Therapeutic Reviews

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Stimulant Laxatives and Opioid-Induced Constipation *AHFS 56:12*

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Choice of Laxatives

The prescription of laxatives is influenced by marketing, fashion, availability and cost, and there is wide variation in their use among clinicians and across countries.[1,2] With the availability of polyethylene glycols (macrogols) and the more recently introduced methylnaltrexone, it is even more important that clinicians understand both the pathophysiology of opioid-induced constipation, and the predominant mechanisms of action of commonly prescribed laxatives.[3,4] Based on this understanding, clinicians should develop a simple, logical and cost-effective approach which optimizes the dose of a stimulant laxative and avoids the concurrent prescription of multiple different types of laxatives as far as possible.[5–8] Because of its wide availability, low cost and recently published data, the example protocol at the end of this article recommends the initial use of senna alone.[9,10]

Constipation and Advanced Illness

Constipation is common in advanced illness.[11,12] The key feature is reduced water in the feces, which results in the passage of hard feces infrequently and with difficulty. Fecal dehydration occurs because of prolonged bowel transit time (allowing more absorption of water by the GI tract), or a reduced ability of the stool to retain water (because of reduced fiber content). Constipation is more common in immobile patients with small appetites and those receiving constipating drugs, particularly opioids.[6,13]

Opioids cause constipation by increasing ring contractions (segmenting activity), decreasing propulsive intestinal activity, and by enhancing the resorption of fluid and electrolytes.[13,14] Whether or not tolerance occurs is unclear; however, opioid-related constipation generally persists in patients with advanced illness and its under-treatment is associated with a reduced quality of life, and may even result in opioid discontinuation.[15-17]

The management of constipation aims to restore the amount of water in the feces by:

- reducing bowel transit time (exercise, stimulant laxatives, osmotic laxatives)
- increasing fecal water (osmotic laxatives, stimulant laxatives)

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• increasing the ability of the feces to retain water (fiber, docusate, osmotic laxatives).

For those with advanced illness, exercise and increased dietary fiber are often not feasible options.[18] Thus, generally, all such patients receiving an opioid regularly also will need a concurrent laxative.[12,19]

Not all patients respond satisfactorily to oral laxatives, and additional approaches are required, e.g., parenteral methylnaltrexone, suppositories or enemas. Data are limited, but suggest that rectal intervention is required by one-quarter to one-third of patients under the care of a palliative care service, and is highest in inpatients.[20–22] Sometimes rectal measures are used electively, e.g., in bedbound frail elderly patients, or patients with paralysis (paraplegia, tetraplegia).[20,21]

Mode of Action and Classification

Laxatives are generally classified according to their predominant action (Box).[23,24]

Stimulant laxatives act through direct contact with the submucosal (Meissner's) plexus and the deeper myenteric (Auerbach's) plexus, resulting in predominantly a motor but also a secretory effect on the bowel. Stimulant laxatives provide a logical approach to the correction of opioid-induced constipation because their motor and secretory effects help counteract the opioid-induced increase in ring contractions (segmenting activity), decrease in propulsive intestinal activity and enhanced resorption of fluid and electrolytes. However, in practice, a combination of a stimulant laxative and a fecal softener is still often prescribed.[4,12,25,26]

Box. Classification of commonly used laxatives

Bulk-forming agents (fiber)
Methylcellulose, e.g., Celevac®
Psyllium (ispaghula) husk, e.g., Fybogel®, Metamucil®, Regulan®
Sterculia, e.g., Normacol®

Fecal softeners
Surface-wetting agents (detergents/surfactants)
Docusate sodium
Poloxamer 188, e.g., in co-danthramer (UK)
Lubricants
Arachis oil
Mineral oil (liquid paraffin)

Osmotic laxatives
Magnesium salts, e.g.,
• liquid paraffin and magnesium hydroxide oral emulsion BP
• magnesium hydroxide suspension (Milk of Magnesia®)
• magnesium sulfate (Epsom Salts)
Lactulose and other non-absorbable sugars
Polyethylene glycols (macrogols)

