MEDNET
MEDICAL EDUCATION NETWORK

PRIORITY PRESS

7th World Congress of the World Institute of Pain (WIP 2014)

Maastricht, The Netherlands / May 7-10, 2014

Pain Management: New Approaches in Opioid-Induced Constipation

Maastricht - As the population ages, the incidence of chronic pain and resulting use of opioids for treatment is increasing. While opioids provide significant analgesic effect, their benefit is accompanied by common side effects. In an already quality-of-life compromised group of patients, the resulting side effect of constipation can lead to challenges in treatment adherence. A significant number of patients do not obtain adequate relief from conventional laxatives, which has resulted in the developent of other agents that antagonize the effect of opiods on bowel function while maintaining their analgesic effect.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

The number of patients suffering from chronic pain is increasing as the population ages and cancer survival times lengthen. This is leading to increased long-term use of opioid analgesics, and a growing need to manage the side effects associated with them.

Constipation is a well-known side effect of opioids, but the burden it imposes on patients is often under-appreciated by medical professionals. "Opioid-induced constipation is a big issue," Dr. Andrew Davies, Clinical Director of Supportive and Palliative Care, Royal Surrey County Hospital, Guildford, UK, told WIP delegates. He continued: "It adds to the burden that patients on long-term opioids suffer, and can be a significant contributor to their morbidity and reduced quality of life."

Prevalence and Burden of Opioid-Induced Constipation

People in chronic pain are prescribed opioids only after other earlier-line pain management strategies have proved inadequate. However, the analgesia opioids provide comes at the cost of side effects for many. The CNS and gut are the main systems affected, owing to the large numbers of opioid receptors they contain, with symptoms that include sedation, dizziness, constipation, nausea, vomiting, dependence and addiction. Estimates of the prevalence of constipation in opioid-treated patients vary, partly due to differing definitions of constipation. Dr. Davies cited data from a survey of 270 opioid-treated cancer patients in which only 15% reported no constipation and were taking no laxatives. A further 13% reported no constipation but were using laxatives. Also reported at WIP 2014 was a survey by Knezevic et al., Illinois Masonic Medical Center, Chicago, US, examining constipation prevalence in patients with chronic non-cancer pain. Constipation (≤3 spontaneous bowel movements (SBM) per week) was reported by 144 of 608 opioid-treated patients (23.7%). In contrast, the prevalence of constipation was 11.3% in non-opioid-treated patients and 9.4% of matched healthy controls (P<0.001 for between-group differences).

Symptoms of opioid-induced constipation (OIC) include abdominal pain, anorexia, early satiety, nausea, abdominal distension, overflow-diarrhoea, flatulence, headache and general malaise. Heartburn, haemorrhoids and anal fissures are common. Intestinal obstruction, intestinal perforation and pulmonary embolism can also be associated with severe constipation. Reduced frequency of bowel movements is the most obvious manifestation of constipation, and hence is used in definitions of the condition and as the primary endpoint in clinical trials. However, it is only one of a range of opioid-induced effects on the gut. "Constipation is not just about the number of bowel movements," said Asbjørn Mohr Drewes, Aalborg University, Denmark. "Only a subset of constipated patients complain of fewer movements," he added. Straining, flatulence, hard stool and abdominal bloating and discomfort can be present even when SBM frequency does not cause the patient concern. Dr. Davies noted that many patients attending his clinic with nausea and vomiting report that they are not constipated because they have regular bowel movements. Yet X-ray images reveal faecal loading as the cause of their symptoms.

Adherence Challenge

Severe long-term constipation is a major burden on already sick opioid-treated patients, and can interfere with pain management by lowering adherence to treatment. "Patients with OIC commonly report reducing or skipping their analgesic dose in an effort to ease constipation", Dr. Davies said. Unlike some other opioid effects, OIC does not reduce over time due to tolerance.

"It is important to recognize the differences between opioid-induced constipation and functional or idiopathic constipation", Dr. Drewes emphasised. The gut has a complex neural network and a high density of various opioid receptors throughout. Exogenous opioids interfere with gut neural signalling in multiple ways, and OIC is part of a wider syndrome of opiate-induced bowel dysfunction. Their effects

on circular muscle result in increased tone and decreased motility. Secretion is also reduced, resulting in hard stools and lower faecal volume, which in turn further decreases motility because peristalsis is influenced by the volume of gut contents. Finally, opioids disrupt sphincter function by increasing sphincter tone. Among other effects, this can dull the sensation that the bowel is full. Thus, opioids are a pan-intestinal problem.

