Loperamide: A Pharmacological Review

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Loperamide is an antidiarrheal medication approved for the control of diarrhea symptoms and is available without a prescription. Loperamide works by a number of different mechanisms of action that decrease peristalsis and fluid secretion, resulting in longer gastrointestinal transit time and increased absorption of fluids and electrolytes from the gastrointestinal tract. It is a phenylpiperidine derivative with a chemical structure similar to opiate receptor agonists such as diphenoxylate and haloperidol. It was designed to maintain the antidiarrheal activity of these drugs, but minimize the negative aspects associated with their effects on the opiate receptor. Because of lo-peramides's low oral absorption and inability to cross the blood–brain barrier, it has minimal central nervous system effects. It also has a longer duration of action than diphenoxylate. However, it has no clinically significant analgesic activity and does not decrease the pain associated with some forms of irritable bowel syndrome and diarrhea. Loperamide is metabolized by the cytochrome P450 (CYP) system and is a substrate for the CYP3A4 isoenzyme. Concurrent administration with CYP3A4 inhibitors may elevate loperamide concentrations. Common adverse reactions to loperamide include cramps and nausea. Loperamide is an effective treatment for patients with painless diarrhea and is considered to be free of abuse potential.
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Key words: Loperamide • Opioid agonist • Central nervous system • Diarrhea • Inflammatory bowel syndrome • Antisecretory activity • Peristalsis

Loperamide is an over-the-counter antidiarrheal medication approved for the control of diarrhea symptoms, including travelers' diarrhea.[1-3] It is also available as a prescription product from generic manufacturers. Loperamide has been shown to be effective in the treatment of acute nonspecific diarrhea, acquired immunodeficiency syndrome (AIDS)–associated diarrhea, cancer

treatment–induced diarrhea, and chronic diarrhea associated with inflammatory bowel disease; in the management of diarrhea-predominant irritable bowel syndrome and lactose intolerance; and in the reduction of the volume of discharge from ileostomies.[2-7]

Loperamide (4-[4-chlorophenyl]-4-hydroxy-N-dimethyl-alpha, alpha-diphenyl-1-piperidine-butanamide hydrochloride) is a phenylpiperidine derivative that was synthesized in 1969 and approved by the US Food and Drug Administration in 1976.[2,8-10] Its chemical structure is related to diphenoxylate, haloperidol, and meperidine (Figure 1), but it has minimal analgesic activity and does not produce euphoria at standard doses.[10-14]