Stimulant laxatives
Acting on small and large bowel
Bisacodyl
Dantron (in co-danthramer and co-danthrusate, UK)
Acting on large bowel
Senna
Sodium picosulfate (UK)

Lactulose, an osmotic laxative, increases the volume of fluid reaching the large bowel where it is also converted by bacterial fermentation into short-chain fatty acids and gases. The resultant lowering of pH and/or release of peptides may stimulate bowel motility.[27] Docusate acts predominantly as a detergent/surfactant, i.e., lowers surface tension, thereby enabling water and fats to penetrate into the substance of the feces. It also may inhibit water absorption in both the small and large bowel.[28]

Characteristics of Stimulant Laxatives

Senna (sennosides) is a naturally-occurring plant-derived anthranoid. It is an inactive glycoside which passes unabsorbed and unchanged through the small bowel and is hydrolyzed by *bacterial glycosidases* in the large bowel to yield active compounds.[29] Thus, senna has no effect on the small bowel but becomes active in the large bowel. Differences in bacterial flora may be partly responsible for differences in individual responses.

Dantron (not available in the USA), a synthetic anthranoid, is not a glycoside and has a direct action on both small and large bowel.[30] Whereas systemic absorption of senna or its metabolites is negligible, dantron is absorbed to some extent from the small bowel with subsequent significant urinary excretion (see Undesirable Effects). Combination products with docusate or poloxamer 188 have been used, and are still widely used by palliative care services in the UK. However, because of concerns regarding carcinogenicity, UK licences for laxatives containing dantron are restricted to constipation in terminally ill patients (see Cautions).

Phenolics such as bisacodyl and sodium picosulfate are also pro-drugs. They are hydrolyzed to the same active metabolite but the mode of hydrolysis differs.[29] Bisacodyl is hydrolyzed by *intestinal enzymes* and thus acts on both the small and large bowel. When applied directly to the intestinal mucosa in normal subjects, bisacodyl induces powerful propulsive motor activity within minutes.[31] Bisacodyl is often given by suppository. The laxative effect is the result of local direct contact with the rectal mucosa after dissolution of the suppository, and after activation by hydrolysis. Thus, the minimum time for response is generally >20 min.[32] In contrast, sodium picosulfate is hydrolyzed by *colonic bacteria* and its action is thus confined to the large bowel. Its activity is potentially more uncertain because it depends on bacterial flora.

Phenolphthalein is another stimulant laxative, and is present in some proprietary laxatives. Phenolphthalein exists in two forms: white and yellow. The yellow form contains several impurities produced during manufacture. These impurities enhance the laxative effect of phenolphthalein so that the comparable dose of the yellow form is only two-thirds that of the pure white form. The active constituent of phenolphthalein is released in two stages: by metabolism in the liver and subsequently in the colon, and it probably undergoes enterohepatic circulation.[33] Some people respond to small doses. However, it can cause a drug rash (see Undesirable Effects) and is generally not considered a first-line laxative.

Onset of action

Bisacodyl tablets 6–12 h; suppositories 20 min–3 h (mean 1 h).[32]
Dantron 6–12 h.
Senna 6–12 h.
Sodium picosulfate 6–24 h (median 12 h).[34]
Note: the latent period may be longer in patients taking opioids.

Evidence Base

Several RCTs of stimulant laxatives have been completed in patients with advanced illness receiving palliative care:[12]

- senna vs. lactulose[35]
- senna vs. misrakasneham (an Ayurvedic herbal remedy)[36]
- senna and lactulose vs. co-danthramer (dantron and poloxamer)[37]
- senna and lactulose vs. magnesium hydroxide and liquid paraffin.[38]

A significant difference between treatments was seen only in the third RCT.[37] The combination of senna and lactulose was significantly better at relieving constipation than co-danthramer. However,

some centers discourage the use of lactulose because of its relative expense and its propensity for causing gastrointestinal discomfort.

