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We report a patient with advanced cancer of unknown primary site and severe pain successfully switched from high dose of controlled-release (CR) morphine to CR oxycodone. A 71-year-old man was admitted to home hospice due to cancer dissemination to bones and cervical lymph nodes after palliative radiotherapy. His main complain was severe pain (NRS 6-8) in the cervical and thoracic spine that was non-responsive to tramadol, subsequently changed to transdermal fentanyl and CR morphine with final daily dose of 240 mg (40 mg for breakthrough pain) and constipation. Regular morphine was stopped and CR oxycodone 80 mg twice daily was started, after 6 weeks increased to the dose of 100 mg twice daily achieving satisfactory analgesia (NRS 3-4). No significant adverse effects were present during CR oxycodone therapy. The patient continued his regimen successfully until seizure episode due to brain metastases development and referral to a hospital for further treatment.

Key words: advanced cancer, adverse effects, analgesia, cancer pain, controlled-release morphine, controlled-release oxycodone, opioid switch.

The use of a high dose of controlled-release oxycodone in a switch from oral morphine: a case report

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Introduction

The management of moderate to severe pain in cancer patients is based on opioid analgesics therapy combined with co-analgesics administration and non-pharmacological measures application depending on the type of pain and cancer. An essential part of palliative care is appropriate other symptoms treatment, psychosocial and spiritual support and good communication with the patient and family [1, 2]. However, when a given opioid therapy fails opioid switch (OS) is one of possible methods to achieve satisfactory analgesia without intense adverse effects [3]. The rationale of OS is limited cross-tolerance between opioid analgesics, probable different receptors occupation and differences in pharmacodynamics and pharmacokinetics [4]. It is estimated that approximately 60-90% of patients benefit from changing opioids [5]. Opioid switch is indicated when pain is not relieved in spite of escalating opioid doses. In most cases, however, severe adverse effects of opioids are indication for OS [6]. There are no clear guidelines which opioids are best for OS [7]. Methadone seems to be effective when morphine or other opioids fails [8]. However, methadone displays complex pharmacokinetics and its dosing needs significant expertise [9]. Moreover, QT prolongation may lead in some patients to increased risk of arrhythmia [10]. One of the commonly used opioids for moderate to severe pain is oxycodone. A limited clinical experience in switching from high doses of morphine to oxycodone exists. In this scenario problems encountered by clinicians might be choosing an appropriate starting oxycodone dose that provides satisfactory analgesia and tolerable adverse effects. The aim of this case report is to depict a patient with disseminated cancer of unknown primary site who was successfully switched from high dose of controlled-release (CR) morphine to CR oxycodone.

Case report

A 71-year-old man was admitted to home hospice due to the progression of cancer. In March 2010 on a computed tomography (CT) scan a cervical tumour (50 mm × 60 mm) with infiltration of the internal jugular vein and common cervical artery was diagnosed. A biopsy revealed squamous cell carcinoma keratodes G1. However, other investigations such as chest x-ray, abdominal ultrasound and laboratory test results were normal and the primary tumour site was unknown. In April 2010 the patient underwent a short course of palliative radiotherapy with a total dose of 30 Gy in ten fractions.

As moderate pain appeared the patient received NSAIDs with increasing doses of CR tramadol up two 150 mg twice daily prescribed by a family physician. In May 2010 the patient was admitted to home hospice due to progressive cachexia and severe pain located in the neck radiating to the occipital region. Tramadol was stopped and substituted with transdermal fentanyl (TF) 25 μg/h

with amitriptyline 25 mg and diclofenac 100 mg once daily, which provided good analgesia.

In June 2010 positron emission tomography (PET) scan unveiled hyper metabolic cervical lymph nodes and dorsal muscles and numerous active metabolic lesions in the left lung, occipital bone and thoracic spine (Th2). In August 2010 scintigraphy revealed additional lesions in occipital bone, spine (C2 and Th2), and in the middle of clavicle. An x-ray unveiled a narrowing space Th1/Th2, atrophy of Th2, compression fracture of Th7, osteoporosis and spondyloarthrosis. Due to pain a single dose (6 Gy) of radiotherapy on the field C2-Th2 was administered and TF dose was increased to 50 μg/h and amitryptyline to 50 mg once daily. For a few months pain was effectively controlled with rescue doses of oral morphine.

