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Editorial comment

Combining an oral opioid-receptor agonist and the antagonist naloxone: A smart drug design that removes some but not all adverse effects of the opioid analgesic

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In the present issue of the *Scandinavian Journal of Pain* Sabine Hesselbarth and co-workers publish the results of a study from "real life" on the outcome of patients treated with a strong opioid of any kind, compared with oxycodone controlled released with naloxone added [1]. The rationale behind this combination is that naloxone taken by mouth is absorbed from the gastrointestinal tract into the portal circulation, but on first passage through the liver most of the naloxone (about 97–99%) is metabolized to inactive metabolites. The minute part of the naloxone that reaches the systemic circulation and crosses the blood–brain barrier is too small to precipitate any anti-analgesic effects.

1. Naloxone in depot-opioid tablets, binds to intestinal wall receptors in the entire GI-tract

On its passage through the GI-tract, the naloxone, gradually released from the controlled release oxycodone tablet, binds to opioid-receptors in the intestinal wall, reducing the effects of the opioid agonist on smooth muscle and secretory function of the intestinal wall. This co-administration of opioid agonist and antagonist is well documented to reduce the most common of the problematic adverse effects of opioids: the obstinate opioid-induced constipation [2,3].

2. Laxative regimens relieve opioid induced constipation, but not other opioid-induced dysfunctions in the GI-tract

It is important to start a pharmacological laxative regimen concomitant with the opioid in order to prevent the opioid-induced constipation that is bound to develop in most patients who need long-term opioid therapy. Examples: combination of *sodium-picosulphate* and *bisacodyl*, or *polyethylene glycol* (PEG), and *senna* or *bisacodyl*, in appropriate dosages [4]. However, all potent laxative regimens have a number of adverse effects, e.g., abdominal bloating and cramps, diarrhoea, and, unpredictable onset times, sometimes causing socially very embarrassing situations for the patient.

An additional problem is the opioid-effect on gastro-intestinal sphincters and reflexes, in particular the lower esophageal sphincter and the pyloric sphincter, leading to gastro-paresis and regurgitation. These symptoms, e.g., "heart burn", nausea, epigastric pain and dyspepsia, are not affected by laxatives, and occur irrespective of the bowel function.

An orally administered, controlled-release formulation of an opioid and naloxone should be well suited for mitigating opioid-induced gut dysfunction in the entire GI-tract, something not possible at the moment with a conventional laxative regimen. For a review of the many aspects of opioid-induced gastro-intestinal dysfunctions, see [4].

3. Opioid antagonists that do not cross the blood–brain barrier

There are a number of peripherally acting opioid antagonists that do not, or only slowly and minimally, cross the blood–brain barrier. *Methylnaltrexone* is available as a preparation for subcutaneous injection. In doses from 8 to 12 mg s.c. methylnaltrexone relieves the patient from peripheral adverse effects of opioids. *Alvimopan* is another peripherally acting opioid-receptor antagonist that does not cross the blood–brain barrier. It is taken by mouth and is on the market in the USA for prevention and treatment of opioid-induced or opioid-prolonged postoperative constipation in patients who receive opioid analgesic drugs for the acute postoperative pain. At present, it is not available for patients on long-term opioid treatment of chronic non-cancer pain.

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4. Systemic ultra-low naloxone dose relieves opioid side effects such as nausea, pruritus, sedation

Naloxone 400 μg in 1000 ml of saline, slowly infused i.v. for 24 hours in an adult patient with a BW above 50 kg will reduce the intensity of nausea, sedation, and itching when these symptoms are opioid-induced [5,6].

5. Systemic ultra-low doses of naloxone may enhance the analgesic effect of an opioid agonists and reduce the risk of opioid-induced hyperalgesia, allodynia, and tolerance

A high enough dose of naloxone is bound to markedly reduce the pain-relieving effect of any opioid-receptor agonist. However, ultra-low doses of i.v. naloxone (0.25 μg/kg/h or lower in adults; 1–1.65 μg/kg/h for children) may reduce side-effects of opioids (pruritus, nausea, sedation) while improving pain control (less need/consumption of analgesics, less opioid-induced hyperalgesia, allodynia, and tolerance) [7–9].

Ultra-low doses of an opioid antagonist will inhibit μ-opioid receptor excitatory G-protein complexes (Gs) while leaving the inhibitory G-protein receptors (Gi) i.e., a probable mechanism behind the improved pain control [7,8].