Two non-blinded dose-ranging studies are also of interest. In cancer patients on an oncology unit, most of whom were receiving opioids, a bowel protocol based on senna alone was as effective as one based on senna and docusate (and more so in patients admitted for palliative care).[9] Secondly, for opioid-induced constipation in patients with advanced illness receiving palliative care, sodium picosulfate alone yielded a satisfactory result in 15/20 patients (normal stool consistency, no need for enemas, suppositories or manual evacuation, and few undesirable effects).[34] Thus, for opioid-induced constipation in palliative care, a reasonable approach would be to optimize the dose of a stimulant laxative before adding a surface wetting agent or an osmotic laxative.

Methylnaltrexone, a peripherally-acting opioid antagonist, represents an alternative (and potentially more specific) approach to the management of opioid-induced constipation (see Quick Practice Guide).[39,40] A recent Cochrane review concluded that there is some evidence that, compared with placebo, methylnaltrexone is effective in patients taking opioids who have not had a good response to conventional laxatives.[12] However, methylnaltrexone requires subcutaneous administration, is relatively expensive, and may not eliminate the need for other laxatives.[41]

Cautions

Because very high doses in rodents revealed a carcinogenic risk,[42–44] UK licenses for laxatives containing dantron are limited to constipation in terminally ill patients.

Undesirable Effects

Laxatives may cause intestinal colic or diarrhea. Bisacodyl suppositories may cause local rectal inflammation. Dantron discolors urine, typically red but sometimes green or bluish. Prolonged contact with skin (e.g., in urinary or fecally incontinent patients) may cause a dantron burn (a red erythematous rash with a well-defined border); if ignored, this may cause painful excoriation. Phenolphthalein occasionally causes a drug rash or photosensitivity. Rarely, it causes encephalitis, which can be fatal.

Dose and Use

The doses suggested here for *opioid-induced* constipation tend to be higher than those recommended in the manufacturer's Product Information. For frail patients not receiving opioids or other constipating drugs, the PO starting doses of a stimulant laxative should generally be lower.

Because round-the-clock opioids constipate, b.i.d. or t.i.d. laxatives may well be necessary, rather than the traditional once daily dose (at bedtime or each morning). Individual titration is necessary (see example protocol). Requirements do not correlate closely with the opioid dose, though generally increase with increasing doses of an opioid.[45]

Bisacodyl

- start with 10–20 mg PO at bedtime
- if necessary, increase by stages to 20 mg PO t.i.d.
- by suppository: 10–20 mg PR once daily.

Senna

- start with 17.2 mg at bedtime or, if taking opioids, 17.2 mg b.i.d.
- if necessary, increase progressively to 17.2 mg → 25.8 mg → 34.4 mg t.i.d.

Sodium picosulfate (UK)

- start with 5–10 mg at bedtime; 10 mg if taking regular opioids
- if necessary, increase daily by 5 mg until a satisfactory result is achieved
- median satisfactory dose = 15 mg at bedtime
- typical maximum dose = 30 mg.[34]

Supply

The drugs listed here are purposely limited to selected products containing only a stimulant laxative. Note that the relative costs vary between countries. For example, in the USA, the cost of senna syrup is more than 10 times the cost of sugar-free senna solution in the UK; and, compared with bisacodyl, the price of senna is relatively higher. In the USA, the cost of bisacodyl suppositories is about 7 times more than the tablets, whereas in the UK the price differential is marginal. The prices below generally reflect those in the USA.

In the USA, the standard senna tablet contains 8.6 mg of sennosides and the syrup contains 8.8 mg/5 mL; in the UK, the tablet contains 7.5 mg and the syrup 7.5 mg/5 ml.

Senna (generic)
Tablets total sennosides 8.6 mg/tablet, 28 days @ 17.2 mg at bedtime = $11.
Oral syrup total sennosides 8.8 mg/5 mL, 28 days @ 10 mL at bedtime = $34.

Bisacodyl (generic)
Tablets e/c 5 mg, 28 days @ 10 mg at bedtime = $4.
Suppositories 10 mg, 28 days @ 10 mg once daily = $28.