In January 2011 a local dermatitis at the site of TF application intensified in spite changing TF formulations and antihistamines administration. In February 2011 the patient underwent switch from TF to CR morphine (120 mg daily) with immediate-release (IR) rescue morphine 20 mg, metoclopramide 10 mg t.i.d., diclofenac 75 mg b.i.d., dexamethasone 3 mg and pantoprazol 20 mg once daily, lactulose 15 ml t.i.d. and pamidronate 90 mg every 4 weeks. In scintigraphy new lesions in the whole spine and ribs appeared. The general patient condition deteriorated, morphine dose was increased to 180 mg daily and carbamazepine was added 200 mg o.i.d. then b.i.d.

In April 2011 due to severe pain (NRS 8) a single dose of 6 Gy on C3-Th5 and after 3 weeks doses of 6 Gy on Th4-Th7 and L3-L5 fields were administered. Morphine dose was increased to 240 mg daily (40 mg for breakthrough pain). The patient also received diclofenac 75 mg b.i.d., dexamethasone 2 mg b.i.d., pamidronate 90 mg every 4 weeks, amitryptyline 50 mg before sleep, carbamazepine CR 200 mg b.i.d., pantoprazol 40 mg o.i.d., alprazolam 0.25 mg, metoclopramide 10 mg and lactulose 15 ml (all t.i.d.) and rectal enemas (bowel movement once or twice a week).

His main complain was severe pain (NRS 6-8) in cervical and thoracic spine, depicted as dull, with burning and tingling, intensifying on head and shoulder movements but also without any factors. The general patient condition was poor with significant cachexia, most of the time spend in bed but able to walk at home. Laboratory tests normal (creatinine, electrolytes, blood count) with moderate haemoglobin level 10 g%. Pain was non-responsive to morphine and adjuvants. Regular CR morphine (240 mg daily) was stopped and CR oxycodone started. Morphine to oxycodone dose ratio used in this patient was 4 : 3 indicating the dose of CR oxycodone 180 mg daily; the dose was reduced by 10%, to the starting CR oxycodone daily dose 160 mg (80 mg twice daily). Analgesia was satisfactory (NRS 3-4) with on average one rescue dose of IR morphine 30 mg per day for 6 weeks with improvement in well-being and bowel movements; lactulose and alax (a combination of stimulant herbs in one tablet) were administered with no need of rectal enema. After that period pain intensified and CR oxycodone dose was increased to 100 mg twice daily providing again satisfactory analgesia. No significant adverse effects were present during oxycodone therapy. The patient continued his regimen until seizure episode appearance due to brain metastases and referral to a hospital for further treatment.

Discussion

This case report is an example of successful switch from high dose of CR morphine to CR oxycodone during the care of a patient with advanced cancer with unknown primary site and severe pain due to tumour infiltration of cervical and thoracic spine. Pain was associated with local tumour invasion and had mixture bone and neuropathic elements. First, it was necessary to switch from TF to CR morphine due to intense local dermatitis [11]. However, pain did not respond to morphine and adjuvants. The next switch from morphine to oxycodone allowed achieving satisfactory analgesia and less constipation. Oxycodone analgesic efficacy may be associated with its action on κ opioid receptors [12]. Another explanation may be oxycodone quicker crossing blood-brain barrier [13] and lack of metabolites such as morphine3-glucuronide that may be responsible for ineffective morphine analgesia [14].

Oral oxycodone is step III analgesic ladder opioid recommended by the EAPC (European Association for Palliative Care) as the first choice for moderate to severe pain in cancer patients along with oral morphine and oral hydromorphone [15]. Oxycodone may be also the first opioid administered to opioid-naive patients [16] or used in patients unsuccessfully treated with weak opioids [17]. Oxycodone is also effective in OS when morphine [18] and buprenorphine fails [19].

Few studies considered high doses of oxycodone in cancer pain. Mercadante *et al.* [20] prescribed CR oxycodone in 212 patients for background analgesia. 129 patients received the dose of less than 120 mg per day (group 1), 43 patients received the dose of 120 to 240 mg daily (group 2) and 40 patients received the dose over 240 mg per day (group 3). Overall, the mean daily dose of oral oxycodone was 141 ±167 mg (range 10-960 mg). The mean daily dose of oral oxycodone was 48.4 ±25 mg, 156.5 ±30.5 mg and 435 ±196 mg in group 1, 2 and 3, respectively. No differences in gender, primary diagnosis and pain mechanism were found. Doses were significantly lower in older patients ($p < 0.0005$). The mean pain intensity was 2.9 ±1.9; adverse effects were of mild intensity and not related to oxycodone doses. High doses of oxycodone were safe and effective.

