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Opioid Analgesics and the Gastrointestinal Tract



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Opioids have been used to manage pain and other ailments for centuries. The constipating effects of opioid analgesic agents are well known and can be used to manage severe diarrhea and control high output ostomies. Loperamide, diphenoxylate, and difenoxin are currently the only opioid-derivatives approved by the FDA for treating diarrhea. Drug-drug interactions and end organ dysfunction may exacerbate systemic side effects of these drugs. In patients who have failed to respond to these agents, other systemic opioids may be considered. The goal of therapy to control gastrointestinal secretion should be to use the lowest effective dose with minimal side effects. Careful monitoring for systemic side effects during the initiation and dose titration phase are crucial to minimize the risks associated with opioid use.

INTRODUCTION

he term "opioid" refers to a large group of compounds and chemicals that share the characteristics of opium. Opium, from the Greek word "opos" for juice, refers to the liquid collected from the unripe seed capsule of *Papaver somniferum L.*, also known as opium poppy. Opium has been used for medicinal purposes for centuries. It is generally agreed that the first written reference to opium poppy is found on

Lingtak-Neander Chan, PharmD, BCNSP, Associate Professor of Pharmacy and Interdisciplinary Faculty of Graduate Program in Nutritional Sciences, University of Washington, Seattle, WA. Sumerian clay tablets inscribed in Cuneiform script about 3000 B.C. Opium was probably used as an euphoriant in religious rituals by the Sumerians (1,2). During the Middle Ages, after opium was introduced to Asia and Europe, more extensive documentation of opium use became available. It wasn't until 1805, that a young German apothecary named Friedrich Wilhelm Sertürner, finally isolated one of the many pharmacologically active ingredients from the plant. He named this alkaloid *morphine*, after Morpheus, the god of dreams in Greek mythology. Shortly after, other alkaloids including codeine and papaverine were discovered, and by the mid-1800's, there was widespread medical use of these compounds (3). The term *opiate* is used today to describe drugs derived from opium.

Receptor Subtype	Confirmed Location	Examples of Clinical Effect
ı	Brain	Analgesia
	Spinal cord	Altered smooth muscle tone
	Myenteric and submucosal plexus	Sedation
	,	Mood alteration
		Nausea and vomiting
\$	Brain	Central analgesia
	Spinal cord	Delayed GI transit time
	Myenteric plexus	Visceral antinociception
5	Brain	Delayed GI transit time
	Myenteric plexus	

PHARMACOLOGICAL ACTIONS OF OPIOIDS

Opioids exert their pharmacological actions by binding to specific cellular receptors. At least three distinctive receptor subtypes (i.e., μ , κ , and δ) have been identified and studied extensively, and are primarily responsible for the observed pharmacological effects. Binding (or blockade) to these receptors alters many clinically important physiological functions (Table 1). Most of the clinical effects observed with opioid use are μ receptor-mediated. A newer receptor known as nociceptin/orphanin FQ peptide (NOP) receptor, as well as variants of μ -receptor genes have been identified; however, the implication of these receptors and receptor variants on pharmacotherapy requires further research and understanding (4-6).

In addition to their well-known effect on regulating pain transmission in the brain, opioid receptors are also widely distributed in the peripheral nervous system and the gastrointestinal tract (GI), such as in the myenteric plexus and the intestines. Opioids essentially affect the physiological functions of the entire GI tract (Table 2) (7,8). The effect of this class of drugs is most profound on motility and secretory functions. For example, morphine delays the transit time from the stomach to the small intestine and inhibits pancreatic and intestinal secretions (9). This explains many of the

observed GI-related side effects associated with opioid use in treating pain. Although these GI side effects are often undesirable, if utilized and monitored carefully, these effects may help alleviate certain symptoms associated with GI dysfunction, such as diarrhea, spasm, and pain.

