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Short Bowel Syndrome in Adults – Part 4B

A Guide to Front Line Drugs Used in the Treatment of Short Bowel Syndrome



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As you may recall from Part IV-A of this series, a 64-year-old woman is hospitalized with hypotension, chronic diarrhea (6-10 per day in the last 4 weeks), fatigue and general malaise. Seven weeks ago, she was hospitalized with acute abdominal pain and severe nausea. Further work-up revealed acutemesenteric infarction due to a superior mesenteric artery thrombus and she underwent extensive resection of the ischemic bowel leaving her with about 100 cm of small bowel from the ligament of Treitz anastomosed to the proximal transverse colon. She was discharged from the hospital 2 weeks later on home parenteral nutrition (PN). Her weight is down 6 kg since hospital discharge 5 weeks ago. In addition to PN, she also takes loperamide 2 mg TID as needed (she has not been using it because “it doesn’t help”), cholestyramine 4g BID, mirtazapine 15 mg daily, levothyroxine 0.075 mg daily and oral glutamine 30g daily. Famotidine, 40 mg, has been added to her PN. Stool output, which is watery and without blood, ranges from 2500 to 3000 mL daily. She is not eating much as she is so depressed and uncomfortable and “it just comes right out anyway”. She is afraid to leave her house for fear of “having an accident”. Part 4B of this 5-part series on SBS focuses on conventional anti-motility agents used in the treatment of short bowel syndrome that will allow you to help this woman control her diarrhea and improve her quality of life.

INTRODUCTION

Chronic Diarrhea

While gastric hypersecretion is a transient complication in SBS, chronic diarrhea is often a long-term and sometimes quite disabling complication experienced by most patients and requires continued intervention and monitoring. A recent study involving patients with SBS found that chronic, uncontrolled diarrhea has a more negative

impact on quality of life than home PN therapy.¹ Therefore, optimizing the antidiarrheal regimen is a critical component in the care for patients with SBS. Established antidiarrheal regimens in the management of SBS are summarized in Table 1.

Antimotility Agents

Since opioid receptors are widely distributed in the GI tract and play a key role in the regulation of GI tract motility, secretion, and sensation,² opioids should be considered the first-line antimotility therapy in the treatment of chronic diarrhea in patients with SBS. Additionally, opioid receptors also regulate chloride secretion and luminal water movement in the colon.

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Opioid agonists therefore also exert an antisecretory effect on the colon. High-level clinical evidence supporting their use is unavailable in the literature. This absence of evidence, however, is not evidence of lack of clinical utility. The lack of high-level published data can be explained by the fact that these compounds have been available for use for decades and their role in clinical management has generally been accepted. There is also a lack of more established alternative therapy in managing patient's symptoms. Additionally, there is no financial incentive for drug manufacturers to conduct such clinical trials. Opioid derivatives used as antimotility agents can be loosely categorized as locally-acting agents with low systemic effects (e.g., loperamide, diphenoxylate) and systemic agents (e.g., codeine, morphine).

Loperamide (e.g., Imodium A-D)

Loperamide is one of the most widely used over-the-counter anti-diarrheal drugs. It is a synthetic opioid. With low systemic absorption and poor penetration across the blood-brain barrier, loperamide is a safe antidiarrheal agent with minimal systemic side effects. Its antimotility action is mediated by both binding to opioid receptors in the intestine as well as inhibiting calcium channels and calmodulin in intestinal smooth muscle.³ It also has an antisecretory effect on the colonic epithelial cells.⁴ Since the oral bioavailability is negligible, loperamide is usually well-tolerated; however, factors that alter the pharmacokinetics and pharmacodynamics of loperamide may potentially exacerbate the untoward effects.

In SBS, an initial dose of 4 mg (2 capsules or tablets, or 30 mL) every 6 to 8 hours is recommended. Loperamide should be taken 30 to 60 minutes prior to a meal and again at bedtime. While the maximal recommended daily dose is 16 mg in generally healthy individuals, in the SBS patient, a dose up to 8 mg every 6 hours (32 mg total) may be needed. In patients with inadequate response (continued watery diarrhea in spite of taking 8 to 16 mg per dose; total dose at 32 mg/day or higher), other pharmacotherapeutic approaches, such as narcotics, etc., should be considered.

