Therapeutic Reviews

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Loperamide *AHFS 56:08*

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Class: Antimotility drug.

Indications: Acute and chronic diarrhea, †ileostomy (to improve fecal consistency).

Contraindications: Colitis (ulcerative, infective, or antibiotic-associated).

Pharmacology

Loperamide is a potent μ-opioid receptor agonist.[1] Although well absorbed from the GI tract, loperamide is almost completely extracted and metabolized by cytochrome P450 in the liver (particularly CYP3A4) where it is conjugated, and the conjugates excreted in the bile. Because of this, little loperamide reaches the systemic circulation.

The antidiarrheal action of loperamide results from direct absorption into the gut wall. Like morphine and other μ-receptor agonists, loperamide increases intestinal transit time by decreasing propulsive activity and increasing non-propulsive activity via its effect on the myenteric plexus in the longitudinal muscle layer.[2,3] Loperamide also increases anal sphincter tone and improves night-time continence in patients with ileo-anal pouches.[4]

Loperamide also modifies the intestinal transport of water and electrolytes by stimulating absorption,[5] and by an antisecretory action mediated by calmodulin antagonism, a property not shared by other opioids.[6-8]

Paradoxically, loperamide reduces the sodium-dependent uptake of glucose and other nutrients from the small bowel.[9] The development of tolerance to the GI effects of loperamide has been demonstrated in animal studies.[10] However, loperamide has been successfully used in patients with chronic diarrhea for several years without evidence of tolerance.[11]

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Loperamide is a substrate for P-glycoprotein, the efflux membrane transporter in the blood-brain barrier, and, although highly lipophilic,[3] loperamide is actively excluded from the CNS.[12,13] Consequently, unlike morphine, which has both central and peripheral constipating effects, loperamide generally acts only peripherally[1] (but see Drug interactions and Undesirable Effects).

Loperamide has an effect on peripheral μ-opioid receptors activated by inflammation, and has been investigated as a possible *topical analgesic* for painful ulcers of the skin or mouth.[14,15] There are preliminary reports of the successful use of orodispersible tablets, e.g., Imodium® Instants (not USA), 2 mg q2−3 h p.r.n., as an adjuvant analgesic for oral pain arising from mucositis or cancer.[16] However, the orodispersible tablets are relatively expensive. Theoretically, the oral solution is a possible alternative, but formulations which contain alcohol should *not* be used as this may exacerbate pain. Oral morphine solution (without alcohol) may be a better option, particularly long term.

Unlike other drugs used for diarrhea, e.g., diphenoxylate and codeine, loperamide has no analgesic effect in therapeutic and supratherapeutic doses. The lack of CNS effects is one reason why loperamide is a popular first-line choice for the control of diarrhea, including when secondary to surgery, radiotherapy or chemotherapy.[17,18]

However, octreotide (see a previous *Therapeutic Review*)[19] is recommended first-line for chemotherapy or radiotherapy-induced diarrhea when severe (i.e., an increase of ≥7 stools/24 h over baseline, hospital admission and IV fluids required for >24 h), and second-line for less severe diarrhea which does not respond to loperamide 16−24 mg/24 h.[17,18,20]

As an antidiarrheal, loperamide is about 3 times more potent mg for mg than diphenoxylate and 50 times more potent than codeine.[21] It is longer acting and, if used regularly, generally needs to be given only b.i.d. However, its maximum therapeutic impact may not manifest for 16−24 h; this has implications for initial dosing.[13] The following regimens are approximately equivalent:

- loperamide 2 mg b.i.d.
- diphenoxylate 2.5 mg q.i.d. (in combined diphenoxylate and atropine tablets)
- codeine phosphate 60 mg q.i.d.

Loperamide is available in a range of formulations. Orodispersible tablets (not USA), which melt on the tongue, are bioequivalent to the capsules and are preferred by some patients. A combination product with simethicone provides more rapid relief of diarrhea and abdominal discomfort from bloating in acute non-specific diarrhea than either loperamide or simethicone alone.[22,23] One suggested explanation is that the surfactant effect of simethicone enhances the contact of loperamide with the gut mucosa. However, both these formulations are only available OTC and are relatively expensive (see Supply).