Bercovitch and Adunsky [21] retrospectively compared high and low CR oxycodone in 97 consecutive patients with cancer pain. Only 18 (18.55%) patients were treated with a high dose of CR oxycodone (mean 231.1 mg per day). The daily mean CR oxycodone dose was 78.6 mg for all patients. Apart from patients with painful bone metastases who consumed higher oxycodone doses ($p = 0.008$), a correlation was not found between demographic parameters and the dose range. No differences were observed in sleep quality and mood as a factor of CR oxycodone doses. Survival was not related with CR oxycodone doses. However, patients that were treated with higher CR oxycodone doses maintained Karnofsky scores higher than 40 points most of the time in comparison to patients receiving low dose CR oxycodone. The use of high dose CR oxycodone was safe and efficient and unrelated with shorter survival.

Ferrarese *et al.* [22] investigated the role and tolerability of high-dose (over 160 mg per day) CR oxycodone for the treatment of cancer (207 patients) and non-cancer pain

(20 patients) in a multi-center Italian study. Pain was poorly controlled at baseline with only 18.1% of patients reporting adequate pain relief (NRS < 3.5). All other patients reported uncontrolled pain, with an average NRS of 7.81. At baseline, 47.89% patients had been in pain for up to 3 months, 32.82% for 3-6 months, and 19.19% for more than 6 months. Patients were switched to CR oxycodone monotherapy. The initial dose was individualized for each patient and titrated over 3-4 days until effective analgesia was achieved. Treatment was continued for an average of 37.24 days. The mean NRS (2.85) was obtained with an average CR oxycodone dose of 221.84 mg per day. Typical adverse effects of opioids (constipation, nausea and vomiting) were recorded in 39.64% patients receiving high-dose CR oxycodone and diminished after the first week of treatment and did not cause withdrawal from the study. High-dose CR oxycodone effectively treated moderate to severe cancer and non-cancer pain.

We used oxycodone to morphine dose ratio 3 : 4 as indicated for morphine to oxycodone switch in a clinical study [23], which was successful providing satisfactory analgesia and good tolerance of the treatment. However, the equivalent dose ratio between oral oxycodone and oral morphine may differ from 1 : 1 to 2.3 : 1 [24, 25]. The oral oxycodone to oral morphine ratio may also depend which opioid is given first: when morphine is given first and then switched to oxycodone it is 3 : 4 and when oxycodone is administered first and then switched to morphine it is 2 : 3. In this randomised, double-blind cross-over study the daily doses of morphine and oxycodone after titration were 180 and 123 mg, respectively [23]. As in Poland oxycodone is available only in oral CR formulations, we have to use IR morphine as rescue medication. However, this approach was successful in patients treated with CR oxycodone [26] and our patient received only one daily rescue dose of morphine, which indicates satisfactory analgesia.

After switch to oxycodone constipation intensity decreased. Although comparative studies do not show much difference between morphine and oxycodone with respect to gastrointestinal adverse effects [24], in some studies nausea and vomiting were less common with oxycodone [23, 26] and oxycodone induced more constipation [23]. The change in constipation intensity in our patient might be attributed to addition of alax tablet to lactulose regimen and individual toleration to morphine and oxycodone gastrointestinal adverse effects. Although in our patient OS from morphine to oxycodone was successful other treatment options might be considered. A change from oral to subcutaneous or intravenous of morphine administration route may be used [27]. Other possibilities include a switch from carbamazepine to gabapentin or pregabalin, which do not interact with morphine metabolism, systemic or local use of lignocaine alone or in combination with corticosteroids injection and addition of subanesthetic doses of ketamine to morphine [28].

To conclude successful and safe switch from high dose of CR oral morphine to oral CR oxycodone is feasible. Although OS is usually performed at in-patient units in the patient depicted OS was safely conducted at home with constant monitoring and our patient received only one rescue dose of morphine per day, which indicates satisfacory analgesia.

