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Prolonged-release oxycodone/naloxone in the treatment of cancer pain — a case report

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ABSTRACT

In moderate and strong cancer pain oxycodone has become one of the most effective and popular opioids. A combination of prolonged-release oxycodone with prolonged-release naloxone is a valued option among patients suffering from pain and opioid-induced bowel dysfunction (OIBD).

We present a case of a male cancer patient with chronic constipation effectively treated with oxycodone/naloxone combination.

Key words: cancer pain, oxycodone, naloxone, opioid-induced bowel dysfunction

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Introduction

For the last few decades, the World Health Organisation's (WHO) analgesic ladder has remained a basis for decisions made in order to palliate chronic pain. However, its basic form, which includes non-opioid drugs, weak and strong opioids, as well as coanalgesic drugs, is undergoing modifications and is being discussed. The role of drugs of the second 'step' of the ladder, treating neuropathic pain, transient pain management, or aiming at minimisation of adverse drug reactions, remains a subject of discussion [1, 2]. The latter issue has a particular importance in a situation when we reach (or we would be able to reach) a desired analgesic effect, but we are forced to stop the treatment when the adverse effects of the therapy exceed its observed advantages. In clinical practice we face such a situation in cases of occurrence and increase of opioid-induced bowel dysfunction (OIBD), among others.

Case report

A 68-year-old man was admitted into the care of a home hospice in advanced stage of right thigh sarcoma with lung metastases. In the 1990s the patient underwent

a bilateral nephrectomy at different times due to polycystic kidney disease, with follow-up haemodialysis for many years. The patient was under the constant care of the nephrologist, he chronically used antihypertensive drugs, and for many years he complained of habitual constipations related to multiple hospitalisations, restriction of fluid intake, and decreased physical activity. Four years before diagnosis of the sarcoma, a successful kidney transplantation from the unrelated donor was conducted. The patient was on immunosuppressive drugs. Due to improvement in the patient's general condition, including an increase in everyday physical activity and decrease in body weight, the doses of the antihypertensive drugs were reduced, and the patient only sporadically required laxatives.

In 2014, the sarcoma of the right thigh was diagnosed. Despite surgical therapy, radiotherapy, and chemotherapy we observed rapid progression of the disease with the development of lung metastases and increased pain in the right lower limb. Due to bad tolerance to tramadolol (nausea, dizziness) and the nephrologist's recommendation to reduce the non-steroidal anti-inflammatory drugs to emergency doses, the primary care physician ordered administration of prolonged-release morphine in an initial dose of 20 mg per day. Due to incomplete pain control (NRS score: 6 at rest, 8 in movement) the

patient reduced his physical activity. At the same time a renewed increase in constipation incidences was observed. The attending physician decided to discontinue morphine, and introduced fentanyl TTS in a dose gradually increasing to 75 µg/h every 3 days. Control of pain at rest was improved (NRS 4), while the intensity of symptoms during physical activity ranged between 7 and 8 NRS score. The patient still complained of persistent feeling of fullness in the abdominal cavity and a sensation of incomplete defecation. Commonly used means (fibre, bran, senna) did not improve his condition. The tolerance of lactulose was bad (nausea), and due to its poor effects patient refused to take the drug. Difficulties in defecation were connected to the necessity of long stays in the toilet, which enhanced the thigh pain.