Bioavailability: <2%.
Onset of action: about 1 h; maximum effect 16−24 h.[24]
Time to peak plasma concentration: 2.5 h (oral solution); 5 h (capsules).[25]
Plasma half-life: 11 h.[25]
Duration of action: up to 3 days.[11]

Cautions

Severe hepatic impairment could increase plasma concentrations of loperamide and the risk of undesirable effects.[26]

Drug Interactions

CYP3A4 inhibitors (e.g., erythromycin, fluconazole, ketoconazole, quinidine, ritonavir) can increase plasma concentrations of loperamide.[26]

Inhibitors of P-glycoprotein (e.g., cyclosporin, clarithromycin, erythromycin, intraconazole, ketoconazole, quinidine, ritonavir, verapamil) could potentially allow more loperamide to cross the blood-brain barrier and cause central opioid effects. Although one study in healthy volunteers of quinidine with loperamide found a blunted respiratory response to CO_2 (indicating respiratory depression),[13] others have failed to demonstrate significant CNS effects.[27]

However, with typical doses of loperamide, it is unlikely that these interactions are clinically relevant.[27]

Undesirable Effects
Ileus, fecal impaction, urinary retention. CNS effects can occur in children <2 years who receive excessive doses,[28,29] or in children after unintentional overdose (e.g., drowsiness).[30] If necessary, use naloxone to reverse these effects.

A patient on clozapine (an atypical antipsychotic) died of toxic megacolon after taking loperamide during an episode of food poisoning. Additive inhibition of intestinal motility was considered the precipitating cause.[31]

Dose and Use
Ensure that the diarrhea is not secondary to fecal impaction.
Acute diarrhea
- start with 4 mg PO stat
- continue with 2 mg after each loose bowel action for up to 5 days
- maximum recommended dose 16 mg/24 h.

Chemotherapy- or radiotherapy-induced diarrhea
- if mild–moderate, give 4 mg stat and 2 mg after each loose bowel action
- if not responding to doses of 24 mg/24 h, switch to octreotide
- if severe, use octreotide first-line.

Chronic diarrhea
If symptomatic treatment is appropriate, the same initial approach is used for 2–3 days, after which a prophylactic b.i.d. regimen is instituted based on the needs of the patient during the previous 24 h, plus 2 mg after each loose bowel action. The effective dose varies widely. In palliative care, it is occasionally necessary to increase the dose to as much as 32 mg/24 h; *this is twice the recommended maximum daily dose.*

Supply
Loperamide (generic)
Tablets 2 mg, 28 days @ 2 mg q.i.d. = $8 OTC.
Capsules 2 mg, 28 days @ 2 mg q.i.d = $11.
Oral solution 1 mg/5 mL, 28 days @ 2 mg q.i.d. = $51 OTC.

Imodium® A-D (Janssen); *all OTC*
Caplets (capsule-shaped tablets) 2 mg, 28 days @ 2 mg q.i.d. = $27.
Tablets chewable 2 mg, 28 days @ 2 mg q.i.d. = $145.
Oral solution 1 mg/5 mL, 28 days @ 2 mg q.i.d. = $70.

Combination products with simethicone
Imodium® Multi-Symptom Relief (McNeil); *all OTC*
Caplets (capsule-shaped tablets) loperamide 2 mg, simethicone 125 mg, 28 days @ 1 q.i.d. = $56.
Tablets chewable loperamide 2 mg, simethicone 125 mg, 28 days @ 1 q.i.d. = $162.

Abbreviations/Key

b.i.d.	Twice daily
CNS	Central nervous system
CYP	Cytochrome P450
GI	Gastrointestinal
OTC	Over the counter (i.e., can be obtained without prescription)
PO	Per os, by mouth
p.r.n.	Pro re nata, as needed/required
q2 h	Every 2 hours, etc.
q.i.d.	Four times daily

References

1. Shannon H, Lutz E. Comparison of the peripheral and central effects of the opioid agonists loperamide and morphine in the formalin test in rats. Neuropharmacology 2001;42:253–261.

2. Van Nueten JM, Helsen L, Michiels M, Heykants JJ. Distribution of loperamide in the intestinal wall. Biochem Pharmacol 1979;28:1433–1434.

3. Ooms LA, Degryse AD, Janssen PA. Mechanisms of action of loperamide. Scand J Gastroenterol Suppl 1984;96:145–155.

4. Hallgren T, Fasth S, Delbro DS, et al. Loperamide improves anal sphincter function and continence after restorative proctocolectomy. Dig Dis Sci 1994;39: 2612–2618.

5. Dashwood MR, Sykes RM, Thomson CS. Autoradiographic demonstration of [3H] loperamide binding to opioid receptors in rat and human small intestine. Prog Clin Biol Res 1990;328:165–169.

6. Merritt JE, Brown BL, Tomlinson S. Loperamide and calmodulin. Lancet 1982;1:283.

7. Zavecz JH, Jackson TE, Limp GL, Yellin TO. Relationship between anti-diarrheal activity and binding to calmodulin. Eur J Pharmacol 1982;78:375–377.