Sodium picosulfate (generic, UK)
Oral syrup 5 mg/5 mL, 28 days @ 10 mL at bedtime = $8.

Example Protocol for Opioid-induced Constipation in Patients With Advanced Illness

Generally, all patients with advanced illness who are prescribed an opioid also should be prescribed senna, with the aim of achieving a regular bowel movement without straining every 1–3 days. Occasionally, rather than automatically changing to senna, it may be more appropriate to optimize a patient's existing regimen.

This protocol also provides a suitable approach to managing constipation in patients not on opioids. In this circumstance, smaller doses may well suffice.

1. Ask about the patient's past and present bowel habit and use of laxatives; record the date of last bowel action.
2. Palpate for fecal masses in the line of the colon; examine the rectum digitally if the bowels have not been open for ≥3 days or if the patient reports rectal discomfort or has diarrhea suggestive of fecal impaction with overflow.
3. For inpatients, keep a daily record of bowel actions.
4. Encourage fluids generally, and fruit juice and fruit specifically.
5. When an opioid is prescribed, prescribe senna (Box A) and titrate the dose according to response.
6. During dose titration and subsequently: if ≥3 days since last bowel action, give suppositories, e.g., bisacodyl 10 mg and glycerol 4 g, or a micro-enema. If these are ineffective, administer a phosphate enema and possibly repeat the next day.
7. If the maximum tolerated dose of senna is ineffective (Box A), halve the dose and add an osmotic laxative, then titrate as necessary, e.g.:
   - lactulose 15 mL once daily–b.i.d. *or*
   - polyethylene glycol (macrogol) 1 sachet each morning
8. Alternatively, prescribe SC methylnaltrexone (Box B).
9. If the stimulant laxative causes intestinal colic, divide the total daily dose into smaller more frequent doses. Alternatively, change to an osmotic laxative (see above), then titrate as necessary.
10. An osmotic laxative may be preferable in patients with a history of colic with senna or other stimulant laxative, e.g., bisacodyl.

Box A. Dose schedule for senna

- if *not* constipated:
  - generally start with 17.2 mg at bedtime
  - if no response after 24–48 h, increase to 17.2 mg at bedtime and each morning
- if already constipated
  - generally start with 17.2 mg at bedtime and each morning
  - if no response after 24–48 h, increase to 25.8 mg at bedtime and each morning
- if no response after a further 24–48 h, consider adding a third daytime dose
- if necessary, consider increasing to 34.4 mg t.i.d., occasionally higher.

Box B. Methylnaltrexone for opioid-related constipation

Methylnaltrexone is relatively expensive ($55 per 12 mg vial) and should be considered only when the optimum use of laxatives is ineffective. Because constipation in advanced disease is generally multifactorial in origin, methylnaltrexone does not replace the need for other laxatives. Most patients who respond do so after 1–2 doses.

- marketed as a SC injection for use in patients with "advanced illness" and opioid-related constipation despite treatment with laxatives
- about 1/3–1/2 of patients given methylnaltrexone have a bowel movement within 4 h, without loss of analgesia or the development of opioid withdrawal symptoms
- dose recommendations (from USA PI):
  - for patients weighing 38–62 kg, start with 8 mg on alternate days
  - for patients weighing 62–114 kg, start with 12 mg on alternate days
  - outside this range, give 150 microgram/kg on alternate days
  - in severe renal impairment (creatinine clearance <30 mL/min), the dose should be halved
  - the interval between administrations can be varied, either extended or reduced, but not more than once daily
- methylnaltrexone is contraindicated in cases of known or suspected bowel obstruction. It should be used with caution in patients with conditions which may predispose to perforation. Common undesirable effects include abdominal pain/colic, diarrhea, flatulence, and nausea; these generally resolve after a bowel movement; *postural hypotension also can occur.*

Abbreviations/Key

b.i.d bis in die, twice daily
e/c enteric coated
PO Per os, by mouth
PR Per rectum
RCT Randomized controlled trial
t.i.d ter in die, three times daily

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