When the naloxone controlled release tablet (with oxycodone) is administered, some of the absorbed naloxone will be able to pass through the liver and into the systemic circulation, although the concentrations of naloxone must be ultra-low. This is the hypothesis for explaining the observation that pain relief is indeed improved in patients treated with the naloxone-oxycodone controlled release formulation, compared with oxycodone controlled release alone [10]. This agrees with findings indicating that morphine consumption in postoperative patients is less when an ultra-low dose of naloxone is administered i.v. in patients using PCA-morphine (Patient-Controlled-Analgesia) [6].

6. Confounding bias effects in non-randomized, non-blinded observational drug trials

An observational study like the one presented by Hesselbarth and co-workers [1] have many significant causes of bias because the patients are not randomized to the treatment alternatives, and the patients and the observers are not blinded for which drug they are receiving. The participating physicians were offered participation in a drug trial and they were recruiting patients to take part. The choice of drugs could then easily have been biased, consciously or unconsciously, so that the magnitude of the observed differences between alternative strong opioids and the oxycodone plus naloxone may have been exaggerated, as admitted by Hesselbarth and her co-authors [1].

So, *why do we publish this not blinded, not randomized prospective observational study* sponsored by the pharmaceutical company that sells the naloxone-containing slow release oxycodone preparation? Clearly, this is a "marketing" trial intended to make more physicians aware of the drug and its effects on opioid-induced constipation in particular.

The drug is well documented to have the effect it was designed to have [2,3,10]. This observational study is therefore not needed to confirm this effect. However, with our long extensive practice as pain clinicians we have seen again and again the devastating effects on the quality of life of patients with chronic pain from cancer and non-cancer causes, when constipation and other adverse effects of opioids are not observed and taken seriously enough by the physicians responsible for the daily management of a painful condition [11]. Some patients will be able to keep their bowel habits by adhering to food intake with enough nutritional fibres, supplemented by laxatives as needed. Many patients, however, are not able to do this and end up with few and far between, hard, impacted and voluminous stool contents in their colon and rectum, and may as a result develop anal fissures, complicated with phlegmonous infections and development of abscesses. The patients may try to halt their opioid medication but are then punished by severe withdrawal symptoms and excruciating pain. It is primarily for these patients we want to publish this observational study, giving us an opportunity to make more physicians and nurses aware of this alternative for patients who do need an opioid analgesic as a part of the management of their pain condition, whether chronic cancer or non-cancer pain.

7. First-pass elimination of naloxone varies from person to person: can enough naloxone pass through the liver to cause withdrawal and break-through pain?

Whereas on average 97–99% of an oral dose of naloxone is inactivated during the first passage through the liver of healthy persons [12], there has to be individual variations in the clearing capacity of the liver. Especially when the dose of oxycodone/naloxone 40 mg/20 mg or even 80/40 is given twice per day, enough unchanged naloxone may pass through the liver, at least in sick cancer patients, to cause withdrawal effects in the CNS. In addition, shunts between the portal and systemic circulation may increase the systemic concentration of naloxone. The first author has personally observed this in very occasional patients, but we do not have a reliable number for how often this happens. The patients discontinue the drug, the half-life of naloxone is short, and this undesirable effect disappears within a few hours. Clinicians should be aware of this possibility.

8. Conclusions and implications

No doubt the oxycodone/naloxone combination slow release drug is a beneficial alternative for chronic pain patients who do require a potent opioid for their pain and who demonstrate a propensity for opioid-induced bowel dysfunction. This combination drug allows the patients to avoid the most common of the severe opioid-induced side effects: the obstinate constipation. In addition, some patients may experience improved pain relief, and, reduction in daytime sedation and pruritis.

The opioid-induced side effect on the urinary bladder, causing urinary retention, is not expected to be reduced by oral intake of naloxone. Elderly with benign prostate hyperplasia, with a higher risk of urinary retention, should ideally receive peripherally acting opioid antagonist not crossing the blood–brain barrier, such as methylnaltrexone, alvimopan, or any of the other drugs being developed for clinical use [4].

In postoperative patients requiring potent opioids the use of opioid antagonists may decrease the incidence of postsurgical bowel dysfunction, i.e., prolonged postoperative ileus and constipation [13].

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