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OPIOID-INDUCED CONSTIPATION IN PALLIATIVE CARE. HOW TO PREVENT? HOW TO TREAT?

ZAPARCIA INDUKOWANE OPIOIDOWYMI LEKAMI PRZECIWBÓLOWYMI STOSOWANYMI W OPIECE PALIATYWNEJ. JAK ZAPOBIEGAĆ? JAK LECZYĆ?

Dorota Ksiądzyna[1 A,D,E,F]
Agnieszka Lewandowska[2 A,B,D,E]

[1] Department of Pharmacology, Wroclaw Medical University
[2] Merciful Jesus Hospice in Zakopane

A – przygotowanie projektu badania | study design, **B –** zbieranie danych | data collection, **C –** analiza statystyczna | statistical analysis, **D –** interpretacja danych | interpretation of data, **E –** przygotowanie maszynopisu | manuscript preparation, **F –** opracowanie piśmiennictwa | literature review, **G –** pozyskanie funduszy | sourcing of funding

SUMMARY

Opioid analgetics (the most potent painkillers) are widely used in palliative care of patients with terminal malignant neoplasms. They often cause such gastrointestinal adverse effects as nausea, vomiting, flatulence, abdominal pain and constipation, referred to as opioid-induced bowel dysfunction (OIBD). While some of them, like nausea and vomiting, disappear or at least tend to diminish with continued use, patients do not develop tolerance to opioid-induced constipation. Constipation is an adverse effect of all opioid analgetics and its severity increases with the dose of an opioid, as well as with the progression of the neoplastic disease, markedly decreasing the patient's quality of life.

The incidence of opioid-induced constipation is significantly reduced by the administration of controlled-release tablets containing an opioid receptor agonist and antagonist (oxycodone + naloxone) which acts as a painkiller and reduces the frequency and/or severity of OIBD symptoms. Nowadays, apart from laxatives (initially usually osmotic and/or stimulant agents), new medications such as methylnaltrexone (a peripheral opioid receptor antagonist), administered in subcutaneous injections, are successfully used in the treatment of opioid-induced constipation.

The aim of this review is to present the incidence, etiology, prophylaxis and treatment of opioid-induced constipation in the population of patients with malignant neoplasms in palliative care.

KEYWORDS: opioid analgetics, constipation, palliative care

STRESZCZENIE

Opioidowe leki przeciwbólowe (najsilniej działające analgetyki) stosuje się powszechnie w leczeniu paliatywnym terminalnej choroby nowotworowej. Do ich częstych działań niepożądanych ze strony układu pokarmowego należą między innymi nudności, wymioty, wzdęcia, bóle brzucha i zaparcia, określane jako zaburzenia jelitowe wywołane przez opioidy (ZJWO). O ile niektóre z nich ustępują lub przynajmniej stają się z czasem mniej nasilone, zaparcie nie podlega zjawisku tolerancji. Zaparcie pojawia się po wszystkich analgetykach opioidowych, a jego nasilenie rośnie wraz z dawką leku i progresją choroby nowotworowej, obniżając jakość życia pacjenta.

Prawdopodobieństwo pojawienia się zaparć zmniejsza zastosowanie tabletek o kontrolowanym uwalnianiu zwierających agonistę i antagonistę receptora opioidowego (oksykodon + nalokson), co zapewnia działanie przeciwbólowe i mniejszą częstość/nasilenie objawów ZJWO. W leczeniu zaparć poopioidowych, poza środkami przeczysz-

czającymi (początkowo najczęściej osmotycznymi i/lub pobudzającymi zwoje nerwowe jelit), stosuje się obecnie z powodzeniem nowe preparaty, jak metylonaltrekson (antagonista receptorów opioidowych o działaniu obwodowym) w postaci iniekcji podskórnych.

Artykuł stanowi podsumowanie danych dotyczących częstości, etiologii, profilaktyki i leczenia zaparć indukowanych przez analgetyki opioidowe w populacji pacjentów z rozpoznanym nowotworem złośliwym w opiece paliatywnej.