8. Daly J, Harper J. Loperamide: novel effects on capacitative calcium influx. Cell Mol Life Sci 2000;57: 149–157.

9. Klaren PH, Giesberts AN, Chapman J, et al. Effect of loperamide on Na+/D-glucose cotransporter activity in mouse small intestine. J Pharm Pharmacol 2000;52: 679–686.

10. Tan-No K, Niijima F, Nakagawasai O, et al. Development of tolerance to the inhibitory effect of loperamide on gastrointestinal transit in mice. Eur J Pharm Sci 2003; 20:357–363.

11. Heel RC, Brogden RN, Speight TM, Avery GS. Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhoea. Drugs 1978;15: 33–52.

12. Heykants J, Michiels M, Knaeps A, Brugmans J. Loperamide (R 18553), a novel type of antidiarrheal agent. Part 5: The pharmacokinetics of loperamide in rats and man. Arzneimittelforschung 1974;24:1649–1653.

13. Sadeque AJ, Wandel C, He H, Shah S, Wood AJ. Increased drug delivery to the brain by P-glycoprotein inhibition. Clin Pharmacol Ther 2000;68:231–237.

14. Nozaki-Taguchi N, Yaksh TL. Characterization of the antihyperalgesic action of a novel peripheral mu-opioid receptor agonist – loperamide. Anesthesiology 1999; 90:225–234.

15. Nozaki-Taguchi N, Shutoh M, Shimoyama N. Potential utility of peripherally applied loperamide in oral chronic graft-versus-host disease related pain. Jpn J Clin Oncol 2008;38:857–860.

16. Regnard C. Personal communication. Newcastle: St. Oswald's Hospice, 2011.

17. Benson AB 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004;22: 2918–2926.

18. Maroun JA, Anthony LB, Blais N, et al. Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian Working Group on Chemotherapy-Induced Diarrhea. Curr Oncol 2007; 14:13–20.

19. Murphy E, Prommer EE, Mihalyo M, Wilcock A. Octreotide. J Pain Symptom Manage 2010;40:142–148.

20. Bhattacharya S, Vijayasekar C, Worlding J, Mathew G. Octreotide in chemotherapy induced diarrhoea in colorectal cancer: a review article. Acta Gastroenterol Belg 2009;72:289–295.

21. Schuermans V, Van Lommel R, Dom J, Brugmans J. Loperamide (R18553), a novel type of antidiarrhoeal agent. Part 6: clinical pharmacology. Placebo-controlled comparison of the constipating activity and safety of loperamide, diphenoxylate and codeine in normal volunteers. Arzneimittelforschung 1974;24:1653–1657.

22. Kaplan MA, Prior MJ, Ash RR, et al. Loperamide-simethicone vs loperamide alone, simethicone alone, and placebo in the treatment of acute diarrhea with gas-related abdominal discomfort. A randomized controlled trial. Arch Fam Med 1999;8:243–248.

23. Hanauer SB, DuPont HL, Cooper KM, Laudadio C. Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone versus loperamide alone and simethicone alone in the treatment of acute diarrhea with gas-related abdominal discomfort. Curr Med Res Opin 2007;23: 1033–1043.

24. Dreverman JWM, van der Poel AJ. Loperamide oxide in acute diarrhoea: a double-blind placebo-controlled trial. Aliment Pharmacol Ther 1995;9: 441–446.

25. Killinger JM, Weintraub HS, Fuller BL. Human pharmacokinetics and comparative bioavailability of loperamide hydrochloride. J Clin Pharmacol 1979;19: 211–218.

26. Baker DE. Loperamide: a pharmacological review. Rev Gastroenterol Dis 2007;7(Suppl 3):s11–18.

27. Vandenbossche J, Huisman M, Xu Y, Sanderson-Bongiovanni D, Soons P. Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance. J Pharm Pharmacol 2010;62:401–412.

28. Friedli G, Haenggeli CA. Loperamide overdose managed by naloxone. Lancet 1980;1(8183):1413.

29. Minton N, Smith P. Loperamide toxicity in a child after a single dose. Br Med J (Clin Res Ed) 1987;294(6584):1383.

30. Litovitz T, Clancy C, Korberly B, Temple AR, Mann KV. Surveillance of loperamide ingestions: an analysis of 216 poison center reports. J Toxicol Clin Toxicol 1997;35:11–19.

31. Eronen M, Putkonen H, Hallikainen T, Vartiainen H. Lethal gastroenteritis associated with clozapine and loperamide. Am J Psychiatry 2003;160: 2242–2243.