OIC is a class effect of all opioids. There is a common misconception that transdermal opioid formulations are less likely to cause constipation. Dr. Drewes said this is not the case. Transdermal delivery still requires the opioid to pass into the blood and thus through the gut, where it will act in the same way as an injected agent.

Treatment Options in OIC

"OIC rarely resolves spontaneously, and tends to become more of a problem over time", continued Dr. Davies. First-line treatment is with conventional laxatives, which are divided into stool softeners, osmotic agents and stimulants. These are inexpensive and available over the counter, and are effective in many people with OIC; however, studies show that 30-40% of patients with OIC do not obtain adequate relief with conventional laxatives (*Am J Surg* 2001 Nov;182 (5A Suppl):11S-18S).

Therefore, the treatment challenge is to mitigate the effects of OIC while maintaining analgesia. Several approaches have been developed. Lubiprostone (*Med Lett Drugs Ther* 2013 Jun 10;55(1418):47-8), currently approved by the FDA for the treatment of OIC and methylnaltrexone (*J Support Oncol* 2009 Jan-Feb;7(1):39-46), which is licensed in Canada for the treatment of OIC in the palliative care setting. A third, naloxegol (*Pain* 2013 Sep;154(9):1542-50), has been submitted for review and approval in Canada.

Lubiprostone is a chloride channel activator that increases passive secretion of sodium ions and water into the gut lumen, promoting small bowel and colonic transit. In 2013 it became the first agent to be licensed specifically for the treatment of OIC, following two placebo-controlled phase III trials showing increased SBM frequency (overall mean change in SBM frequency over the two trials of 1.9, vs 1.3 with placebo, $P \leq 0.001$). Nausea was the most frequent adverse effect, reported by 89% of patients.

Another approach is to combine the opioid with an antagonist that selectively blocks the action of opioids on receptors in the gut, whilst maintaining the analgesic effect on the CNS. A pooled analysis of two phase III trials of a fixed-dose combination of prolonged release oxycodone with naloxone found a significant improvement in a patient-reported measure of bowel function compared with oxycodone alone (*BMC Clin Pharmacol* 2010 Sep 29;10:12).

PAMORAs

Another class, peripherally acting mu-opioid receptor antagonists (PAMORAs) bind with high affinity to block mu-opioid receptors in the periphery but are generally unable to cross the blood-brain barrier, so do not act on the CNS. Subcutaneous methylnaltrexone is a PAMORA for the relief of OIC in patients with advanced medical illness (typically with a life expectancy of <3 months). It has a very rapid onset of action, typically within less than one hour. In phase III studies, laxation was achieved within 4 hours in 52-62% of patients.

Naloxegol is an oral PAMORA that is under review for the treatment of OIC at the time of writing. It is a pegylated derivative of naloxone. The increased molecular size and weight provided by the PEG side chain impedes the crossing of the blood-brain barrier, preserving the central analgesic effect of opioid therapy and acting peripherally to alleviate constipation. Naloxegol is administered OD and has a consistent onset, which could assist with adherence. In the placebo-controlled phase III trials KODIAC-04 and KODIAC-05, responder rates to naloxegol 25 mg/day were 44.4% and 39.7%, respectively, compared with 29.4% and 29.3% with placebo. Response was defined as ≥3 SBM/week with ≥1 SBM increase from baseline for at least 9 of the 12 weeks of treatment, and at least 3 of the last 4 weeks. This effect was maintained in the subgroup of patients classed as laxative-inadequate responders. Abdominal pain and nausea were the most commonly reported treatment-emergent adverse events, but affected fewer than 20% of patients.

Summary

Treatment of OIC is a rapidly evolving area. New, targeted approaches to this serious problem have the potential to reduce the burden of constipation on patients being treated with opioids, without compromising analgesia. This in turn may improve pain management by improving adherence to analgesia. □

To view an electronic version of this publication along with related slides if available, please visit mednet.ca/go/?pn=pp14-015e

Medical Education Network Canada Inc. 132 chemin de l'Anse, Vaudreuil, Quebec J7V 8P3

PP14-015E SS