SŁOWA KLUCZOWE: opioidowe leki przeciwbólowe, zaparcie, opieka paliatywna

Background

Malignant neoplasms constitute, next to cardiovascular diseases, the most frequent cause of death in developed countries [1]. In cases where all available treatments have failed, patients in advanced stages require effective palliative care which includes, inter alia, pain management. Currently, the most effective pain medication are opioid analgetics administered as second (the so-called weak opioids, e.g. tramadol, codeine) and third (the so-called strong opioids, e.g. morphine, oxycodone, fentanyl, buprenorphine) steps of analgesic ladder, according to World Health Organization guidelines [2].

The vast majority of patients in palliative care diagnosed with malignant neoplasms are administered opioid analgetics. A large percentage suffer from opioid-induced adverse effects in the gastrointestinal system, such as dryness in the mouth, nausea, vomiting, flatulence, abdominal pains and constipation, referred to as opioid-induced bowel dysfunction (OIBD) [3]. While some symptoms, e.g. nausea and vomiting, disappear or at least tend to diminish over time, patients do not develop tolerance to opioid-induced constipation, which means not only that the constipation is chronic, but also can become more severe during the course of opioid treatment and have significant negative effect on the quality of life of patients in terminal stage of neoplastic disease [4].

A significant percentage of patients who receive opioids for neoplasm-related pain complain of constipation, which becomes more frequent as the disease progresses [5–6]. According to the available sources, the incidence of constipation in the described population differs: 29.7% [7], 32% [8], 72% [9], 80% [4]. In a study by Dzierżanowski et al. constipation occurred in 65% of the study population, including 76% who were administered strong opioids [10]. Constipation occurs in as many as 88% of patients treated with morphine to ease neoplasm-related pain [11].

These significant disproportions can stem from different methodologies employed in studies, different definitions of constipation and the specifics of the study population, for which the frequency of passing stool may not be the key diagnostic criterion and the subjective assessment of the difficulties connected defecation is not always possible in advanced cases of neoplastic disease. Therefore, different scales are employed to assess constipation in the discussed population, e.g. bowel function index [12]. Usually constipation is diagnosed when the frequency of defecation is < 3 in the previous week or the subjective assessment (difficulties in passing stool, passing hard stool, passing stool with exertion, feeling of incomplete bowel emptying) rates > 3 on the numeric scale [13].

Opioid-induced constipation is caused by how these analgetics, which are antagonists of opioid μ receptors on the *muscularis mucosa* and the gastrointestinal nerve plexus, work and directly and indirectly (via intestinal and central nervous system) affect the gastrointestinal system [14].

Opioid-induced nausea and vomiting have mostly central background, i.e. they are a result of stimulation of the chemoreceptor trigger zone in the brainstem with possible vestibular component, as walking can increase their frequency. They occur mostly in the initial stages of treatment, because the patients later develop a tolerance.

The effect of opioid analgetics on the gastrointestinal system is complex and includes decreased secretion of hydrochloric acid, rhythmic contractions and relaxation of stomach walls, increased resting tension in intestines and decreased amplitude of propulsive contractions, which lengthens the intestinal passage, stool movement and facilitates its dehydration. Moreover, sphincter tension increases, which is accompanied by the rectum being less sensitive to stretching. The result of these changes is nosocomial medication-induced constipation, which in extreme cases manifests with clinical symptoms of ileus.

All opioid analgetics cause constipation which usually constitute the main adverse effect of properly administered opioids used in prolonged treatment in palliative care. In studies on large populations, there is usually no link between the frequency of constipation and the method of administering the opioid [12, 15], but there is a correlation between the dosage and the severity of constipation [16].

Considering that there frequently are concomitant factors which can induce constipation in the discussed group, e.g. prolonged immobilisation, nutrition deficiencies, electrolyte imbalance, insufficient fluid supply, stenosis of the gastrointestinal tract resulting from the underlying condition, treating opioid-induced constipation can be a challenge. It is noteworthy that some of the patients are not given recommendations on preventing constipation and treatment can be ineffective [17]. For example, in the study by Dzierżanowski et al.

every fifth patient of a palliative care facility did not receive early treatment for constipation once opioids were introduced and 77% of the study subjects continued to be constipated despite being administered laxatives [10]. Taking the above into consideration, all initiatives aimed at disseminating relevant knowledge, e.g. guidelines from scientific societies [18] are worth promoting.

