



Editorial comment

Advances in understanding and treatment of opioid-induced-bowel-dysfunction, opioid-induced-constipation in particular

Nordic recommendations based on multi-specialist input

Audun Stubhaug^{a,b,*}^a Department of Pain Management and Research, Division of Emergencies and Critical Care, Oslo University Hospital, Norway^b Medical Faculty, University of Oslo, Norway

In this issue of the *Scandinavian Journal of Pain* Helene Nordahl Christensen and her co-workers [1] and Asbjørn Mohr Drewes and his co-workers [2] focus on the under-diagnosed, undertreated, and even inappropriately treated adverse effects on the gastrointestinal tract of opioids prescribed for relief of acute and long-lasting pain.

1. Opioids induce gastrointestinal dysfunction (OIBD), constipation in particular, and conventional laxatives may cause additional problems with negative effects on health-related quality of life

Nordahl Christensen et al. [1] with data from an Internet-based follow-up of patients who had been dispensed opioids for non-cancer pain, confirm that a majority of these patients suffer a significant burden of abdominal symptoms from opioid side effects. Their data confirm that there is a high degree of self-management of opioid-induced constipation (OIC) with laxatives, and that there is a low degree of satisfaction with laxatives. Such adverse effects of opioids on functions of the gastrointestinal tract and the unsatisfactory self-management with laxatives contribute to a low health-related quality of life among patients with pain-conditions that are treated with opioids.

2. A Nordic multi-specialist working group for increased awareness of OIBD and advice on treatment of OIBD

There is a need for knowledge-based guidelines, or practice-advisory statements, on how to manage OIBD. The report by Asbjørn Mohr Drewes and his Nordic Working Group composed

of different specialists with knowledge and expertise in this area, published in this issue of the *Scandinavian Journal of Pain* [2] is a thorough literature review of all aspects of opioid-induced bowel dysfunction, giving evidence-based guidelines in the form of GRADE-system-statements and recommendations [2].

3. First line treatment for OIBP is laxatives and lifestyle changes

Following more liberal prescription-practice for opioids as part of the management of chronic pain conditions, opioid-induced bowel dysfunction has increased in prevalence. In guidelines for opioid-treatment of chronic pain, information to patients about adverse effects on the gastrointestinal system is included. Mostly patients receive general advice on increasing diet-fibre, as well as “drink extra water and exercise” [3]. Such advice is not always sufficient. Therefore, as shown by Nordahl Christensen et al. [1], patients often end up buying laxatives over the counter (OTC). Pharmacists, as well as nurses in hospitals and in nursing homes, by force of habit and long tradition, advise patients to drink lactulose solutions, sometimes adding bisacodyl, senna, polyethylene glycol. Lactulose may increase intestinal gas and bloating, with minor effect on opioid-induced constipation [2]. The effects of more potent laxatives, e.g. pikosulphate, are difficult to predict, causing social anxieties. Patients may end up with periods of severe constipation alternating with periods of forceful bowel movements and diarrhoea [2].

4. Opioid tapering and opioid rotation may help relieve OIBD

To reduce opioid side-effects, opioid tapering should always be considered. There are evidence that certain opioids such as tapentadol, methadone and transdermal fentanyl may improve bowel function compared with some oral mu-opioids [2].

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* Corresponding author at: Department of Pain Management and Research, Division of Emergencies and Critical Care, Oslo University Hospital, PB 4956 Nydalen, 0424 Oslo, Norway. Tel.: +47 23026161.

E-mail address: audun.stubhaug@medisin.uio.no

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5. Specific treatment of opioid-induced gastrointestinal bowel dysfunction with opioid antagonists

There are opioid-receptors in the enteric nervous system in the walls of the entire gastrointestinal tract [2]. Opioid agonists bind to these receptors and cause a prolongation of transit times, especially in the colon, reduced enteric secretions into and increased absorption of fluids from the gut lumen. Stools become more compact, making defecation difficult, often painful and incomplete [2]. In the upper parts of the gastrointestinal tract, gastric emptying is delayed, causing gastro-oesophageal regurgitation and dysphagia. Sphincter of Oddi contracts causing elevated pressure in the hepatic and pancreatic ducts.

Whereas potent laxatives can counteract constipation, they do not have any effect on opioid-induced upper gastro-enteric dysfunction. Opioid receptor antagonists can reverse most of these effects, as shown by studies of naloxone given by mouth. If naloxone also enters the central nervous system, analgesic effects of opioids will be abolished and patients on long-term opioid treatment will suddenly experience severe and extremely unpleasant withdrawal symptoms [4]. However, when appropriate doses of naloxone are co-administered in slow-release tablets with oxycodone, parts of the gastrointestinal dysfunctions are prevented without precipitating withdrawal [4,5]. This is due to the almost complete hepatic first-pass elimination of the naloxone that is absorbed from the gastrointestinal tract.

6. Peripherally acting μ -opioid receptor (MOR) antagonists [2] (PAMORAs) prevent opioid-induced bowel dysfunctions in pain patients who need long-term opioid treatment

Peripherally acting μ -opioid receptor (MOR) antagonists (PAMORAs) do not cross the blood-brain-barrier, and do not counteract the analgesic effect of opioids. Treating OIBD with a peripherally acting μ -opioid receptor antagonist is a significant improvement in the treatment of pain patients on opioids. This is also highly relevant for cancer patients with severe pain that requires opioid treatment [6].

There are now several PAMORAs, but only two are marketed in the Nordic countries. *Methylnaltrexone (Relistor®)* is a quaternary molecule that does not cross the blood-brain-barrier. It is administered by injection and has a fast-onset reversal of opioid-agonist-effects in the gastrointestinal tract [2].

Naloxegol (Moventig®) is naloxone to which is attached a long side-chain that makes it impossible for this molecule to get through the blood-brain barrier. It is taken by mouth at a daily dose of

25 mg. Besides reversing the opioid-induced constipation, naloxegol can be expected to diminish opioid-effects on sphincters of the gastrointestinal tract.

Combination treatment with drugs like prucalopride and linaclotide together with irrigation therapy should be considered in difficult cases.

7. Concluding remarks

Better compliance with opioid-prescription and opioid-follow-up strategies [3,7] will eventually reduce the burden on chronic pain patients from iatrogenic opioid misuse and bowel dysfunction [7]. Conventional laxatives, lifestyle changes and opioid rotation may counteract opioid side-effects on gastrointestinal organs, opioid-induced constipation in particular. Orally administered PAMORAs are representing an important new treatment option. A synthesis of current best evidence is published as recommendations from the group of specialists lead by Abjörn Mohr Drewes in this issue of the *Scandinavian Journal of Pain*, based on new knowledge from high quality clinical research [2].

Conflict of interest

The author has no conflicts of interest.

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