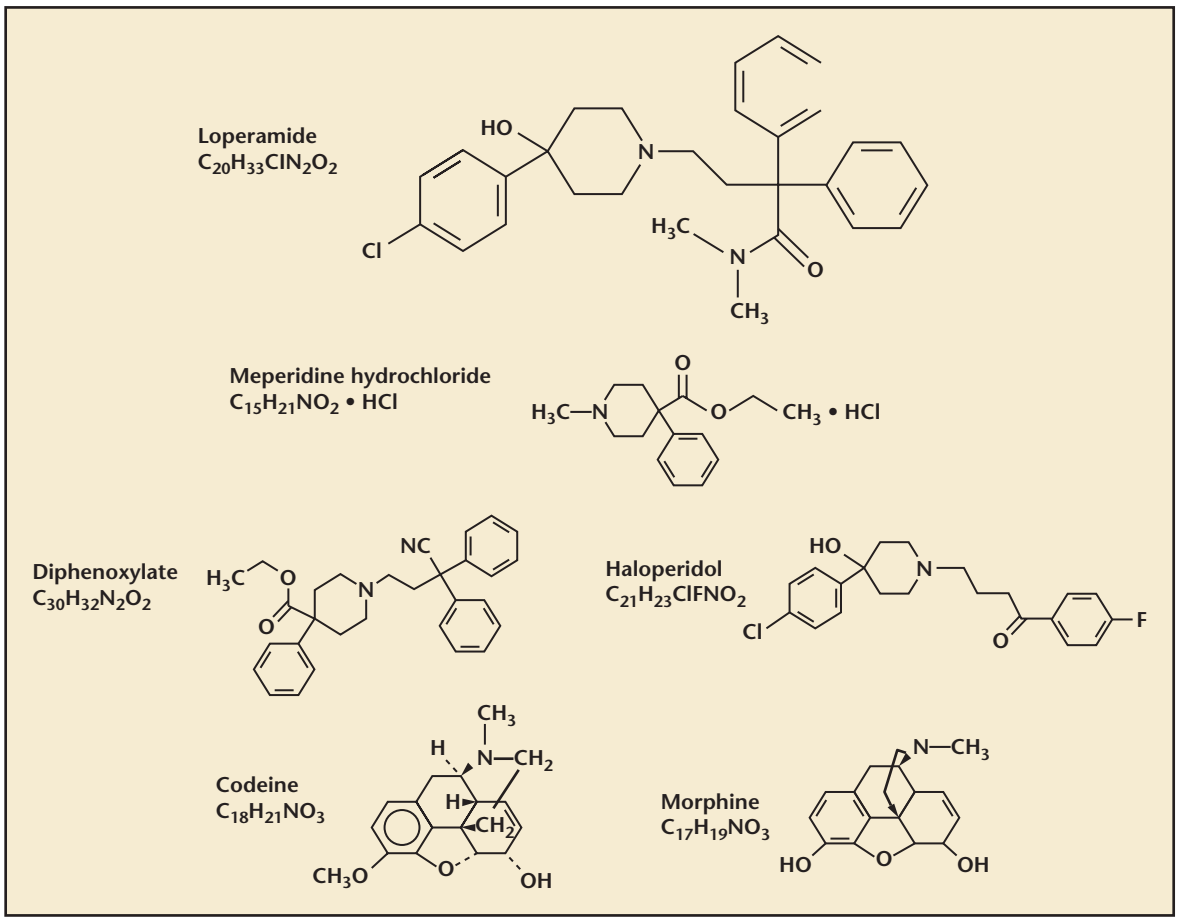
Loperamide was designed to maintain the antidiarrheal activity of morphine and diphenoxylate and minimize the negative aspects associated with the effects of these drugs on the opiate receptor (abuse, opioid central nervous system [CNS] activity). The series of loperamide compounds that were designed to replace morphine and diphenoxylate were derived by combining features of haloperidol neuroleptics and isopropamide anticholinergics. This produced a compound that was an effective antidiarrheal agent with a minimal amount of CNS side effects.[15]

Loperamide is useful in the treatment of diarrhea and irritable bowel syndrome because it inhibits intestinal secretion and peristalsis, thereby slowing the intestinal transit time and allowing more fluids and electrolytes to be absorbed; at rest, it improves anal sphincter tone. However, it has minimal effect on the pain associated with irritable bowel syndrome.[2,7-9,11,12,16-25] A systematic review of the randomized, controlled trials of loperamide for the treatment of irritable bowel syndrome found 4 clinical trials. These trials determined that loperamide was effective in improving diarrhea (decreased frequency of bowel movements and improved stool consistency), but did not decrease abdominal pain or distention, if present.[26]

Pharmacokinetics

Loperamide is not well absorbed following oral administration. The

Figure 1. *Chemical structure of loperamide. Data from Gold Standard, Inc.*[2]



systemic bioavailability is about 0.3% because of substantial first-pass metabolism that occurs prior to systemic absorption.[27,28] Peak plasma concentrations occur within 2.5 hours of oral administration of the solution and 5 hours of the gelatin capsule.[2,3] A 4-mg dose of loperamide will produce a peak plasma level of 0.002 nM.[15]

Small amounts of loperamide are excreted unchanged in the feces (30% to 40%) and urine (2% to 10%).[2,8] The majority of the drug is removed from the body by hepatic metabolism through the cytochrome P450 (CYP) isoenzymes (CYP2C8 and CYP3A4) with an elimination half-life of 10.8 hours.[2]

The plasma protein binding of loperamide is 97%.[2] Loperamide does not cross the blood–brain barrier.[17,19,29-31] The poor CNS penetration of this hydrophobic drug is a result of the high cross-sectional area at the hydrophilic/hydrophobic interface and the fact that it is a substrate for P-glycoprotein.[15,32,33] Consequently, the combination of low oral absorption and the inability to cross the blood–brain barrier explains why loperamide therapy is associated with minimal CNS effects.