Prophylaxis and treatment

Usually the progression of a neoplastic disease causes the patients to become less and less unassisted, and more and more dependent on others, in many cases close family members. A key feature of effective prophylaxis and treatment of opioid-induced constipation is educating the patients and caregivers, both in the form of spoken instructions and information brochures. The information received should stress such issues like diagnosis, prophylaxis, pharmacological and non-pharmacological methods of treating constipation and identifying adverse effects of administered medication. In case of doubt, patients and caregivers should be able to seek professional counsel from palliative care personnel.

Just because the patient is administered opioids, does not mean there are no other causes of constipation and means supplementing water-electrolyte deficiencies (dehydration, hypercalcaemia, hypokalaemia), endocrine conditions (diabetes mellitus, hypothyroidism) or attempts to modify the dosages of other medication that can cause constipation (diuretics, anti-cholinergic medication, anticonvulsants, some medication for hypotension). An alternative route of treatment can be changing an opioid for a different one from the same group (so-called opioid rotation), e.g. tramadol can substitute codeine or dihydrocodeine, and fentanyl and buprenorphine – morphine and oxycodone. In spite of a lack of clear evidence supporting the parenteral delivery route (patches with buprenorphine and fentanyl) over oral (controlled-release morphine), such change can prove beneficial for some patients.

Numeric scale, where constipation is usually one of the studied factors, is recommended for monitoring the effectiveness of treating constipation, with 0 pts corresponding to no constipation and 10 pts to very severe constipation [19].

The general rules for prophylaxis and treatment for constipation are not significantly different in their assumptions from those for symptomatic treatment of constipation with different aetiology. If the patient's conditions allows it, prolonged immobilisation should be avoided. Patients should be provided with sufficient liquids (usually at least 2l/day) and, when possible, fibre-rich diet, i.e. 20–30 g of fibre/day (wheat bran, oat flakes, fruit, vegetables) and/or dietary supplements containing fibre. However, some patients do not tolerate such diet due to flatulence and increased passing gas.

Moreover, it is important to provide privacy and seated position (when possible), the most effective from the point of view of the abdominal prelum, during defecation, e.g. by using special toilet chairs.

Due to the frequent and chronic character of constipation among patients treated with opioid analgetics, laxatives should be introduced together with the opioid.

Drugs for increasing faeces volume, similarly as natural fibre, require the ingestion of at least 2 litres of fluids per day. They are reserved for patients in relatively good overall condition, without dysphagia or anorexia-cachexia syndrome. Insufficient fluid supply can cause the formation of mucus plugs and symptoms of ileus. The effectiveness of the preparations in opioid-induced constipation is lower than other laxatives, especially in patients in advanced stages of neoplastic disease.

Table 1. Medication used to treat constipation [20]

Group	Examples
Drugs for increasing faeces volume	Natural – methyl cellulose, psyllium seeds Synthetic – polycarbophil
Laxatives	Docusate Glycerine in suppositories Mineral oils, e.g. paraffin oil
Osmotic drugs	Non-absorbable sugars – lactulose, sorbitol Non-absorbable salts – magnesium hydroxide (so-called milk of magnesia), magnesium sulfate (so-called bitter salt), magnesium citrate, sodium sulfate (Glauber's Salt), trisodium phosphate Polyethylene glycol (PEG), macrogols
Gastro-intestinal irritants	Plant origin anthranoids – aloes, senes Diphenylmethane derivatives – bisacodyl
Mucous chloride channel activators	Lubiprostone
Opioid receptor antagonists	Methylnaltrexone, naloxone, alvimopan
$5HT_4$ serotonin receptor agonists	Tegaserod, cisapride, itopride, prucalopride
Guanylyl cyclase agonist	Linaclotide