Due to the disease stage, the oncologist decided to refer the patient to the care of a home hospice. At admission, the patient's general condition was moderate, with full logical contact. He was able to move around the apartment on his own, he also decided on his own about taking numerous drugs. The patient was supported by his wife in his everyday functioning. In her opinion, the pain control was insufficient. The patient's wife thought that the patient dissimulated because he did not want to worry his family. On the other hand, she thought that her husband overestimated the problem with proper defecation (*"Instead of reporting to the doctor the thigh pain, he constantly asks about the constipations, and yet he hardly eats"*). Due to the above-mentioned pain intensity (NRS 4 at rest and 7 in movement) and a sensation of significant discomfort in the abdominal cavity (flatulence, periodically painful distension) the hospice physician decided to include a preparation of oxycodone with naloxone in a total dose of 30 mg + 15 mg every 12 hours. The fentanyl TTS was discontinued. Significant reduction of dyspeptic symptoms, remission of nausea, and an increase in the frequency of defecations to three times per week was obtained. However, the patient reported a lack of improvement of the pain relief and temporary intensification of the ailments. The dose was increased to 40 mg of oxycodone in combination with 20 mg of naloxone every 12 hours. A decrease in the intensity of pain to 1–2 points at rest and 4 in movement and normalisation of the defecation rhythm was reached. In the case of the transient pain occurring 1–2 times a day (NRS 6–7) an oral solution of oxycodone was used. A dose of 15 mg was assessed as sufficient by the patient.

Continued progression of the disease was observed as well as the necessity of staying in bed due to his general condition, increasing exhaustion, and dependence on the carers, and also concerning the administration of drugs.

In this period, a difficult to explain increase in pain was observed for several days, although the ailments were well controlled at rest. The answer was found after a conversation with the patient's wife. Unsure

about what drugs her husband had already taken (as mentioned earlier, the patient previously controlled them on his own), she significantly reduced the dose of the recommended oxycodone/naloxone because of the fact that constipations subsided (*"Now I do not give him this thing for the constipations"*). Thus, the indications and necessity of regular use of the analgesic in the dose recommended by the physician was explained to the patient's wife one more time. The pain ailments were again significantly alleviated. The patient died due to the advanced stage of the neoplastic process with depletion. The 40/20 mg oxycodone/naloxone dose every 12 hours provided good pain control until the patient's death.

Discussion

Relieving the pain ailments is one of the main aims of palliative care of terminally ill patients [2]. Establishing the causes, type, and intensity of pain and implementation of adequate procedure [3] remains the subject of attention. An increasingly broad role in chronic pain treatment is played by the application of drugs in the third step of the analgesic ladder, including oxycodone [4–6]. The drug, similarly to other strong opioids, is used in cases when there is no effect of applying the first- and second-step drugs, in cases of intolerance to drugs of the third step, and in cases of rotation of opioids [7]. Clinical research indicates the effectiveness of oxycodone in visceral and somatic pain and in treating neuropathic pain [8–10]. The results of the meta-analysis conducted by Wang et al. confirm the high effectiveness of oxycodone in controlling pain in comparison to codeine sulphate, tramadol, and other strong opioids [8].

However, therapeutic possibilities are often limited by the adverse drug reactions, including the opioid-induced bowel dysfunction, occurring in patients treated for cancer pain as well as for pain not related to cancer [11]. Incidence of constipations is also influenced by factors that are not directly connected to opioids, among others (similarly to the presented patient), coexisting conditions, other taken drugs, decrease in fluid intake, overusing laxatives in the past, and others. The laxatives prescribed prophylactically and during the opioid therapy can improve bowel function. Nevertheless, a significant number of patients do not obtain reduction of OIBD symptoms due to their complex nature [11]. OIBD can occur in 65–85% of patients treated with opioids, despite the fact that the majority of patients (80–90%) takes laxatives [12, 13]. Due to the complex nature of OIBD and 'environmental' factors (no privacy, bad hygienic conditions, feeling of embarrassment, etc.) commonly used laxatives do not give (as in the described case) expected results [13]. In the studies by Papagallo et al., among patients suffering from cancer pain, constipation

(less than three full defecations per week) related to the taken opioids was diagnosed in about 40% of patients (in comparison to 7.6% in the control group). Among those who required laxatives, the expected effect of treating constipations was reached only in 46% of patients treated with opioids (84% in the control group) [11].

The basic symptoms of OIBD do not go away and can even increase with the course of taking opioids [4, 14]. Constipations, forming dry, hard stools, flatulence, convulsive abdominal pain, heartburn, nausea, and vomiting are often the reasons for using too low drug doses or even resigning from the treatment [13, 15]. Those symptoms decrease patients' comfort of life and their everyday activity, and lower the anti-pain effectiveness of analgesics [11–13]. Moreover, the convulsive abdominal pain from intolerance to anthracene compounds or nausea and flatulence with the usage of lactulose can additionally deteriorate the quality of life of patients.