Diphenoxylate (e.g., Lomotil®) and Difenoxin (Motofen®)

Diphenoxylate is also a synthetic opioid and likely exerts its antimotility effect by binding to the opioid receptors in the intestine. At low doses, diphenoxylate

primarily has antimotility effects; however, at high doses (e.g., over 40 mg daily), it produces typical opioid systemic effects such as euphoria and sedation suggesting an increased systemic effect. Difenoxin is an active metabolite of diphenoxylate. It is rapidly and extensively absorbed after oral administration with peak effects occurring within 40 to 60 minutes in most patients. Although commercially available in the U.S., it is less commonly used than diphenoxylate.² To reduce the abuse potential for these drugs, they are formulated with the anticholinergic agent atropine. Excessive use of diphenoxylate/difenoxin-atropine combination can lead to symptoms ranging from unpleasant sensations similar to those with cholinergic discharge, to serious cardiovascular symptoms such as palpitation and tachycardia.

The typical dose for diphenoxylate is two tablets (or 10 mL) four times daily as needed; generally before meals and at bedtime. Although atropine is an anticholinergic agent and may decrease GI secretion, the amount in the combination is too low to cause clinically significant side effects other than acting as a deterrent for opioid abuse.

Given the extensive clinical experience, both loperamide and diphenoxylate can be considered as first-line antimotility agents in SBS. Based upon both the pharmacokinetic and side effect profile, loperamide is usually considered the preferred agent for initial therapy.

Paregoric

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. Paregoric also contains glycerin, benzoic acid, and generally 45% alcohol. Although paregoric elixir has been used to manage pain, GI discomfort, and other ailments since the early eighteenth century, its role in the treatment of chronic diarrhea has diminished considerably because of its high potential for addiction and abuse. Drugs with more limited effect on the brain such as loperamide and diphenoxylate are preferred. According to one study, 4 mL of paregoric solution is approximately equipotent to one diphenoxylate/atropine tablet in controlling diarrhea.⁵

Opium tincture

Opium tincture, USP or deodorized tincture of opium typically contains 10 mg/mL of morphine. One of the

Table 1. Antidiarrheal Agents Used In Short Bowel Syndrome

Drug	Dose/Form/ Frequency	Comments
Imodium® (loperamide) Tablet, Liquid	4 mg as initial dose, followed by 2 – 8 mg QID, titrated according to response. A daily dose of 16 to 64 mg/day may be needed for SBS.	<ul style="list-style-type: none"> Limited CNS effects Enterohepatic circulation of loperamide can be disrupted with extensive resection of ileum and up to 16 mg per dose may be needed.¹²⁻¹⁴
Lomotil® (diphenoxylate/atropine) Tablet, Liquid	2.5 – 5 mg up to every 6 hours, maximal recommended daily dose = 20 mg of diphenoxylate. Oral liquid strength = 0.5 mg/mL or 2.5 mg/5mL	<ul style="list-style-type: none"> Atropine crosses blood brain barrier; in elderly and others may be problematic Atropine added to discourage drug abuse by producing anticholinergic side effects if > 10 tablets ingested
Tincture of Opium (Laudanum) Liquid Only	0.3–2.0 mL up to QID (avoid using droppers due to the various sizes—safer to dose in mL)	<ul style="list-style-type: none"> Not available at all pharmacies May not be covered by patient's insurance plan Requires measuring out into dropper/mL <ul style="list-style-type: none"> Caution in those with poor eyesight High cost (see Table 2) Has a very objectionable taste
Codeine Tablet, Liquid	15 – 60mg up to QID	<ul style="list-style-type: none"> Avoid use of codeine/acetaminophen combinations due to the risk of acetaminophen toxicity CYP2D6 genotyping should be considered
Morphine immediate-release	2 – 10mg QID	<ul style="list-style-type: none"> Use with caution in patients with renal impairment or fluid disorders May cause histamine release and pruritus Sustained-release morphine may not work in patients with severely short intestine Suggested doses are based on analgesic potency; titrate doses per clinical response
<p>For Oral/Enteral: It is important to remember that the dose conversion between codeine, morphine, and other opioid agents is based on analgesic potency. The actual doses for diarrhea/antisecretion may vary and should be titrated based on an individual's response.</p> <p><i>Approximately:</i> 1 mL opium tincture = 65 mg codeine = 10 mg morphine</p> <p>Note: 1. All opioid analgesic agents can have an antidiarrheal effect 2. Avoid the use of “drops” to prevent dosing errors; use graduate oral syringes instead</p>		

