The Role of Loperamide in Gastrointestinal Disorders

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Loperamide is an effective therapy for a variety of diarrheal syndromes, including acute, nonspecific (infectious) diarrhea; traveler's diarrhea; and chemotherapy-related and protease inhibitor–associated diarrhea. Loperamide is effective for the "gut-directed" symptom of diarrhea in patients with painless diarrhea or diarrhea-predominant irritable bowel syndrome. Loperamide and diphenoxylate are commonly used to treat diarrhea in numerous settings of inflammatory bowel disease. Loperamide has also been observed to increase anal sphincter tone, which may lead to improvement of fecal continence in patients with and without diarrhea. Loperamide is generally well tolerated at recommended nonprescription doses, with the most common side effects related to the impact on bowel motility (abdominal pain, distention, bloating, nausea, vomiting, and constipation).

[Rev Gastroenterol Disord. *2008;8(1):15-20*]

Key words: Loperamide • Diarrhea • Traveler's diarrhea • Chemotherapy • Irritable bowel syndrome • Inflammatory bowel disease • Microscopic colitis • Incontinence, fecal

Loperamide is a phenylpiperidine derivative synthesized in 1969 and approved by the US Food and Drug Administration in 1976.[1] Although its chemical structure is similar to that of diphenoxylate (the antidiarrheal component of Lomotil [Pfizer; New York, NY]) and meperidine, loperamide was designed to induce antidiarrheal properties similar to those of opiate agonists, such as morphine and diphenoxylate, without central nervous system (CNS) side

effects and potential for abuse. Loperamide is available in several different over-the-counter formulations (tablets, chewable tablets, capsules, a liquid formulation, and a combination of loperamide with simethicone) and has been an effective therapy for a variety of diarrheal syndromes, in the reduction of ileostomy volume, and for the treatment of fecal incontinence.

Clinical Pharmacology

Loperamide is an orally administered opiate receptor agonist that binds to the μ-opiate receptor in the gut, resulting in decreased peristalsis. Loperamide is poorly absorbed, with approximately 0.3% systemic availability due to extensive first-pass metabolism before systemic exposure.[2] Peak plasma concentrations are reached within 4 hours after an average half-life for gastric emptying of 0.6 hours and a half-life for arrival in the colon of 7.4 hours.[3] Another important and clinically relevant property is that loperamide does not cross the blood–brain barrier,[4] which, along with low oral absorption, accounts for the absence of CNS effects. Loperamide is extensively metabolized via N-demethylation to inactive metabolites and is a substrate for hepatic cytochrome P450 isoenzymes CYP2C8 and CYP3A4.[5]

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Loperamide has a higher binding affinity for peripheral opiate receptors than morphine (approximately 50 times more potent[4]), and its activity is blocked by naloxone.[6] The duration of action is also longer than that of other opiates, including diphenoxylate and codeine.[1,7] The main mechanism for its antidiarrheal effect is inhibition of intestinal motility[8] by directly affecting cholinergic and noncholinergic neuronal mechanisms.[9] In addition to the antiperistaltic activity, loperamide inhibits small-intestinal secretion by influencing both proabsorptive and secretory peptides and local release of 5-hydroxy-tryptamine, as well as inhibiting calmodulin and L-type calcium channels (reviewed by Baker[1]).

Loperamide has also been observed to increase anal sphincter tone, which may lead to improvement of fecal continence in patients with and without diarrhea.[10] Additionally, loperamide reduces sensitivity of the recto-anal inhibitory reflex, increases internal anal sphincter tone and has an effect on rectal compliance in incontinent patients with diarrhea, and increases the threshold volumes for minimal perception and urgency to defecate.[11,12]

Clinical Efficacy

Acute Diarrheal Syndromes

Acute nonspecific diarrhea. Loperamide has been demonstrated to be efficacious in the setting of acute, nonspecific (infectious) diarrhea compared with placebo, with reduction of unformed stools, and an increased time to liquid stools.[13,14] Loperamide (4 mg initial dose) has also been compared with diphenoxylate (5 mg) in (1) a study of more than 200 patients, in which the onset of action was faster with loperamide[15]; (2) a study of more than 300 patients with acute diarrhea, in which 4-mg initial dosing followed by 2 mg after each subsequent unformed stool (up to 10 doses daily) was successful at controlling diarrhea in 47% of patients within 24 hours and 86% of patients within 48 hours, compared with 37% and 75% of patients receiving 5 mg of diphenoxylate followed by 2.5 mg after each unformed stool[16]; and (3) in a 340-patient trial comparing 4 mg initial dosing with loperamide with 5 mg diphenoxylate with repeated dosing of 2 mg or 2.5 mg, respectively, after each subsequent liquid bowel movement, in which patients taking loperamide had significantly better control of diarrhea (98.7% vs 92.3%; $P = .01$) and fewer unformed stools over 72 hours.[17] Other studies have compared loperamide with bismuth subsalicylate in adult students with acute, infectious diarrhea.[18] Over a 2-day study period up to 8 mg loperamide significantly reduced the average number of unformed bowel movements relative to bismuth subsalicylate (up to 4.9 g), controlled diarrhea significantly longer, and shortened the time to the last unformed stool. In a similar comparative trial in adults, DuPont and colleagues[19] also demonstrated superiority of loperamide compared with attapulgite in reducing the mean number of unformed stools within 12 hours and reducing the mean time to the last unformed stool.

