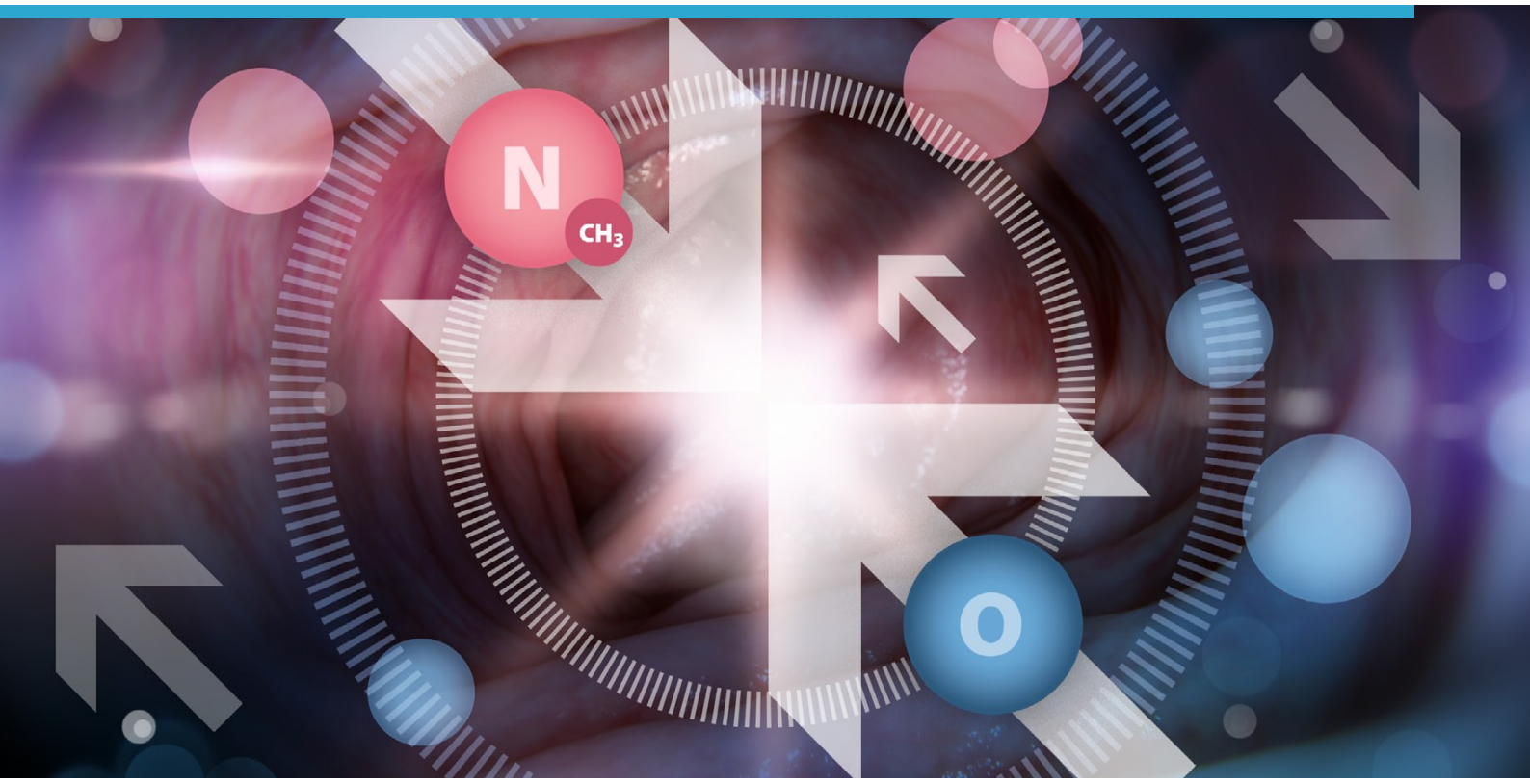

Methylnaltrexone is a subsidised treatment option **for opioid-induced constipation** in palliative care

KEY PRACTICE POINTS:

- Methylnaltrexone antagonises the effects of opioids in the gut without crossing the blood brain barrier and can be used to treat opioid-induced constipation without affecting opioid analgesia
- As of 1 January, 2018 methylnaltrexone subcutaneous injection can be prescribed, fully subsidised with Special Authority approval, to patients who are receiving palliative care
- Half of patients will have a bowel movement within four hours of administration, typically within the first 30–60 minutes
- Patients can continue taking other treatments for constipation, such as oral laxatives

Methylnaltrexone injections are now subsidised for the treatment of opioid-induced constipation for patients in palliative care. This treatment might be considered for patients with persistent symptoms despite use of other treatments such as oral laxatives, suppositories or enemas.

Constipation is a common problem in patients receiving palliative care

Constipation is reported to be the third most common symptom in patients in palliative care, following pain and anorexia.[1] A variety of factors can contribute to the development of constipation in palliative care settings, including:[1,2]

- Dehydration
- Changes in diet
- Immobility
- Metabolic disturbances such as hypercalcaemia, hypokalaemia or uraemia
- Co-morbidities such as neurological disorders, hypothyroidism, diabetes
- Medicines which cause constipation as an adverse effect, including opioids, antiemetics, anticholinergics and chemotherapy

Opioids affect the function of the gastrointestinal system

Opioids are often used in palliative care for pain relief. Constipation is a common adverse effect of these medicines because they slow colon transit time due to effects on opioid receptors in the gastrointestinal system. Morphine, for example, approximately doubles gastrointestinal transit time.[3] Constipation is reported to occur in over 40% of patients taking opioid medicines long-term, however, it can develop at any time, including when they are first initiated.[4, 5] The analgesic effects of opioids can diminish over time as patients develop tolerance, but studies show that tolerance to the effects of opioids in the colon does not occur and opioid-induced constipation does not diminish with continued use.[6]