12. "Can high dose loperamide be used to reduce stoma output?" Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals: <http://www.evidence.nhs.uk/search?q=%22Can+high+dose+loperamide+be+used+to+reduce+stoma+output%22>
13. Nightingale J, Woodward JM on behalf of the Small Bowel and Nutrition Committee of the British Society of Gastroenterology. Guidelines for management of patients with a short bowel. *Gut* 2006;55(Suppl IV):iv1–iv12.
14. Forbes A. Intestinal failure and short bowel syndrome. *Medicine* 2007;35(4):231-235.

most dangerous medication errors is the confusion between paregoric (especially if labelled as camphorated tincture of opium) and opium tincture. Given the same volume, there is a 25-fold difference in the amount of opiate extract between these products. If prescribed incorrectly, serious overdosing and fatalities can result. 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 1-2 mL, every 6-8 hours when treating diarrhea. Because safer and possibly more

effective alternatives such as loperamide are available, both paregoric and opium tincture have very limited role in the management of SBS. See Tables 1 and 2 for clinical considerations and cost when prescribing opium tincture.

Codeine and Morphine

Both codeine and morphine can be used as antitomotility and antisecretory agents in patients with SBS as both compounds bind to the opioid receptors in the GI

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tract leading to decreased GI secretion and increased orocecal transit time. Although codeine has an antidiarrheal effect, about 10% of an administered dose is metabolized by the enzyme CYP2D6 to morphine, a more potent metabolite.^{6,7} In patients with decreased CYP2D6 enzyme activity (i.e., poor metabolizers), either from genetics or drug interactions (e.g., CYP2D6 inhibitors such as citalopram, fluoxetine, paroxetine), the antidiarrheal effect of codeine could be reduced compared with patients having normal CYP2D6 activity.⁸ Conversely, DNA variations also occurs in a subgroup of patients resulting in more active CYP2D6 enzyme activities. These “ultra-rapid metabolizers” convert codeine to morphine faster and more completely than in other people and are more likely to have higher than normal amounts of morphine in their blood after taking codeine. High levels of morphine can result in respiratory depression and failure, which may be fatal.

Data from an international clinical pharmacogenetics databank show that 77-92% of the population are phenotypically “normal” CYP2D6 metabolizers. The allele frequency for poor-metabolizer is about 5-10% and ultra-rapid metabolizer between 1-2%.⁹ Therefore, codeine is generally a safe and effective treatment option for a majority of the patients as long as the dose is initiated cautiously and patient-specific side effects are carefully monitored (e.g., sedation, rash, nausea, respiratory depression). In at-risk patients, such as children, patients with adverse reactions or unpredictable response to codeine previously, or if there is concern about a particular patient’s CYP2D6 phenotype based on his/her clinical response/drug dosing to other CYP2D6 substrates (e.g., tricyclic antidepressants), CYP2D6 genotyping should be performed before drug initiation to optimize the patient’s codeine regimen and minimize serious adverse events.⁷ Genotyping can be performed using tissue samples obtained from either buccal swabs or whole blood samples. Before ordering the test, clinicians should discuss with the laboratory personnel in their institution to ensure that samples are properly collected so the test results can be accurately documented in the patient’s medical record. Pharmacogenetic testing is now covered by most insurance companies.

Since both codeine and morphine are well-absorbed, systemic side effects are the primary concerns when used as antimotility agents. Renal failure can increase the accumulation of morphine and its active metabolites

and potentially increases the risk of experiencing systemic side effects; in this situation, start at one-half the usual dose.

Considerations when Using Opioid-based Antidiarrheal Agents

When a patient with SBS (or non-SBS high ostomy output) is showing inadequate response to aggressive dosing of loperamide or diphenoxylate, clinicians often find themselves in a clinical conundrum – When should a systemic opioid be used? Should I add it to the other antidiarrheal or should I stop the other drug first? Does the bowel anatomy determine whether or which opioid to use? What is the treatment endpoint? Would the use of opioid be in violation of federal regulations? Could drug addiction become a problem for the patient? How much opioid can I prescribe? In the following, we attempt to provide some guidance and clarification on these points.