The commonly prescribed opioids can be classified into three major groups based primarily on their chemical structures (Table 3). The morphine-like derivatives include the natural alkaloids such as morphine and codeine. The piperidine and phenylpiperidine group of opioid receptor agonists includes fentanyl, diphenoxylate (lomotil), and loperamide (imodium); these compounds are synthetic analogs and structurally very different from morphine. The third group of opioid receptor agonists is the diphenylheptylamine class of agents, which include methadone and prophoxyphene; these synthetic compounds have a longer pharmacological action than morphine. Because of the distinctive difference in chemical structure among these three groups of opioids, cross-hypersensitivity from one group to another is unlikely. For example, fentanyl or methadone can often be safely prescribed and tolerated by a patient who has a true, immune-mediated allergy to morphine or codeine.

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Table 2 Opioid physiological effects in different segments of the GI tract (4,7,8)							
Location of GI Tract	Clinical Effect	Symptom					
Lower esophageal sphincter	Inhibition of relaxation	Abdominal discomfort					
Gallbladder	Contraction, reduced secretion	Upper abdominal discomfort, pain, delayed gastric emptying					
Stomach	Delayed gastric emptying, increased pyloric zonal contraction and acid release	Nausea, vomiting, abdominal discomfort					
Small intestine	Increased tonic and segmental contraction (spasm), increased overall transit time of food, decrease secretion	Constipation, delayed gastric emptying, bloating, cramps					
Colon	Increased segmentation, decreased frequency of contraction and secretion	Constipation, hard and dry stools, bloating and distention, spasm, cramps, pain					
Anus/Rectum	Decreased rectal sensitivity, increased internal sphincter tone	Straining, constipation					

UNTOWARD EFFECTS OF OPIOIDS RECEPTOR AGONISTS

The untoward effects of opioid receptor agonists are generally explained by their pharmacological actions. Drugs that readily cross the blood-brain-barrier may have a more profound effect in causing respiratory depression, dysphoria, and mental confusion. Constipation, ileus, and occasionally abdominal pain can be explained by their action on the GI tract. Nausea and vomiting are also common side effects of opioids. While the mechanism is not well-understood, the interaction with opioid receptors in the chemoreceptor trigger zone and the vomiting center in the medulla is thought to play an important role (10–11).

Pruritus and flushing are also recognized side effects of opioids. The primary mechanism of these unpleasant effects involves opioid-induced histamine release. Morphine and meperidine have the most profound effect in inducing histamine release and tend to cause severe itching. The role of μ and κ opioid receptors in regulating sensations of pain and chronic pruritus on the skin has also recently been implicated (12). Opioid-induced histamine release is also the primary explanation in some patients who become hypotensive, particularly after intravenous morphine adminis-

tration. Studies suggest that fentanyl and its analogs do not cause histamine release and may be preferred in patients who are hemodynamically unstable (13,14).

Increasingly, neurotoxicity is being reported as a complication associated with opioid use (15-17). The reported symptoms include rigidity, myclonus, hyperalgesia, and occasionally localized seizure activity. The risk factors contributing to opioid-associated neurotoxicity may include older age, use of larger doses of opioids, severe malnutrition, and the presence of end organ failure. The physiological mechanism behind this effect is uncertain. Accumulation of neuroexcitatory opioid metabolite has been suggested to play a relevant role, especially in patients receiving chronic opioid therapy. There are no convincing data linking a specific agent with a significantly increased risk of neurotoxicity. When opioid-associated neurotoxicity is present, changing the type of opioid or reducing the dose may be useful in eliminating or reducing the severity of the symptoms (18–19).

OPIOID HYPERSENSITIVITY

Oftentimes, symptoms related to opioid-induced histamine release (e.g., pruritus, mild redness with no eruption) are mischaracterized as symptoms of allergy. True

opioid hypersensitivity, although rare, may occur in some patients. Anaphylactoid reactions have been reported with the use of intravenous morphine and codeine. Other symptoms that suggest a hypersensitivity reaction may include urticaria, severe skin rashes with eruptions, and severe hypoxia due to airway obstruction or pulmonary edema without respiratory depression. Specific IgE antibodies that react with morphine and codeine have been identified (20,21). As mentioned before, because of the distinctive difference in chemical structure among different groups of opioids, cross-hypersensitivity from one group to another is unlikely.

USE OF OPIODS TO MODULATE GITRACT FUNCTION

Most opioid alkaloids have several physiological effects on the GI tract. These effects include (7):

- 1. Alteration of tonic/segmental contractions;
- 2. Decreased motility and increased transit time;
- 3. Inhibition of endogenous secretions.