Clinical Pharmacology

Effects on the Gastrointestinal Tract

Peristaltic activity. Opiate receptor agonists (eg, morphine, diphenoxylate, opium, codeine) have been used for centuries for the treatment of diarrhea.[22] Loperamide is an opioid agonist. Like the other opioids, loperamide's stimulation of the opiate receptors in the periphery results in decreased peristalsis.[9,21,22] However, there are differences in binding affinity for these receptors between loperamide and the other opiate receptor agonists used to treat diarrhea. In addition, loperamide has no clinically significant analgesic activity and does not cross the blood–brain barrier. Consequently, loperamide has a different clinical and adverse reactions profile than diphenoxylate and morphine.[8,9,30,31,34,35]

Loperamide is 50-fold more potent in vitro than morphine and has a longer duration of action at the opiate receptor. Administration of naloxone can block the activity of loperamide at the opiate receptor, but to a lesser degree than that observed with morphine. This demonstrates that loperamide has a higher binding affinity for peripheral opiate receptors than morphine.[15,29]

Like the other opiate receptor agonists, loperamide binds to the mu-opiate receptor in the gut and produces some of its results through the modulation of serotonin release and its effects on the neurokinin NK_3-receptor.[8,34,36] Loperamide also closely resembles the neurokinin NK_2 antagonist ligand set and is able to antagonize the NK_2 receptors at micromolar concentrations.[34]

In the castor oil test, loperamide has a longer-lasting activity than diphenoxylate, codeine, morphine, dextromoramide, and phenazocine when administered at equal doses. In rats, loperamide is the most specific (antidiarrheal specificity/duration) drug in producing antidiarrheal effects and has a wide safety margin (see Table 1).[8]

Antisecretory activity. In animal models, loperamide is able to markedly inhibit small intestinal secretion induced by cholera toxin and prostaglandin E_2. This action appears to be independent of changes in adenylate cyclase or tissue concentrations of

Table 1
Antidiarrheal Activity in the Castor Oil Test and Specificity/Duration for Selected Medications in Rats

	Antidiarrheal Activity: Castor Oil Test		Antidiarrheal Specificity	
Medication	ED_{50} 4 h, mg/kg	ED_{50} 8 h, mg/kg	at 4 h	at 8 h
Codeine	28.8	70.0	1.97	0.81
Morphine	30.9	60.7	1.09	0.81
Diphenoxylate	1.41	4.77	9.08	2.68
Difenoxine	0.31	0.91	13.1	4.46
Loperamide	0.61	1.81	262	88.4

ED_{50}, median effective dose.
Data from Ooms LA et al.[8]

cyclic adenosine monophosphate, but is probably related to effects on the opiate receptor because naloxone is able to decrease the antisecretory effect of loperamide.[8,21,22] These effects may also be the result of the drug's ability to influence peptides that are proabsorptive (neuropeptide Y, peptide YY, and somatostatin) or secretory (vasoactive intestinal peptide, bombesin, neurotensin, substance P, and neurokinins).[22]

In addition to these effects, loperamide, difenoxin (active metabolite of diphenoxylate), and morphine affect enteric 5-hydroxy-tryptamine (5-HT). The antisecretory activity of these drugs can be abolished by depleting available 5-HT with a 5-HT synthesis inhibitor; however, exogenous administration of 5-HT results in intestinal secretion. This tends to indicate that the antisecretory effects of the opiate agonist are related to the local release of 5-HT (neurones or epithelial EC cells) and not dependent on systemic distribution of 5-HT.[22]

The antisecretory mechanisms of these opioid-like drugs may be similar as it relates to their activity on 5-HT, but there are differences in the effects of these drugs on the noradrenergic neurons. Only morphine and difenoxin affect the noradrenergic neurons; loperamide has no effect. Administration of phentolamine, an adrenoceptor antagonist, blocks the antisecretory activity of morphine and difenoxin, but not the antisecretory activity of loperamide.[22]