Several studies have also compared loperamide with placebo in pediatric patients with acute diarrhea in both the ambulatory setting[20] and in hospitalized children.[21] In outpatients and in hospitalized children treated with oral rehydration solution, loperamide 1 to 2 mg or 0.4 to 0.8 mg/kg/d led to a reduction of unformed stools and a shorter time to the last unformed stool, as well as better weight gain in the hospitalized children.

Finally, in studies enrolling more than 900 adults with acute, infectious diarrhea, when formulated with simethicone (Imodium Advanced; McNeil PPC; Fort Washington, PA) loperamide reduced the time to the last unformed stool by 75% compared with placebo, while relieving "gas-related" symptoms, such as gas pain, cramps, pressure, and bloating.[22,23]

Traveler's diarrhea. Loperamide also has been evaluated compared with bismuth subsalicylate and antibiotics for the treatment of acute, nondysenteric diarrhea in travelers. In an open-label, randomized study[24] comparing loperamide with bismuth subsalicylate in 219 patients, loperamide reduced the median number of unformed stools within 4 hours and provided more relief from diarrhea and abdominal pain compared with bismuth. In studies comparing antibiotics or loperamide alone, or in combination, diarrhea resolved in the shortest amount of time in patients receiving loperamide in combination with sulfamethoxazole/trimethoprim.[25] Loperamide in combination with ciprofloxacin reduced the number of liquid stools at 48 and 72 hours in US military personnel with traveler's diarrhea[26] and in combination with rifaximin demonstrated significant reductions in median time until passage of the last unformed stool and mean number of unformed stools compared with either drug alone.[27]

Iatrogenic Diarrhea

Chemotherapy-related diarrhea. Loperamide has become a standard therapy for uncomplicated cancer treatment–induced diarrhea,[28] on the basis of efficacy demonstrated in clinical studies of patients who received 5-fluorouracil[29] or irinotecan.[30] In these settings, high daily doses (ie, 2 mg every 2 hours) for up to 3 days may be necessary to control symptoms and prevent hospitalization for dehydration.[31] When loperamide has been compared with octreotide in chemotherapy-induced diarrhea, the outcomes have been more mixed. In one study of 40 patients,[32] more patients responded to octreotide 0.5 mg subcutaneously compared with loperamide 4 mg 3 times daily; however, in a second trial[33] loperamide 4 mg every 6 hours outperformed octreotide administered as a continuous intravenous infusion of 150 up to 2400 μg daily.

Protease inhibitor–associated diarrhea. Loperamide, when administered with norfloxacin and/or metronidazole, has been effective at reducing stool frequency and improving stool consistency in HIV-positive patients receiving nelfinavir[34] and in ambulatory HIV-positive patients with chronic diarrhea.[35]

Miscellaneous settings. Loperamide has been effective as a prophylactic agent to prevent diarrhea secondary to prostaglandins administered to terminate pregnancy,[36] and it increased stool consistency and improved continence in obese patients taking orlistat.[37]

Chronic Diarrheal Syndromes

Irritable bowel syndrome. Several studies[38–41] have evaluated the efficacy of loperamide in the treatment of irritable bowel syndrome. Although loperamide significantly reduced stool consistency and reduced defecation frequency compared with placebo, there were no improvements in the intensity of abdominal pain related to meals or defecation, and there was a higher intensity of nocturnal pain in patients receiving loperamide. Hence the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force deemed loperamide successful in improving stool frequency and consistency but without benefits on "global" irritable bowel symptoms.[42] Nevertheless, loperamide is effective for the "gut-directed" symptom of diarrhea in patients with painless diarrhea or diarrhea-predominant irritable bowel syndrome.[43–50] Whether the addition of simethicone to loperamide will impact on the symptoms of bloating or abdominal pain in the setting of irritable bowel syndrome, similar to the impact on gas-related symptoms in acute diarrhea,[22] has not been evaluated.