Therefore, many of these drugs can be used to manage excessive stool, fistula, or ostomy output. The two compounds with the most extensive experience in the management of diarrhea are loperamide and diphenoxylate. Together with difenoxin (marketed under the brand name Motofen as a combination product with 0.025 mg of atropine), a metabolite of diphenoxylate, these are the only opioids with an FDA-approved indication for the treatment of diarrhea. Loperamide is available over-the-counter without a prescription, whereas both diphenoxylate and difenoxin are prescription drugs and are classified as controlled substances (Schedule V and Schedule IV, respectively) according to the federal law because of their higher potential for abuse and physical dependence.

Loperamide

Loperamide is a derivative of meperidine. It exerts its antimotility action through binding to opioid receptors in the intestine as well as inhibiting calcium channels and calmodulin in intestinal smooth muscle. In addition, it inhibits fluid secretion by the colonic epithelial cells. Because of its limited oral bioavailability and

Table 3 Three major groups of commonly prescribed opioids

Morphine-like derivatives

- Morphine
- Codeine
- · Semi-synthetic derivatives:
 - Hydrocodone
 - Oxycodone
 - Hydromorphone
 - Heroin

Piperidine and phenylpiperidine group

- Meperidine
- Diphenoxylate
- Loperamide
- Fentanyl
- Sulfentanil
- Alfentanil
- · Remifentanil

Diphenylheptylamines

- Methadone
- Prophoxyphene

poor penetration across the blood-brain barrier, loperamide is a good antidiarrheal agent with minimal side effects, especially central nervous system-related effects. However, factors that alter the pharmacokinetics and pharmacodynamics of loperamide may exacerbate the untoward effects. Oral loperamide absorption can be increased by raising the pH in the gut. Therefore, patients with untreated gastric hypersecretion following massive intestinal resection may theoretically experience less clinical response. Inhibiting the function of an intestinal efflux pump, P-glycoprotein (Pgp), will increase the oral absorption and systemic effects of loperamide (22). P-gp is an energy-dependent (ATP) epithelial transporter evolved presumably as a defense mechanism to keep extrinsic, likely harmful compounds from entering and being retained by the body. It is a transmembrane glycoprotein extensively expressed in many organs, including the GI tract, kidney, and the brain. Thus, inhibition of P-gp may also increase the access of loperamide into the brain, potentially causing side effects similar to other systemic opi-

oids (23,24). Since many drugs can change the intestinal luminal pH and P-gp function, clinicians must carefully assess whether drug-drug interaction is the likely precipitating factor for the patient experiencing untoward effects (Table 4). Caution should also be exercised when loperamide is used concurrently with itraconazole or gemfibrozil, as these drugs increase plasma loperamide concentration and oral absorption by decreasing the elimination of loperamide from the body (i.e., decrease systemic clearance). Concurrent use of these two drugs will have an additive effect and further increase loperamide plasma concentration (25). This also implies that other drugs and nutrients with potent inhibitory effects on P-gp and drug metabolizing enzymes CYP2C9 and CYP3A4 can enhance the systemic effects of loperamide. In addition to the drugs listed on Table 4, caution should be exercised in patients receiving clopidogrel, delavirdine, efavirenz, fluconazole, metronidazole, and sulfonamide (e.g., Bactrim) antibiotics because of their documented inhibitory effect on CYP2C9 enzyme. The typical dose of loperamide is 4 to 8 mg daily (one-two tablets, every six-to-eight hours) as needed, taken one half hour prior to meals, with a maximal recommended daily dose of 16 mg.

