterone and 18-hydroxycortisone secretion in man. J Clin Endocrinol Metab 1982;54:869–71.
105. Brown JC, Cook MA, Dryburgh JR. Motilin, a gastric motor activity-stimulating polypeptide: the complete amino acid sequence. Can J Biochem 1972; 51:533–7.
106. Polak JM, Pearse AG, Heath CM. Complete identification of endocrine cells in the gastrointestinal tract using semithin sections to identify motilin cells in human and animal intestine. Gut 1975; 16:225.
107. Mitzness P, Bloom SR, Domschke W, Domschke S, Wunsch E, Demling L. Release of motilin after duodenal acidification. Lancet 1976;1:888–9.
108. Itoh Z, Aizawa I, Talceuchi S, Couch EF. Hunger contractions and motilin. In: Van trappen G, ed. Proceedings of the 5th International Symposium on Gastrointestinal Motility. Heventals, Belgium: Typoff-Press, 1976:48–55.
109. Itoh Z, Takahashi I, Nakaya M. Interdigestive contractions in the gallbladder controlled by motilin. Regul Pept 1980;(Suppl 1):555.
110. Zara GP, Thompson HH, Pilot MA, Ritchie HD. Effects of erythromycin on gastrointestinal tract motility. J Antimicrob Chem 1985;16(Suppl A):175–9.
111. Pilot MA, Ritchie HD, Thompson H, Zara GP. Alterations in gastrointestinal motility associated with erythromycin (abstr). Br J Pharmacol 1984;81:168P.
112. Itoh Z, Nakaya M, Suzuki T, Arai H, Wakabayashi K. Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. Am J Physiol 1984;247(Gastrointest Liver Physiol 10): G688–94.
113. Kondo KT, Torii S, Omura S, Itoh Z. Erythromycin and its derivatives with motilin-like biological activities inhibit the specific binding of ^{125}I-motilin to duodenal muscle. Biochem Biophys Res Commun 1988;150:877–82.
114. Peeters T, Matthijis G, Depoortere I, Cachet T, Hoogmartens J, Van trappen G. Erythromycin is a motilin receptor agonist. Am J Physiol 1989; 257(Gastrointest Liver Physiol 20):G470–4.
115. Depoortere I, Peeters TL, Matthijs G, Van trappen G. Macrolide antibiotics are motilin receptor agonists. Hepatogastroenterology 1988;35:198.
116. Minocha A, Galligan JJ. Erythromycin inhibits contractions of nerve muscle preparations of guinea pig small intestine. J Pharmacol Exp Ther 1991; 257:1248–52.
117. Armstrong DN, Ballantyne GH, Modlin IM. Erythromycin stimulates ileal motility by activation of dihydropyridine-sensitive calcium channels. J Surg Res 1992;52:140–6.
118. Inatomi N, Satoh H, Maki Y, Hashimoto N, Itoh Z, Omura S. An erythromycin derivative, EM-523, induces motilin like gastrointestinal motility in dogs. J Pharmacol Exp Ther 1989;251:707–12.
119. Hasler WL, Heldsinger A, Owyang C. Erythromycin contracts rabbit colon myocytes via occupation of motilin receptors. Am J Physiol 1992;262(Gastrointest Liver Physiol 25):G50–5.
120. Hasler W, Heldsinger A, Soudah H, Onyang C. Erythromycin promotes colonic transit in humans: mediation via motilin receptors. Gastroenterology 1990;98:A358.
121. Tomomasa T, Kuroume T, Arai H, Wakabayashi K, Itoh Z. Erythromycin induces migrating motor complex in human gastrointestinal tract. Dig Dis Sci 1986;31:157–61.
122. Janssens J, Peeters TL, Van trappen G, *et al.* Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. N Engl J Med 1990;322:1028–31.
123. Armstrong DN, Ballantyne GH, Modlin IM. Erythromycin for reflex ileus in Ogilvie's syndrome. Lancet 1991;337:1991.
124. Miller SM, O'Dorsio TM, Thomas FB, Mekhjian HS. Erythromycin exerts a prokinetic effect in patients with chronic idiopathic intestinal pseudo-obstruction. Gastroenterology 1990;98:A375.
125. Sjolund K, Ekman R, Akre F, Linder P. Motilin in chronic idiopathic constipation. Scand J Gastroenterol 1986;21:914–8.
126. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics. New York: MacMillan, 1985:491–531.
127. Kreuger H. The action of morphine on the digestive tract. Physiol Rev 1937;17:619–45.
128. Konturek SJ. Opiates and the gastrointestinal tract. Am J Gastroenterol 1980;74:285–91.
129. Kaufman PN, Krevsky B, Malmud LS, *et al.* Role of opiate receptors in the regulation of colonic transit. Gastroenterology 1988;94:1351–6.
130. Ruoff HJ, Fladung B, Demol P, Weihrauch TR. Gastrointestinal receptors and drugs in motility disorders. Digestion 1991;48:1–17.
131. Burks TF. Actions of drugs on gastrointestinal motility. In: Johnson LR, ed. Physiology of the gastrointestinal tract. Vol. 1. New York: Raven Press, 1987:723–43.
132. Schang JC, Devroede G, Perrault R. Naloxone therapy in small intestinal pseudo-obstruction: preliminary results about two cases. Am J Gastroenterol

1984;79:828.
133. Kling N. Naloxone in opiate-induced colonic pseudo-obstruction. S Afr Med J 1991;79:53.
134. Kreek MJ, Schaefer RA, Hahn EF, Fishman J. Naloxone, a specific opioid antagonist, reverses chronic idiopathic constipation. Lancet 1983;1: 261–2.
135. Kreek MJ, Paris P, Bartol MA, Mueller D. Effects of short term administration of the specific opioid antagonist naloxone on fecal evacuation in geriatric patients. Gastroenterology 1984;86:1144A.
136. Fotherby KJ, Hunter JO. Idiopathic slow-transit constipation: whole gut transit times, measured by a new simplified method, are not shortened by opioid antagonists. Aliment Pharmacol Ther 1987; 1:331–8.
137. Kreek MJ, Marsh F, Kutscher J, Schmugler J, Connor B, Schaefer RA. Effects of short term administration of naloxone on fecal evacuation in patients with idiopathic chronic constipation and irritable bowel syndrome. Gastroenterology 1985;88:1457A.
138. Katz MD, Erstad BL. Octreotide, a new somatostatin analogue. Clin Pharm 1989;8:255–73.
139. Lux G, Femppel J, Lederer P, Rosch W, Domschke W. Somatostatin induces interdigestive intestinal motor and secretory complex-like activity in man. Gastroenterology 1980;78:A1212.
140. Peeters TL, Janssens J, Van Trappen FT. Somatostatin and the interdigestive migrating motor complex in man. Regul Pept 1983;5:209–17.
141. Hartsock M, Little AG. Somatostatin stimulation of the normal esophagus. Am J Surg 1992;163:159–62.
142. Richards WO, Geer R, O'Dorisio TM, *et al.* Octreotide acetate induces fasting small bowel motility in patients with dumping syndrome. J Surg Res 1990;49:483–7.
143. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med 1991;325:1508–9.
144. Cullen JJ, Eagon JC, Dozois EJ, Kelly KA. Treatment of acute postoperative ileus with octreotide. Am J Surg 1993;165:113–9.
145. Soudah HC, Hasler WL, Owyang C. Somatostatin analog stimulates rectosigmoid motility and promotes colonic transit in humans via a cholinergic pathway. Gastroenterology 1991;180:A497.