Although lifestyle changes and laxative treatment can offer limited benefit for patients with constipation caused by opioid medicines, opioid-receptor antagonists target the cause of constipation in such patients

Opioid-induced bowel dysfunction

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Constipation is a well-documented and recognised side effect of opioid therapy. However, patients may describe a wider range of opioid-induced gastrointestinal (GI) symptoms, including abdominal pain, bloating, heartburn, GI reflux disorder, anorexia, delayed digestion and formation of dry, hard stools. Opioid-induced bowel dysfunction is a generic term that encompasses this array of GI symptoms.

Constipation can be defined as the passage of small, hard faeces infrequently and with difficulty. Recent clinical practice guidelines for palliative care suggest that the frequency of bowel motions should take into account the usual bowel habits of individual patients. Nevertheless, comprehensive assessment is recommended for those patients defaecating less often than three times a week.

More than half of patients with advanced cancer suffer constipation,1 although the incidence is widely variable and depends on how constipation is defined. In those taking opioid analgesics, around seven out of eight patients taking opioids,1 using a method that encompasses this array of GI symptoms.

Opioid-induced constipation (OIC) can prompt dose reduction or treatment cessation in a third of patients taking daily opioids for persistent non-cancer pain,1 resulting in a reduction in effective pain management by as much as 30%.2

A thorough review of the pathogenesis of constipation is available. Briefly, opioids exert their GI effects via opioid receptors located throughout the entire GI tract. The main physiological effects of opioid receptor stimulation are decreased peristalsis and intestinal fluid secretions, increased sphincter tone and enhanced fluid absorption. It is often said that, in contrast to adverse effects such as nausea and sedation, tolerance does not occur to the constipating effects of opioids. However, follow-up data from one small study suggest that some patients may not require continued laxative therapy.

The role that central opioid receptors play in constipation is not well understood, but they probably contribute to constipation to a lesser extent (via the sympathetic nervous system), suggesting that oral opioids (via action on peripheral opioid receptors within the GI tract) may cause more constipation than parenteral and transdermal formulations. Evidence for this in practice is limited. Nonetheless, long-term patients switching opioids due to analgesic tolerance or side effects often obtain adequate pain relief with lower equivalent doses of the new drug — and therefore may have less constipation (note opioid equivalences, eg, fentanyl 25µg/hour patch equivalent to 90mg oral morphine/day).

There is also controversy regarding the likelihood of constipation with tramadol, an analgesic that acts via both opioid and monoaminergic pathways. The British National Formulary states that tramadol causes fewer of the typical opioid-related side effects (including constipation). However, this conclusion is drawn from studies of small numbers of patients and is likely to be proportional to the lower potency of tramadol (at commonly prescribed doses) relative to strong opioids.

Additional causes of constipation include conditions that make passing faeces more difficult or painful (eg, haemorrhoids or low back pain), reduced appetite or fluid intake, lack of mobility and some other medications (eg, anticholinergics, verapamil).

Standard treatments

Non-pharmacological interventions can have a role in the management and prevention of constipation, although their benefit can be limited. Increasing fibre and fluid intake sufficiently to have a marked effect on constipation is probably unrealistic for most palliative care patients. Improvements in mobility may be achievable but the aim should be to gain improvement in quality of life measures, with any reduction in constipation being seen as an additional benefit. For patients with persistent pain, such lifestyle changes may only be achieved secondary to rehabilitation of the condition causing pain.

Only senna, lactulose (at high doses which are not well tolerated) and macrogols have any supporting evidence in treating OIC and this evidence is often of low quality.3 Despite this, one small study demonstrated that adherence to a simple laxative protocol can significantly reduce rates of constipation (from 70% to 26%).4 Recent consensus guidelines advocate prescribing prophylactic laxatives for those patients taking opioids,5 using a combination of a stimulant (eg, senna) and a stool softener (eg, docusate).

DISCUSSION POINTS

- When reviewing patients taking long-term opioids, do you always ensure prophylactic laxatives are prescribed? If the opioid dose is reduced or stopped, laxative therapy should be reviewed accordingly.
- Take a thorough history (other conditions, underlying pathology, what the patient considers to be his or her “normal” bowel habits), examine patient factors (obesity, mobility, diet, normal fluid intake) and consider concomitant medicines. How might this information affect management?
- How do your patients define “constipated” and what would they consider a reasonable outcome? Consider the following questions: Does it cause them pain or discomfort? Is it affecting their quality of life? Have they considered resorting to manual evacuation?
- Consider whether other methods of pain management are being explored fully (eg, exercise, pacing, non-opioid analgesics, non-pharmacological methods, etc).
Side effects

Laxative therapy is not without side effects. Stimulant laxatives can cause abdominal cramping, which can be minimised by co-prescription of a softener. Bulk-forming laxatives (e.g., ispaghula husk) are not recommended for OIC because, in the absence of adequate fluid intake, they can contribute to intestinal obstruction. Macrogols are increasingly prescribed and would appear to offer some advantages in terms of patient preference but can be expensive when prescribed at higher doses.

It should be noted that laxatives only treat constipation and can exacerbate other symptoms of opioid-induced bowel dysfunction; they do not address the cause of the problem.

Recent developments

The concept of using low-dose opioid antagonists for constipation is not new. The aim is that opioid receptors in the gut are targeted specifically by the antagonist, in preference to central receptors, to ensure analgesia is maintained. Two new medicines using this approach have become available in the UK: subcutaneous methylnaltrexone (Relistor) and a combination of sustained-release (SR) oxycodone and SR naloxone (Targinact) for oral administration.

Subcutaneous methylnaltrexone (a quaternary amine derivative of naltrexone which cannot cross the blood-brain barrier) has been compared with placebo in a two-week, double-blind, randomised, placebo-controlled trial.\(^1\) Patients were required to have received opioids for two or more weeks and had taken laxatives for at least three days without effect. Bowel movements occurred significantly faster and more frequently in the treatment group.

Methylnaltrexone has been approved by the Scottish Medicines Consortium for restricted use by palliative care specialists “when response to usual laxative therapy has not been sufficient”. The National Institute for Health and Clinical Excellence has decided not to appraise the medicine, stating that “a drug with such a small impact on population health and NHS budgets does not merit the investment in resources associated with a NICE appraisal”.

When given orally, naloxone binds preferentially to the opioid receptors in the GI tract and has an extremely low bioavailability (<1%) due to extensive first-pass metabolism. In double-blind, randomised, clinical trials, a combination of SR oxycodone and SR naloxone has been shown to have similar analgesic efficacy to SR oxycodone alone (greater than placebo)\(^2\) and to improve bowel function index scores significantly\(^3,4\) in non-malignant persistent pain scenarios. The bowel function index incorporates an average of three scores: ease of defaecation, feeling of incomplete evacuation and personal judgement of constipation.

These trials are discussed further in a recent review by the Midlands Therapeutics Review and Advisory Committee.\(^5\)

Conclusion

Laxatives remain the first-line treatment for OIC and should be prescribed prophylactically using either macrogols or a combination of stimulant laxative and a stool softener. Peripheral opioid receptor antagonists should be considered for those patients requiring long-term opioid therapy where constipation occurs despite prophylaxis with laxatives. Although the evidence supporting the newly marketed agents for OIC is not flawless, there is also a lack of evidence supporting traditional laxatives.

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