Diphenoxylate and Difenoxin

Diphenoxylate is also a synthetic derivative of meperidine. At low doses, diphenoxylate primarily causes constipation. However, at high doses (e.g., over 40 mg daily), it produces typical opioid systemic effects such as euphoria and sedation and may lead to opioid dependence with chronic use. The typical dose for diphenoxylate is two tablets (or 10 mL) four times daily as needed for diarrhea. Each dose contains 2.5 mg of diphenoxylate plus 0.025 mg of atropine. Although atropine is an anticholinergic agent and may decrease GI secretion, the amount in the combination is too low to cause clinically significant antispasmodic effects other than acting as a deterrent for deliberate overuse and abuse. Excessive use of diphenoxylate/atropine combination can lead to serious cardiovascular symptoms such as palpitation and tachycardia due to the

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Table 4

Common inhibitors of P-gp and their therapeutic use. These drugs may potentially increase the likelihood of systemic side effects associated with loperamide use (47)

Antiarrhythmic

- Amiodarone
- Propafenone
- Quinidine

Antimicrobial

- · Clarithromycin
- Erythromycin

Vasopressin antagonist for treatment of hyponatremia

Conivaptan

Immunosuppressant

- Cyclosporine
- Tacrolimus

Calcium channel blocker

- Diltiazem
- Verapamil

Protease inhibitor

- Indinavir
- Nelfinavir
- Ritonaovir
- Saquinavir

Antifungal

- Itraconazole
- Ketoconazole
- Posaconazole

Tyrosine kinase inhibitor for treatment of certain cancers

Lapatinib

Antimalarial

• Mefloquine

Selective estrogen receptor modulator

Tamoxifen

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Table 5 Multifactorial processes that determine enteral drug absorption

- Dose
- Dosage form (e.g., elixir, tablet, suspension)
- Specific mechanisms that regulate the absorption process of an individual compound
- Presence and the activity of specific active transporters, length and quality of the functional gut
- Total absorptive surface area of the intestinal epithelium
- Possibly the magnitude of intestinal adaptation after resection

anticholinergic effect. Difenoxin is an active metabolite of diphenoxylate. It is rapidly and extensively absorbed after oral administration with peak effects occurred within 40 to 60 minutes in most patients. It is also marketed in combination with atropine to reduce its potential for abuse.

Systemic Opioids

Other systemic opioids may be used to treat severe diarrhea when the patient has failed to tolerate or respond to the first-line agents (i.e., loperamide and diphenoxylate/atropine); however, non-GI-related side effects are of particular concern and often limit their use for this purpose. The absolute minimal amount of functional small bowel required for drug absorption is not known. Patients who initially fail to adequately absorb drugs shortly after bowel resection may eventually respond to some oral medications. For example, therapeutic effects were achieved with oral cyclosporine and phenytoin in patients with jejunoileal bypass, although high doses were required (26,27). A multifactorial process determines the adequacy of enteral drug absorption. These factors may include dose administered, dosage form/pharmaceutical formulation, the presence and activity of specific active transporters, as well as length and functional status of the remaining intestine (Table 5). In patients with

severe secretory diarrhea who are unable to absorb medications from the GI tract, systemic opioids may be given parenterally (intravenous, intramuscular, or subcutaneous) as antidiarrheal agents.

The most accurate conversion method from loperamide or diphenoxylate to other systemic opioids such as morphine is unknown. The general recommendation is to use the lowest effective dose to control GI symptoms with minimal non-GI effects. The systemic opioids with more clinical experience as antidiarrheal agents are morphine and codeine. Although fentanyl and its related compounds can also decrease diarrhea, their high potency and lipophilicity may lead to very significant systemic effects such as sedation and respiratory depression before diarrhea is adequately controlled. The more potent synthetic opioid methadone also decreases GI motility to a similar magnitude as morphine and may be helpful in severe diarrhea, although clinical experience in using this drug to treat secretory diarrhea is very limited (28–31). Morphine, codeine, and methadone can also be administered subcutaneously. The dose conversion among the commonly used opioids is summarized in Table 6. It is important to emphasize again that loperamide, diphenoxlyate/atropine, and difenoxin/atropine are the only drug/drug combinations that have been approved by the FDA for the treatment of diarrhea. The risks versus benefits of systemic opioids, especially given by nonoral route, must be carefully determined and weighed before initiating therapy. More importantly, establishing a comprehensive monitoring plan for untoward side effects and conducting patient education are essential steps to increase patient's safety. Other factors that need to be taken into account, especially if these drugs are used in the outpatient setting, include insurance coverage, convenience, availability and feasibility of administration by the patient.