Activated calmodulin is responsible for intestinal ion transport by phosphorylation of intestinal peptides that appears to be a result of the interaction between calcium and calmodulin.[8] Loperamide is a potent calmodulin antagonist with 50% inhibitory concentration of 5 microM.[15] By modulating the access of calcium to calmodulin or the levels of calcium and calmodulin, or by modifying the interaction of calcium-activated calmodulin with receptors, loperamide can produce changes in bowel function. Loperamide inhibits calmodulin function in the gastrointestinal tract, unlike the opioids that have no effect on calmodulin.[8,15]

Another possible pathway involved with the antisecretory ability of loperamide is the blockade of L-type calcium channels. Loperamide is capable of inhibiting L-type calcium channels at submicromolar concentrations. Its binding affinity for the L-type calcium channel is sufficient to block verapamil's binding to the same receptor (see Table 2).[15]

Other possible mechanisms involved with the antidiarrheal activity of loperamide include blockade of neuronal voltage-dependent calcium channels, blockade of store-operated calcium channels, and inhibition of basolateral K+ conductance, N-methyl-D-aspartate-evoked currents, maitotoxin-elicited calcium influx, and forskolin-elicited secretion.[8,14,15,37-39] The importance of these mechanisms has not been determined.

Table 2
Loperamide's Mechanisms of Action

Decreases Peristaltic Activity
Stimulates opiate receptors in the periphery
Binds to the mu-opiate receptor in the gut
Modulates serotonin release and its effects on the neurokinin NK_3-receptor
Antagonizes the NK_2 receptors at micromolar concentrations
Antisecretory Activity
Influences proabsorptive or secretory peptides
Affects enteric 5-HT
Inhibits calmodulin function in the gastrointestinal tract
Inhibits L-type calcium channels at submicromolar concentrations

5-HT, 5-hydroxy-tryptamine.
Data from Daly JW and Harper J,[15] Du Luca A and Coupar IM,[22] and Keiser MJ et al.[34]

Contraindications

Loperamide should not be administered to patients with a known hypersensitivity reaction to loperamide hydrochloride.[1,3]

Warnings/Precautions

Loperamide should not be used without medical supervision if the patient's stools are bloody or black in color.[1] If either of these are present, acute dysentery, intestinal obstruction, or perforation should be ruled out prior to loperamide therapy.[2,3] Patients are instructed to contact their doctor if they have fever, mucus in the stool, or a history of liver disease prior to the over-the-counter use of loperamide to treat diarrhea.[1]

Chronic use of loperamide may inhibit intestinal motility and prolong transit time, which may predispose some patients to the development of megacolon. All patients receiving chronic therapy should be monitored for signs of toxicity (eg, constipation, abdominal distention, ileus).[2]

In cases where diarrhea is caused by poisoning or infection with

enterotoxin-producing bacteria (eg, pseudomembranous colitis), antidiarrheal therapy should not be used. In most of these cases, the diarrhea is a protective mechanism and should not be inhibited.[2]

Some patients may experience drowsiness or dizziness while using loperamide. Therefore, all patients should be warned to be careful when driving or operating machinery while using loperamide.[1] Loperamide is considered free of abuse potential.[10,13,25]

Adverse Reactions

Common adverse reactions related to the use of loperamide in the treatment of diarrhea include cramps, nausea, dyspepsia, drowsiness, fatigue, tiredness, dizziness, headache, and dry mouth.[1,2,3,7,25] Most adverse reactions are self-limiting because of the short-term administration of the drug for most indications.[2,3]

Most adverse reactions of loperamide are self-limiting because of the short-term administration of the drug for most indications.