Threshold to Start Systemic Opioid

There is no established threshold and high quality research is sorely needed to guide practice decisions. Based on the pharmacology and physiology, it is our opinion that starting a systemic opioid drug is reasonable when the following criteria are met:

- The patient has received the maximal recommended doses of the first-line antimotility agents and:
 - Stool output remains over 1500 mL per day, OR
 - Recurrent admissions for dehydration with stool/ostomy output < 1500mL, OR
 - The reduction of stool output from baseline is less than 50%, OR
 - The patient remains dehydrated with persistent orthostatic hypotension, OR
 - The patient develops intolerable side effects from the first-line agent(s) that are unrelated to the systemic side effects of narcotics (e.g., bloating), OR
 - The total pill count reveals that it is unreasonable to ask the patient to take 16-24 pills to slow their gut, when potentially a single 30 mg tablet of codeine QID will be as effective, or even more so.

Table 2. Commonly Used Narcotics for Short Bowel Syndrome

Store	Product	Form	Dose	Frequency	Amount/day	\$ Per month (cash price)*
UVA Pharmacy	Codeine	Tablets	60mg	QID	240mg	67.00
	Codeine, liquid	Liquid	10mL		40mL	408.05
	Tincture of Opium	Liquid	1mL		4mL	780.00
Wal-mart	Codeine	Tablets	60mg	QID	240mg	169.88
	Codeine, liquid	Liquid	10mL		40mL	301.78
	Tincture of Opium	Liquid	1mL		4mL	Not available**
Walgreen's	Codeine	Tablets	60mg	QID	240mg	101.99
	Codeine, liquid	Liquid	10mL		40mL	316.79
	Tincture of Opium	Liquid	1mL		4mL	615.99
CVS	Codeine	Tablets	60mg	QID	240mg	126.99
	Codeine, liquid	Liquid	10mL		40mL	Not available**
	Tincture of Opium	Liquid	1mL		4mL	Not available**

Note: Codeine tabs come in 15mg, 30mg, 60mg. Liquid codeine = 30mg/5mL. Tincture of opium should always be dosed in mL, not drops due to significant variation of dropper sizes available and potential for error in dosing.

*All costs are cash price as of March 2014 **Not available means they cannot get it at all, even by special order

- The patient cannot tolerate or has developed adverse events from the first-line antimotility agents;
- There are no clinical contraindications to using systemic narcotics (e.g., allergic reactions, delirium, underlying respiratory problem such as obstructive sleep apnea); and
- The patient has no known history of drug abuse (although this should not be an absolute contraindication; 1-2 septic episodes on PN/IV fluids and the potential for recurrent abuse may be the lesser of evils).

Is there benefit to use both loperamide and systemic narcotics at the same time? What if a patient does not have an ileum – can loperamide still be utilized?

Opioids interact and regulate the enteric nervous system primarily through 3 different opioid receptors – μ , δ , and κ receptors. Binding of opioids to these receptors results in a decrease in intestinal motility and secretion. Loperamide is only selective to μ opioid receptors. Therefore, the addition of the non-selective agonist, such as morphine, may provide a synergistic effect in reducing GI motility and secretion, especially in patients with insufficient response to loperamide alone. The combined use of loperamide and codeine was demonstrated in a randomized, controlled study to be safe and exert a synergistic effect on ileostomy output.¹⁰

Although animal data have shown that loperamide has a more profound effect in the small intestine than in the colon, it can still be used in patients with a significant portion of the ileum removed because opioid receptors are also present in the colon.^{3,11} Loperamide will provide some antisecretory effect and can reduce the frequency and severity of diarrhea.

What is the treatment endpoint and duration of therapy?

The treatment endpoint is patient-specific but should be directed to improving the frequency and severity of diarrhea and preventing dehydration. The patient should be assessed regularly for treatment response and side effects. The goal when using a narcotic agent as an anti-diarrheal is to use the lowest effective dose to achieve the overall therapeutic endpoint. It is reasonable to titrate the narcotic down every few weeks as long as the patient is clinically stable.

What are some of the reasons clinicians give for not using narcotics in the treatment of patients with short bowel syndrome?