Paregoric, USP, also known as camphorated tincture of opium, is an oral liquid that contains 0.4 mg/mL of anhydrous morphine as its main active ingredient. *It is very important not to confuse paregoric with opium tincture*, tincture of opium, or deodorized tincture of opium because each of these products typically contains 10 mg/mL of morphine. In other words, given the same volume, the amount of opiate extract present in these products are 25-fold higher than that of paregoric.

Table 6 Dose conversion for systemic opioids (4,48,49)						
Drug Name ^a (examples of common brand names)	Parenteral Dose (mg) (IV/IM/SC)	Oral Dose ^b (mg)	Average Half-life (hours)			
Morphine sulfate (MS Contin, Oramorph SR, Roxanol, MSIR)	10	30	1.9 ± 0.5°			
Codeine (Generic product)	120	200	2.9 ± 0.7^{d}			
Fentanyle (Actiq, Duragesic, Fentora, Sublimaze)	0.1	N/A	3.7 ± 0.4^{f}			
Hydromorphone (Dilaudid, Palladone)	1.5	7.5	2.4 ± 0.6			
Methadone (Dolophine, Methadose)	3 to 5 ^g	10 ^g	27 ± 12 ^h			
Oxycodone (M-oxy, Roxicodone, OxyContin, ETH-Oxydose, OxyFAST)	N/A	20	2.6 ± 0.5^{i}			

Note: None of these drugs have received an FDA-approved indication for treating diarrhea.

- a. Dose conversion for paregoric and opium tincture not included because of lack of data and the presence of other compounds in the formulations. Accurate conversion is not possible.
- b. Some of the oral liquid formulations contain sorbitol or mannitol, which may worsen diarrhea. Since the exact amount of inactive ingredients are usually not published, check with the drug manufacturer for clarification if necessary.
- c. Minimal changes in cirrhosis and children; significantly increased in neonates.
- d. Affected by genetic polymorphism. Half-life and pharmacodynamic effects are prolonged in CYP2D6 poor-metabolizers.
- e. Fentanyl is also available as transdermal patches, buccal tablets, transmucosal lozenges. These formulations have not been studied in the management of diarrhea. Dose conversion is formulation specific and clinical response may be very unpredictable in patients with intestinal failure. Because of the differences in various drug delivery systems, a microgram-to-microgram approach in dose conversion from one formulation to another may not apply. Fentanyl buccal tablets contain mannitol (amount not disclosed by the manufacturer), which may cause diarrhea if large amount is ingested.
- f. Increased in cirrhosis and elderly patients.
- g. Conversion ratio varies depending on the dose; 1-to-1 dose conversion from PO to SC for methadone has been reported in cancer patients.
- h. Decreased in children.
- i. Value listed for immediate-release product.

Serious overdosing and patient fatalities have been reported in the literature due to product confusion. To minimize the risk of medication error, it is helpful to remember that opium tincture should be dispensed and administered with small droppers or oral syringes and each dose should not exceed 1 mL when treating diarrhea. The dose for paregoric, on the other hand, is 5 mL

to 10 mL (one-to-two teaspoons). Paregoric also contains glycerin, benzoic acid, and generally 45% alcohol. Current research suggests that the pharmacological actions of paregoric are not limited to the effect on opiate receptors, but a synergic action of all of its ingredients (32). Although paregoric elixir has been used to manage pain, GI discomfort, and other ailments since

the early eighteenth century, its use in the treatment of chronic diarrhea has diminished because of its high potential for addiction and abuse. Drugs with more limited effect on the brain such as loperamide and diphenoxylate are much preferred. According to one study, 4 mL of paregoric solution is approximately equipotent to one diphenoxylate/atropine tablet in controlling diarrhea (33).

Although codeine has an antidiarrheal effect, about 10% of an administered dose is metabolized by the enzyme CYP2D6 to morphine, which is a more potent compound (34). In patients with decreased CYP2D6 enzyme activity, either from genetics or drug interactions, the antidiarrheal effect of codeine will be less compared with patients having normal CYP2D6 activity (35). With the approval of a genotypic kit for several CYP enzymes by the FDA, it may help further individualize therapy in some cases (AmpliChip® CYP450 Test, Roche Diagnostics, N.A.). Consult with a pharmacist in patients with poor clinical response to codeine to assess whether genetic polymorphism or drug interaction might be playing a role.