Drug Interactions

Concurrent use of loperamide with drugs that can cause constipation or inhibit intestinal motility (eg, opioids, antimuscarinics, drugs with anticholinergic effects) or are used to treat diarrhea (eg, alosetron) sometimes lead to severe constipation, obstruction/impaction, or paralytic ileus.[2,7] The decrease in gastrointestinal motility induced by loperamide may increase the risk of gastrointestinal irritation from sustained-release, solid-dosage forms of potassium salts, or the rate of absorption from other sustained-release dosage forms (eg, theophylline from Theo-24).[2,7]

Some drugs used to treat constipation (eg, lubiprostone) can cause diarrhea. In most of these cases, drug-induced diarrhea or loose stools will resolve with continued administration or by withholding the medications. Concurrent administration of loperamide may antagonize the effects of the other drug.[2]

Concurrent administration with cholestyramine is not recommended. Cholestyramine may bind loperamide in the gastrointestinal tract and decrease its ability to work.[2]

The impact of pramlintide therapy on blood glucose control may be increased with loperamide therapy.[2] Pramlintide improves glucose control by slowing gastric emptying and the rate of nutrient delivery to the small intestine. Concurrent use of loperamide with other drugs that can slow gastrointestinal motility or nutritive absorption may potentiate the lowering of blood glucose concentrations.

Loperamide is metabolized by the CYP system. It is a substrate for the CYP3A4 isoenzyme. Inhibition of this isoenzyme may increase the plasma concentrations of loperamide. Ritonavir can increase the peak plasma concentration of loperamide by 17%, the time to maximum concentration by 56%, the area under the concentration versus time curve (AUC) by 223%, and the amount excreted in the urine by 118%. It can decrease the clearance of loperamide by 70%. Concurrent administration with CYP3A4 inhibitors should be handled with caution and the patient monitored for increased side effects from the elevated loperamide concentrations.[2]

Tipranavir can decrease loperamide's AUC by 30% and the dosing interval minimum concentrations by 26%, whereas saquinavir decreases the AUC by 54%.[2]

P-glycoprotein inhibitors may increase gastric absorption and decrease elimination from the CNS. Loperamide is affected by P-glycoprotein transport. Quinidine and ritonavir are inhibitors of P-glycoprotein transport. Concurrent administration with these drugs results in a 2-fold to 3-fold increase in loperamide plasma concentrations and may also interfere with its transport out of the brain.[2] However, concurrent administration with 2 P-glycoprotein inhibitors (ritonavir-boosted tipranavir and ritonavir alone) results in no evidence of opioid effects in the CNS.[40,41] Other known P-glycoprotein inhibitors include amiodarone, cyclosporine, erythromycin, and verapamil.[2] None of these metabolism drug interactions appear to be clinically important because of loperamide's very low systemic bioavailability.

Dosing

The recommended over-the-counter dose of loperamide for adults and adolescents (> 12 years of age) for the control of symptoms associated with diarrhea is 4 mg after the first loose stool. If additional doses are required, they should be administered after each subsequent loose bowel movement and the dose decreased to 2 mg, with no more than 8 mg administered in any 24-hour period. The dose for pediatric patients (9 to 11 years; 60 to 95 lbs) is 2 mg after the first loose stool. The dose after subsequent loose stools is 1 mg up to a total of 6 mg in any 24-hour period. The dose for younger pediatric patients (6 to 8 years; 48 to 59 lbs) is 2 mg after the first loose stool and 1 mg after each subsequent loose stool, up to 4 mg in any 24-hour period. The over-the-counter labeling for loperamide does not provide a recommendation for children under 6 years of age or weighing less than 48 lbs.[1,42]

The recommended non–self-medicated doses for loperamide are listed in Table 3.[2]

Table 3
Prescribed Doses of Loperamide for the Treatment of Selected Medical Conditions