Inflammatory bowel disease. Loperamide and diphenoxylate are commonly used to treat diarrhea in numerous settings of inflammatory bowel disease,[51–53] and the use of such antidiarrheals has been incorporated into the Crohn's Disease Activity Index.[54] Their use should be avoided in the settings of severe or worsening colitis or impeding bowel obstruction. Studies comparing loperamide with diphenoxylate have demonstrated that loperamide is more efficacious for the treatment of diarrhea.[55–57] In addition, loperamide has been efficacious in reducing diarrhea after ileocolic resections,[58] in the setting of short bowel syndrome,[59,60] and to reduce ileostomy output after proctocolectomy.[61,62] Furthermore, loperamide has been effective for the treatment of diarrhea after colectomy and ileorectal anastomosis and after proctocolectomy and restorative ileoanal anastomosis.[63,64] High-dose loperamide suppositories, 20 mg twice daily, have been shown to reduce mean stool frequency and to improve the volume at which patients developed the urge to evacuate after restorative proctocolectomies.[65]

Loperamide is effective for the "gut-directed" symptom of diarrhea in patients with painless diarrhea or diarrhea-predominant irritable bowel syndrome.

One differentiating property between loperamide and diphenoxylate is the former's ability to decrease stool frequency and pouch contractions[63] and increase resting anal sphincter tone.

Microscopic colitis. Loperamide has been effective for reducing

diarrhea in patients with collagenous or lymphocytic colitis[66,67] and may be used as an adjunct to budesonide, which has been the most consistently effective treatment to date.[68]

Fecal Incontinence

The beneficial impacts of loperamide on anal sphincter tone and rectal compliance have led to its assessment for the treatment of fecal incontinence. As already mentioned, loperamide has improved continence in patients undergoing proctocolectomy and restorative ileoanal pouches.[63,64] Loperamide (12 mg daily) has also been evaluated in patients with chronic diarrhea and fecal incontinence, in whom it reduced episodes of incontinence and urgency.[10,69]

Safety

Loperamide is generally well tolerated at recommended nonprescription doses, with the most common side effects related to the impact on bowel motility (abdominal pain, distention, bloating, nausea, vomiting, and constipation).[70] Other common side effects include drowsiness, fatigue, dizziness, headache, and dry mouth and are usually self-limiting.[1] Hypersensitivity reactions and paralytic ileus are rare.[71]

Loperamide is contraindicated in patients with abdominal pain in the absence of diarrhea and should not be used alone in patients with acute diarrhea due to invasive organisms (eg, *Salmonella*, *Shigella*, *Campylobacter*) or in patients with untreated pseudomembranous colitis or *Clostridium difficile*. However, in conjunction with antibiotics loperamide did shorten the duration of diarrhea in patients with *Shigella* or enteroinvasive *Escherichia coli*.[72]

Loperamide is contraindicated in the setting of severe or progressing colitis and has been associated with risks of toxic megacolon in patients with severe colitis.[51,53,73]

Concurrent use of loperamide with drugs that inhibit intestinal motility or can cause constipation can lead to severe constipation, obstruction, fecal impaction, or paralytic ileus.[1] Concurrent use of cholestyramine is not recommended because it may bind to loperamide and prevent absorption.

Loperamide has not been associated with teratogenicity[74] and is categorized as Class B for pregnancy and of low risk for breast feeding.

Dosing

Loperamide is available over the counter in several formulations and doses, including in combination with simethicone. The latter formulation has been effective in reducing bloating in patients with acute diarrhea.[22] In acute, nonspecific diarrhea the recommended over-the-counter dose is 4 mg initially, followed by 2 mg after each subsequent bowel movement up to a total dose of 8 mg in 24 hours. Patients with chronic diarrhea may take up to 4 mg every 6 hours for a total of 16 mg daily. The dose can be adjusted according to efficacy and side effects but in chronic diarrhea is best taken on an empty stomach 1 hour before meals and always taken with plenty of liquids to avoid dehydration.[1] Pediatric doses for children weighing more than 30 kg are 2 mg 3 times daily on the first day up to 6 mg daily and for children weighing 20 to 30 kg are 2 mg twice daily with a maximum daily dose of 4 mg.[1]

Disclosure: Dr. Hanauer has served as a consultant for McNeil-PPC, Inc.

Main Points

- Loperamide is an effective therapy for a variety of diarrheal syndromes. The main mechanism for its antidiarrheal effect is inhibition of intestinal motility by directly affecting cholinergic and noncholinergic neuronal mechanisms.
- Loperamide was designed to induce antidiarrheal properties similar to those of opiate agonists, such as morphine and diphenoxylate, without central nervous system side effects and potential for abuse.
- Loperamide has also been observed to increase anal sphincter tone, which may lead to improvement of fecal continence in patients with and without diarrhea.
- The American College of Gastroenterology Functional Gastrointestinal Disorders Task Force deemed loperamide successful in improving stool frequency and consistency but without benefits on "global" irritable bowel symptoms.
- Loperamide and diphenoxylate are commonly used to treat diarrhea in numerous settings of inflammatory bowel disease, and the use of such antidiarrheals has been incorporated into the Crohn's Disease Activity Index.
- Loperamide is available in several different over-the-counter formulations and is generally well tolerated at recommended nonprescription doses, with the most common side effects related to the impact on bowel motility (abdominal pain, distention, bloating, nausea, vomiting, and constipation).

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