It needs to be remembered that we can talk about the opioid-induced constipations when a patient using weak or strong opioid suffers from lowered frequency of defecations (below three per week) or when a patient reports difficulties with defecation, sensation of incomplete defecation, discharging stool with strong effort, or evacuating hard stool. The so-called Bowel Function Index (BFI) can also be helpful in the assessment of the problem [14, 16, 17]. The three basic parameters: difficulties in defecation, sensation of incomplete defecation, and assessment of the constipation intensity occurring in the last 7 days are scored on a scale from 0 to 100 (or 0 to 10). An average score of over 28.8 (over 2.9, respectively) gives a diagnosis of constipation [14, 18]. Assessment using the BFI allows confirmation of the effectiveness of the oxycodone/naloxone compound preparation in OIBD. It is worth noting the results of the research by Hermanns et al., in which implementation of pain treatment using oxycodone/naloxone resulted in reduction of the BFI score value from 41.6 ± 31.6 to 16.5 ± 19.6 ($p < 0.001$) with an increase in the estimated quality of life by 47% at the same time [16].

Incidents of adverse drug reactions can be the reason for the decision to change one opioid to another (rotation of opioids). In the mentioned work of Wang et al. better tolerance and much less frequent incidence of nausea and constipations was proven in patients treated with oxycodone in comparison to the remaining groups ($p = 0.01$) [8]. In the research of Rosti et al., concerning factors predisposing patients under pain treatment to OIBD, an association between different opioids and different risk of the incidence of these symptoms was shown. Morphine was associated with the highest frequency of constipation, and the lowest risk was noted for oxycodone and buprenorphine TTS. The OIBD incidence was significantly influenced by the coexistence of neoplastic disease, old age, and using fentanyl [12].

The search for proper procedures, based on mechanisms of OIBD development, led to use of a combination of a strong opioid with an opioid receptor antagonist in treating patients with constipations for cancer pain [11]. Naloxone shows a much stronger affinity to opioid receptors in the intestinal wall than does oxycodone. Its peripheral action leads to the improvement of bowel function and reduction of the problem of constipation. Additionally, naloxone is almost entirely eliminated in the liver, while the active form of oxycodone is absorbed into the blood circulation and its central analgesic action is undisturbed. Clinical research confirms that naloxone does not lower the painkilling effectiveness of oxycodone in treating cancer pain as well as non-cancer pain [16, 17, 19, 20]. The combination of oxycodone with naloxone remains an effective analgesic in this mechanism, simultaneously showing a significant beneficial influence on prophylaxis and treatment of OIBD [19–22]. The basic contraindications to use oxycodone/naloxone include hepatic dysfunction, nephrolithiasis, paralytic ileus, other obstructive and inflammatory intestine conditions, pancreatitis, diarrhoea, and hypersensitivity to the ingredients of the preparation. Proper selection of the drug dose is necessary. In the presented case, the estimated initial dose proved not entirely effective (perhaps due to the insufficient analgesic effect of fentanyl TTS). Good control was achieved after implementation of the daily dose of 80 + 40 mg and 15–30 mg of oxycodone solution in cases of transient pain. In our patient's opinion, he did not require a higher total dose of oxycodone, although there was such a possibility. It is noteworthy that the maximum daily dose of oxycodone/naloxone is 160/80 mg per day.

Summary

The management of pain with the use of preparations combining oxycodone and opioid receptors' antagonist ensures reduction of pain while preventing or decreasing OIBD symptoms at the same time. It improves not only the patient's physical condition but also his/her psychological condition and contact with the surrounding environment allowing him/her to participate in family life [8]. The compound preparation of oxycodone/naloxone, being an effective analgesic, reduces constipations and other dyspeptic symptoms, thus improving the quality of patients' lives.

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