	Acute Nonspecific Diarrhea Including AIDS-Associated Diarrhea With Identifiable Infection		Chronic Diarrhea		Diarrhea-Predominant Irritable Bowel Syndrome	
	Dose	Daily Maximum	Dose	Daily Maximum	Dose	Daily Maximum
Adults	4 mg PO initially, followed by 2 mg PO after each unformed stool	16 mg	4 mg PO initially, followed by 2 mg PO after each unformed stool. Dosage can be decreased for maintenance therapy to 4-8 mg/day, which is given as a single daily dose or in divided doses	16 mg	2-4 mg PO up to 4 times daily. Dosage can be decreased for maintenance therapy to 4-8 mg/day, which is given as a single daily dose or in divided doses	16 mg
Children 9-11 years (> 30 kg)	2 mg PO 3 times per day on the first day, followed by a single dose of 0.1 mg/kg PO after each unformed stool	6 mg	Not established: doses used have been 0.08-0.24 mg/kg/day PO given in 2-3 divided doses	2 mg/dose, 6 mg/day		
Children 6-8 years (20-30 kg)	2 mg PO twice per day on the first day, followed by a single dose of 0.1 mg/kg PO after each unformed stool	4 mg	Not established: doses used have been 0.08-0.24 mg/kg/day PO given in 2-3 divided doses	2 mg/dose, 4 mg/day		

AIDS, acquired immunodeficiency syndrome; PO, orally.
Data from Gold Standard, Inc.[2]

The over-the-counter loperamide products are available in 2-mg strength.[1] Unless a particular brand is recommended, dosing recommendations should be made for a specific product, or based on milligrams and not a general number of dosage units (eg, 2 tablets). Available dosage forms include tablets, chewable tablets, capsules, and a liquid formulation.[1-3] A formulation of loperamide with simethicone has been shown to be efficacious in the reduction of diarrhea and bloating in patients with acute diarrhea.[42,43]

The drug should be taken on an empty stomach (1 hour before or 2 hours after a meal). It should be taken with plenty of clear fluids to help prevent dehydration in patients with diarrhea.[1]

Conclusion

Loperamide is an effective treatment option for patients with painless diarrhea. It works by a number of different mechanisms of action that decrease peristalsis and fluid secretion, resulting in a longer gastrointestinal transit time and increased absorption of fluids and electrolytes from the gastrointestinal tract. Despite its structural similarity to several of the opioid analgesics, it is devoid of clinically significant analgesic activity and thus does not decrease the pain associated with some forms of irritable bowel syndrome and other conditions associated with painful diarrhea.

Loperamide has a longer duration of action than diphenoxylate and less potential for abuse. Therefore, an anticholinergic agent (eg, atropine) has not been added to the loperamide formulation (unlike diphenoxylate), and it is available without a prescription. ■

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Main Points

- Loperamide is an opioid agonist that inhibits intestinal secretion and peristalsis, slowing intestinal transit time and allowing more fluids and electrolytes to be absorbed. It has proven to be effective in the treatment of diarrhea and irritable bowel syndrome; however, it has minimal analgesic activity.
- Like the other opioids, loperamide's stimulation of the opiate receptors in the periphery results in decreased peristalsis. However, there are differences in binding affinity for these receptors between loperamide and the opiate receptor agonists: loperamide is 50-fold more potent in vitro than morphine and has a longer duration of action at the opiate receptor.
- Loperamide inhibits calmodulin function in the gastrointestinal tract, unlike other opioids that have no effect on calmodulin. By modulating the access of calcium to calmodulin or the levels of calcium and calmodulin, or by modifying the interaction of calcium-activated calmodulin with receptors, loperamide can produce changes in bowel function.
- Warnings and precautions cited for treatment with loperamide include inhibition of intestinal motility and prolonged transit time with chronic use, predisposing some patients to the development of megacolon. All patients receiving chronic therapy should be monitored for signs of toxicity.
- Loperamide is metabolized by the cytochrome P450 (CYP) system and is a substrate for the CYP3A4 isoenzyme. Inhibition of this isoenzyme may increase the plasma concentrations of loperamide; therefore, concurrent administration with CYP3A4 inhibitors should be handled with caution and the patient monitored for increased side effects from elevated loperamide concentrations.
- Over-the-counter loperamide products are available in 2-mg strength; dosage forms include tablets, chewable tablets, capsules, and a liquid formulation. Unless a particular brand is recommended, dosing recommendations should be made for a specific product, or based on milligrams and not a general number of dosage units.
- Loperamide is an effective treatment option for patients with painless diarrhea, with a longer duration of action than diphenoxylate and less potential for abuse.

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