Proactive measures should be taken to reduce opioid-induced constipation

When initiating an opioid medicine in a patient receiving palliative care, co-prescribe stool softeners and stimulant laxatives, such as docusate sodium with sennoside B.[2, 7] Osmotic laxatives such as macrogols or lactulose can be used if patients experience cramps while taking stool softeners and stimulant laxatives.[2] Laxatives provide relief for approximately half of patients with opioid-induced constipation.[4] More invasive rectal treatments, such as suppositories or enemas, are recommended as second-line treatments for constipation in palliative care guidelines.[1] Manual evacuation is regarded as a third-line treatment if other treatments have not improved symptoms sufficiently or are not tolerated.[1] However, this procedure can be uncomfortable and distressing for patients, and is associated with an increased risk of complications such as rectal tears or bleeding.[8] The use of a peripherally acting opioid antagonist, such as methylnaltrexone bromide, is now an alternative third-line approach to managing opioid-induced constipation.[1]

Methylnaltrexone treats opioid-induced constipation by antagonising the effects of opioids in the colon

Naltrexone is an opioid antagonist used in the treatment of opioid or alcohol dependence.[9] The addition of a methyl group to naltrexone results in a medicine which does not cross the blood brain barrier and only exerts peripheral effects. Methylnaltrexone can therefore be used to antagonise the effects of opioid medicines in the colon without reducing the analgesic effects of opioids.[6] It is neither effective nor indicated for treating opioid or alcohol dependence.

Methylnaltrexone is now subsidised with Special Authority approval

As of 1 January, 2018, methylnaltrexone injection can be prescribed fully subsidised with Special Authority approval to patients who are receiving palliative care and who have trialled oral and rectal treatments for opioid-induced constipation, but these have either been ineffective or not tolerated. Only one application for Special Authority is required; subsequent doses can be given, if necessary, without further application and there is no time limit for approvals.[10]

Half of patients have a bowel movement within four hours of methylnaltrexone administration

In clinical trials involving patients in palliative care with opioid-induced constipation who have been taking oral laxatives, half have a bowel movement within four hours of receiving a methylnaltrexone injection, typically within the first 30–60 minutes.[11] By comparison, 15% of patients administered a placebo injection have a bowel movement within four hours.[11]

If patients do not have a bowel movement after the first dose, subsequent doses can be trialled

Methylnaltrexone should not be administered more than once daily. Patients can receive subsequent methylnaltrexone injections at 24 hour intervals if they have not had a bowel movement following the first dose.[9] Treatment with oral laxatives can continue during this time. Patients should be monitored and undergo regular review to identify if further intervention is required, such as manual evacuation, if they continue to have constipation.

Consider stopping methylnaltrexone if there is a lack of response after a few doses. Evidence shows that the response to the first dose is generally predictive of the response to any subsequent doses and only a minority of patients who do not have a bowel movement following an initial dose do so after the second or third dose.[12–14]

For patients with continuing constipation, administer methylnaltrexone as needed

If treatment with methylnaltrexone is successful but patients have continuing problems with opioid-induced constipation, methylnaltrexone can be administered every other day as an ongoing treatment, or less frequently on an as-required basis.[12]

Administering methylnaltrexone

Methylnaltrexone is administered by subcutaneous injection in the upper arm, abdomen or thigh.[15] Ensure that patients have ready access to toilet facilities or assistance available to use a bedpan, as the laxative effects of methylnaltrexone can begin within 30 minutes of injection.[11]

Contraindications and cautions

Methylnaltrexone should not be used in patients with

suspected bowel obstruction, post-operative ileus or acute abdomen.[9, 16]

The use of methylnaltrexone has not been studied in patients who have undergone a colostomy, who have a peritoneal catheter, diverticular disease or faecal impaction and therefore should be used with caution in these patients.[16]

Caution is advised if methylnaltrexone is used in patients with conditions that could weaken the stomach or intestinal wall.[16] There have been rare case reports of gastrointestinal perforation following methylnaltrexone administration. In the United States, seven cases were reported over approximately 18 months, with most patients having a co-morbid gastrointestinal condition such as gastric ulcers or colon cancer.[17]

Dosing

The majority of patients can be administered 0.4 mL or 0.6 mL:[16]

- Patients weighing 38–62 kg: 0.4 mL (8 mg)
- Patients weighing 62–114 kg: 0.6 mL (12 mg)

Outside of these body weight ranges clinicians should calculate the volume required at a dose of 0.15 mg/kg.[16] If patients only require part of a vial as a dose, the remainder should be discarded.[16]

Halve the dose in patients with severe renal impairment: Patients with a creatinine clearance of less than 30 mL/min should receive half the usual dose for their body weight.[16] Use of methylnaltrexone in patients undergoing dialysis or with end-stage renal impairment is not advised as no studies have been conducted in these patients.[16]

Patients may experience gastrointestinal adverse effects

In clinical trials the most common adverse effects reported by patients are gastrointestinal:[4, 11, 15]

- Abdominal pain or cramps, occurring in 17–30% of patients; this is typically rated as mild to moderate in severity [18]
- Nausea, occurring in 11–21% of patients
- Flatulence, occurring in 8–13% of patients
- Diarrhoea, occurring in 5–6% of patients; fluid administration may be required to prevent hypovolaemia and acute kidney injury in some patients who develop diarrhoea[19]

This article is available online at:
bpac.org.nz/2018/methylnaltrexone.aspx

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