Based on the findings from a few studies conducted in patients with mostly cancer pain, it has been suggested that transdermal fentanyl may cause less constipation compared with oxycodone and morphine (36–38). This led to the speculation that fentanyl may be an inferior antidiarrheal agent. However, two recent studies conducted in hospice patients showed comparable constipating effects among patients receiving transdermal fentanyl, long-acting morphine, and longacting oxycodone (39,40). It is not clear whether these studies reporting constipation as an adverse effect in cancer and hospice patients can be extrapolated to the treatment of chronic diarrhea, especially in patients with short bowel or intestinal failure. It is possible that the difference in the route of drug administration alters the effect on the GI tract. More importantly, in patients with severe intestinal dysfunction, the clinical response of orally administered medications can be very erratic and unpredictable.

Additional caution and consideration must be made when prescribing transdermal fentanyl to patients with extreme body weight. Due to the route of drug delivery and the lipophilic nature of fentanyl, obese patients or patients with significantly decreased

body fat mass (e.g., wasting diseases, severe proteinenergy malnutrition), may experience an altered pharmacokinetic profile of fentanyl leading to less predictable pharmacodynamic responses.

DRUG DOSING AND END ORGAN DYSFUNCTION

Renal Failure

The opioids most affected by renal function are morphine and meperidine. Morphine has several pharmacologically active metabolites, of which morphine-6-glucuronide (M6G) has been more extensively studied (41). The pharmacological activity of M6G to the μ -receptor is comparable to that of morphine. It has a potent analgesic effect as well as other less desired effects on the central nervous system. This highly active metabolite is mostly eliminated by the kidneys. In the presence of renal failure, especially acute renal failure, M6G would accumulate in the body and slowly distribute to the brain causing neurological side effects and even respiratory depression (42). Since acute renal failure secondary to dehydration may occur in the presence of severe diarrhea or vomiting, morphine should be used with extreme caution in these patients until they are adequately fluid resuscitated and a stable fluid status is achieved. Close monitoring of systemic side effects is crucial, and in some cases, smaller doses may be needed to minimize toxicity. The synthetic opioid meperidine should be avoided in patients with renal impairment due to the accumulation of the neurotoxic metabolite that can provoke seizures.

Hepatic Dysfunction

The pharmacokinetics of most opioids, including loperamide and diphenoxylate, has not been extensively investigated in patients with hepatic disease. Since hepatic biotransformation plays an important role in the deactivation of most of these drugs, it is reasonable to believe that patients with hepatic dysfunction, such as those with chronic liver failure or documented cirrhosis (especially Child-Pugh class B or C,), or severe cholestasis, may experience more pronounced pharmacological response, including untoward effects (43,44). Because of this uncertainty, lower doses should be used

Table 7

Antidiarrheal Medications Commonly Used in Short Bowel Syndrome

General Guidelines

- Give 30-60 minutes before meals or snacks, but not more than every 6 hours.
- If patient gets up in the middle of the night and does not mind taking a medication, then dose every 6 hours and take advantage of a time when foods/fluids are not competing for absorptive surface area.
- Use immediate-released oral tablets, or elixir forms; avoid sustained-release products.
- Titrate up to maximal dose or the maximal tolerated dose by individual patient based on side effects and then some if necessary; try increasing doses every 2-4 days.
- Increase dose until the stool consistency is adequate for patient or the side effect becomes unacceptable to the patient/unable to perform activities of daily living—whichever comes first.

Antidiarrheals—Oral/Enteral

Loperamide

 Initial, 2–6 mg up to QID, may be increased up to 12–24 mg at a time in patients with disrupted entero-hepatic circulation

Diphenoxylate/Atropine

• 2.5–5.0 mg up to QID

Codeine

• 15–100 mg up to QID

Morphine

• 2.0–20 mg up to QID

Tincture of Opium*

0.3–1.0 mL up to QID

Paragoric*

• 5.0-10 mL BID-QID

For Oral/Enteral:

It is important to remember that codeine, morphine, and methadone equivalents are not exact and different references have different approximate equivalents.