- Risk of narcotic addiction
 - This begs the question, is this risk higher than the risks involved with keeping a patient on PN or IV fluids requiring a central venous catheter?

The goal of using any narcotic drug is to use the minimal effective dose and continually reassess the need for this therapy. The risk of causing narcotic addiction in a patient with no history of substance abuse is minimal.

- Drug abuse potential
 - There is no doubt that a clinician should carefully select the “best” patients to receive narcotic therapy. Patients with active drug seeking or narcotic abuse behavior should generally not be considered appropriate candidates to receive prescription narcotic drugs as antimotility, antidiarrheal agents. At the same time, clinicians must carefully assess whether it is appropriate to discharge a patient with a documented history of narcotic abuse with a central catheter in place even though the intention of the catheter is for IV fluids or PN.
- Narcotics require a monthly prescription to be handed directly to the patient. Prescriptions cannot be faxed/mailed directly to the pharmacy.
- There are concerns that using high doses of narcotics may result in an audit from the Drug Enforcement Agency (DEA). While it may be easy to support this practice from a busy physician’s office that sees a fair number of SBS patients, it may require the office to be closed down while the audit is completed.

Overall, there is much misconception and lack of understanding among healthcare providers about the use of narcotic agents in the management of chronic diarrhea. Although this indication is an off-label use of narcotic drugs, the rationale is well-supported by science and the efficacy is supported by clinical literature. In the process of evaluating the appropriateness of narcotic therapy, clinicians should follow federal and state regulations, exercise good clinical judgment in patient selection, and implement a patient-specific monitoring plan. Our experience suggests that a carefully executed management plan with low-dose narcotic therapy can reduce PN use and unnecessary hospitalizations.

SUMMARY

Anti-diarrheal agents are part of the cornerstone of therapy in the treatment of short bowel syndrome. If not well controlled, not only are hydration and nutrient utilization at risk, but also overall quality of life is seriously threatened. It is of particular importance in the SBS population to consider the site of absorption, formulation, frequency, and timing of each drug, as well as cost and availability before it is ordered. Setting and monitoring endpoints for each intervention (i.e., how long you will give each intervention time to achieve efficacy or not), is also fundamental. Keep in mind that there are only so many hours in the day, and patients need to fit “life” in between all their medications, meals/snacks and fluids. When the “Total Pill Count” of the lesser gut slowing medications exceeds a certain number, it is time to use stronger agents that will not only be more effective, but also require fewer pills per day. ■

References

1. Winkler MF, Hagan E, Wetle T, et al. An exploration of quality of life and the experience of living with home parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2010;34(4):395-407.
2. Chan LN. Opioid Analgesics and the Gastrointestinal Tract. *Practical Gastroenterology* 2008;XXXII(8):37.
3. Stoll R, Ruppin H, Domschke W. Calmodulin-mediated effects of loperamide on chloride transport by brush border membrane vesicles from human ileum. *Gastroenterology.* 1988;95(1):69-76.
4. Epple HJ, Fromm M, Riecken EO, et al. Antisecretory effect of loperamide in colon epithelial cells by inhibition of basolateral K⁺ conductance. *Scand J Gastroenterol.* 2001;36(7):731-7.
5. Barowsky H, Schwartz SA. Method for evaluating diphenoxylate hydrochloride. Comparison of its anti-diarrheal effect with that of camphorated tincture of opium. *JAMA.* 1962;180:1058-1061.
6. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype. *Clin Pharmacol Ther.* 2012;91(2):321–326.
7. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. *Clin Pharmacol Ther.* 2014;95(4):376–382.
8. Mikus G, Trausch B, Rodewald C, et al. Effect of codeine on gastrointestinal motility in relation to CYP2D6 phenotype. *Clin Ther Pharmacol.* 1997;61:459-466.
9. Hicks JK, Swen JJ, Thorn CF, et al; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013;93(5):402-8.
10. King RFGJ, Norton T, Hill GL. A double-blind cross-over study of the effect of loperamide hydrochloride and codeine phosphate on ileostomy output. *Aust N Z J Surg* 1982;52:121-124
11. Galligan JJ, Akbarali HI. Molecular Physiology of Enteric Opioid Receptors. *Am J Gastroenterol.* 2014;2(1):17-21.