References

1. Hanks GW, Conno F, Cherny N, et al.; Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001; 84: 587-93.
2. Krajnik M, Wordliczek J, Dobrogowski J. Standardy leczenia bólu u chorego na nowotwór. Terapia 2010; 248-249: 3-9.
3. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995; 10: 378-84.
4. Hardy JR, Quigley C, Ross JR. Opioid rotation. In: Opioids in Cancer Pain. Davis MP, Glare P, Quigley C, Hardy JR (eds.). 2nd edition. Oxford University Press, Oxford 2009; pp. 301-12.
5. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. Cancer 1999; 86: 1856-66.
6. Mercadante S, Bruera E. Opioid switching: a systematic and critical review. Cancer Treat Rev 2006; 32: 304-15.
7. Leppert W. Postępy w leczeniu farmakologicznym bólu nowotworowego analgetykami opioidowymi. Wspolczesna Onkol 2009; 13: 66-73.
8. Leppert W. The role of methadone in cancer pain treatment – a review. Int J Clin Pract 2009; 63: 1095-109.
9. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 1998; 16: 3216-21.
10. Leppert W. Methadone cardiotoxicity in pain management – an important issue for clinicians. Clinical medicine insights. Therapeutics 2010; 2: 1-6.
11. Schmid-Grendelmeier P, Pokorny R, Gasser UE, Richarz U. A comparison of the skin irritation potential of transdermal fentanyl versus transdermal buprenorphine in middle-aged to elderly healthy volunteers. Curr Med Res Opin 2006; 22: 501-9.
12. Khotib J, Narita M, Suzuki M, Yajima Y, Suzuki T. Functional interaction among opioid receptor types: up-regulation of μ- and δ-opioid receptor functions after repeated stimulation of κ-opioid receptors. Neuropharmacology 2004; 46: 531-40.
13. Boström E, Simonsson US, Hammarlund-Udenaes M. In vivo blood-brain barrier transport of oxycodone in the rat: indications for active influx and implications for pharmacokinetics/pharmacodynamics. Drug Metab Dispos 2006; 34: 1624-31.
14. Flemming K. The use of morphine to treat cancer-related pain: a synthesis of quantitative and qualitative research. J Pain Symptom Manage 2010; 39: 139-54.
15. King SJ, Reid C, Forbes K, Hanks G. A systematic review of oxycodone in the management of cancer pain. Palliat Med 2011; 25: 454-70.
16. Tessaro L, Bandieri E, Costa G, Fornasier G, Iorno V, Pizza C, Pastacaldi G, Micheletto G. Use of oxycodone controlled-release immediately after NSAIDs: a new approach to obtain good pain control. Eur Rev Med Pharmacol Sci 2010; 14: 113-21.
17. Leppert W. Role of oxycodone and oxycodone/naloxone in cancer pain management. Pharmacol Rep 2010; 62: 578-91.
18. Riley J, Ross JR, Rutter D, Wells AU, Goller K, du Bois R, Welsh K. No pain relief with morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. Support Care Cancer 2006; 14: 56-64.
19. Leppert W. Successful switch from transdermal buprenorphine to oral controlled-release oxycodone in a patient with locally advanced prostate cancer: a case report and review of the literature. Wspolczesna Onkol 2011; 15: 186-9.
20. Mercadante S, Ferrera P, David F, Casuccio A. The use of high doses of oxycodone in an acute palliative care unit. Am J Hosp Palliat Med 2011; 24: 242-4.
21. Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. J Pain Palliat Care Pharmacother 2006; 20: 33-9.
22. Ferrarese F, Becchimanzi G, Bernardo M, et al. Pain treatment with high-dose, controlled-release oxycodone: an Italian perspective. Ther Clin Risk Manag 2008; 4: 665-71.
23. Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. Pain 1997; 73: 37-45.
24. Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, Babul N, Ford I. Randomized, double-blind, cross-over trial comparing

safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol 1998; 16: 3222-9.
25. Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: are they all equally dangerous? J Pain Symptom Manage 2009; 38: 409-17.
26. Lauretti GR, Oliveira GM, Pereira NL. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. Br J Cancer 2003; 89: 2027-30.
27. Enting RH, Oldenmenger WH, van der Rijt CC, Wilms EB, Elfrink EJ, Elswijk I, Sillevis Smitt PA. A prospective study evaluating the response of patients with unrelieved cancer pain to parenteral opioids. Cancer 2002; 94: 3049-3056.
28. Leppert W. Pain management in patients with cancer: focus on opioid analgesics. Curr Pain Headache Rep 2011; 15: 271-9.

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