1 mL opium tincture = 25 mL Paregoric = 65 mg codeine = 10 mg morphine = 5 mg methadone = 5 mg oxycodone.

Note:

 Avoid the use of "drops" to avoid dosing errors; both paregoric and tincture of opium are 20 drops/mL; however, the syringe sizes differ*

*In general 1 mL = 20 drops for most medications; however, due to inaccuracies of droppers, this type of dosing is not recommended, especially in light of easy access to graduated syringes. Adapted and used with permission from: Parrish CR. The Clinician's Guide to Short Bowel Syndrome. *Pract Gastroenterol*, 2005;XXIX(9):67.

initially in these patients. Based on the pharmacokinetic profiles, loperamide is preferred over diphenoxylate. Diphenoxylate has an active and more potent metabolite, difenoxin. In the presence of hepatic disease, it is possible that excessive accumulation of both diphenoxylate and difenoxin may occur, which can lead to more profound systemic side effects. Shorter acting

agents such as fentanyl and hydromorphone are preferred over those with longer elimination half-life, such as methadone. Meperidine should be avoided because of the risk of accumulating nor-meperidine, a pharmacologically active but neurotoxic metabolite. Close monitoring for systemic side effects is essential to ensure the safety of these drugs.

Impact of Obesity

Since loperamide and diphenoxylate are ususally poorly absorbed, obesity is expected to have little impact on their disposition and pharmacodynamic effects. Both loperamide and diphenoxylate are found to be equally effective in reducing diarrhea in obese patients following jejuno-ileostomy (45). Increased accumulation in the body is probably unlikely unless severe hepatic and/or renal failure is present. Conversely, the pharmacokinetics of other systemic opioids can be significantly altered by obesity. This is especially the case for the highly lipophilic drugs such as fentanyl. Increased volume of distribution (i.e., larger total amount of the drug present throughout the body) and prolonged elimination half-life has been reported with fentanyl and its analogs in obese patients. These changes in pharmacokinetic parameters translate into increased and prolonged systemic effects (46). Morphine has multiple active metabolites, therefore the pharmacodynamics are difficult to predict in obese patients; the pharmacokinetics of morphine in this patient population have yet to be formally investigated.

Treatment Strategy

Generally speaking, when using opioids, the goal of therapy should be to use the lowest effective dose with minimal side effects. Because of its safety profile, loperamide should be considered as the first-line agent in treating diarrhea and excessive ostomy output. If the desired clinical effect cannot be accomplished in twoto-three days with maximal dosing, diphenoxylate may be added at low doses. The maximal dose of diphenoxylate should be determined individually based on clinical response as well as side effects. If intravenous opioid is to be administered, discontinue loperamide and diphenoxylate first and then start the systemic agent at low doses. It is important to remember that the doses between parenteral and oral routes are different. End organ function may also affect the magnitude of systemic adverse effects. If the patient develops intolerance or hypersensitivity, switching to a different class of agent is usually tolerated. If overdose is suspected, the opioid should be discontinued immediately. An opioid receptor antagonist such as naloxone can be used to acutely reverse the effect of systemic opioids;

however, the duration of action is short-lived and may transiently trigger withdrawal symptoms such as pain, diarrhea, excessive sweating, lacrimation, rhinorrhea, anxiety, restlessness, and muscle aches. For a summary of typical dosing of opiods in patients with intestinal failure or short bowel syndrome, see Table 7.

SUMMARY

Opioids are highly effective drugs in controlling pain, as well as in managing many GI-related disorders. Due to its low oral bioavailability, loperamide and diphenoxylate are usually safe to use with minimal adverse effects. However, the systemic effects, especially on the central nervous system, may be enhanced or exacerbated by drug-drug interactions. Loperamide is preferred over diphenoxylate in severe hepatic dysfunction. If there is a lack of response to oral agents, or efficacy is likely to be limited by severe intestinal failure with consequent malabsorption (i.e., extreme short gut, post-op hypersecretory, etc.), systemic opioids should be tried. Careful monitoring for systemic side effects such as drowsiness, sedation, and respiratory depression, especially during the initiation and dose titration phase, are crucial to minimize the risks associated with these drugs.

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