The basic treatment comprises of an osmotic laxative, such as lactulose and polyethylene glycol, and drugs stimulating nerve plexuses of the colon, and, if required, other groups of drugs (table) [20]. Among stimulants, the most frequently used is senes and among osmotic drugs lactulose, although macrogols are usually better tolerated. Due to the fact that the population of patients with neoplastic disease in palliative care are usually not studied for effectiveness and tolerance for laxatives, it is difficult to unambiguously state which drugs are better and, therefore, each case is treated individually. Combination therapy with several laxatives with different mechanisms of action is one of the available treatment modalities. Treating consti-

pation, similarly as treating neoplasm-induced pain, requires subsequent introduction of different groups of laxatives, usually according to the recommended scheme: level I – osmotic drugs (lactulose or macrogol) and stimulants (antranoids or polifenols), level II – rectal suppositories, level III – rectal infusions with physiological saline (100–200 ml) or phosphates (120–150 ml)/manual stool extraction after sedation (anti-anxiety medication) and anaesthesia (local and general) to limit pain/discomfort connected with the procedure as much as possible. Detailed data on dosage of particular drugs can be found in the guidelines of the Polish Society of Palliative Medicine Expert Group [18].

Metoclopramide, one of the most popular prokinetic agents, stimulates mainly the peristalsis of the upper gastrointestinal tract and is not recommended in prolonged treatment [20]. On the other hand cisapride was withdrawn in many countries due to severe adverse effects (documented cases of fatal arrhythmia) [20]. An alternative to these two prokinetics is itopride, available in Poland, but its effectiveness was not assessed among patients administered opioid analgetics due to neoplasm-induced pain, similarly as in the case of many other drugs used to treat constipation with different etiology, e.g. prucalopride, linaclotide or lubiprostone [20].

Recently, drugs for opioid-induced constipation have emerged on the Polish market, e.g. tablets with controlled-release containing an opioid receptor agonist and antagonist (oxycodone + naloxone) in 2:1 proportion, which act as painkillers and decrease OIBD symptoms, including constipations, in treating neoplasm-induced [21] and non-neoplasm-induced [22] pain. The drug is available under the name Targin®, in four doses (5/2.5; 10/5; 20/10; 40/20 mg of oxycodone and naloxone, respectively) and is provided free of charge within the limit (with the exception of 40/20 mg dose) in the following indication: neoplasm-induced pain – in patients suffering from opioid-induced constipation. The maximum recommended daily dose is 80 mg + 40 mg in two divided doses.

Another drug is methylnaltrexone, an opioid receptor antagonist with peripheral effect (trade name: Relistor®, vials: 12 mg/0.6 ml), available in Poland as fully paid (registered indication in Europe: treatment of opioid-induced constipation in patients with advanced diseases, in palliative care, in whom response to laxatives was insufficient). The effectiveness of a single subcutaneous dose is 50–60% [23–24], without the loss of pain-reducing effect of opioid and without the symptoms of withdrawal syndrome. Methylnaltrexone can be administered ad hoc and regularly, every 2 days, when treating persistent opioid-induced constipation. Administering this drug is recommended with caution, as it carries a significant risk of fatal intestine perforation and the absolute contraindications include symptoms of gastrointestinal tract obstruction and acute abdominal conditions.

Conclusions

Constipation, which is a frequent adverse effect of opioid analgetics, regardless of their mode of administration, carries significantly negative effect on the quality of life of patients in terminal stages of neoplastic disease. Despite the availability of different laxatives and new drugs, treating opioid-induced constipation is suboptimal. The cause can be insufficient awareness of the staff providing palliative care to patients suffering from neoplasm-induced pain of the need for prophylaxis and treatment for constipation and of the availability of modern opioid analgetics, as well as the patient's and their family's resistance to taking more drugs or disregarding the problem of constipation altogether in view of the underlying condition, i.e. advanced neoplastic disease.

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Correspondence address:
Dorota Ksiądzyna
Department of Pharmacology
Wroclaw Medical University
J. Mikulicza-Radeckiego str. 2
50-345 Wrocław
phone: +48 71 784 1438
e-mail: dorota.ksiadzyna@umed.wroc.pl

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