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Review

Role of oxycodone and oxycodone/naloxone in cancer pain management

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Abstract:
Oxycodone is a valued opioid analgesic, which may be administered either as the first strong opioid or when other strong opioids are ineffective. In case of insufficient analgesia and/or intense adverse effects such as sedation, hallucinations and nausea/vomiting a switch from another opioid to oxycodone might be beneficial. Oxycodone is administered to opioid-naive patients with severe pain and to patients who were unsuccessfully treated with weak opioids, namely tramadol, codeine and dihydrocodeine. Oxycodone effective analgesia may be attributed to its affinity to μ and possibly κ opioid receptors, rapid penetration through the blood-brain barrier and higher concentrations in brain than in plasma. Oxycodone displays high bioavailability after oral administration and may be better than morphine in patients with renal impairment due to the decreased production of active metabolites. Recently an oral controlled-release oxycodone formulation was introduced in Poland. Another new product that was launched recently is a combination of prolonged-release oxycodone with prolonged-release naloxone (oxycodone/naloxone tablets). The aim of this review is to outline the pharmacodynamic and pharmacokinetic properties, drug interactions, dosing rules, adverse effects, equianalgesic dose ratio with other opioids and clinical studies of oxycodone in patients with cancer pain. The potential role of oxycodone/naloxone in chronic pain management and its impact on the bowel function is also discussed.

Key words:
cancer pain, constipation, controlled-release oxycodone, immediate-release oxycodone, oxycodone, oxycodone/naloxone, pain treatment

Introduction

Cancer pain treatment is based on the analgesic ladder, which was established in 1986 by the World Health Organization (WHO) [100]. In most cancer patients, pain is successfully relieved using opioids alone or in combination with adjuvant analgesics (co-analgesics) in accordance with the WHO analgesic ladder. Cancer pain management guidelines in Poland [18, 35] are based on EAPC (European Association for Palliative Care) recommendations. Morphine use is recommended by the Expert Working Group of the EAPC at the 3rd step of the WHO analgesic ladder, which is comprised of additional opioids (oxycodone, fentanyl, buprenorphine, methadone, hydromorphone*) for the treatment of moderate to severe pain intensity [31]. Each step of the WHO analgesic ladder: non-opioids, weak opioids (analgesics for mild to moderate pain) and strong opioids (opioids for moderate to severe pain intensity) is accompanied with adjuvant analgesics (co-analgesics), which enhance opioid analgesia (e.g., bisphosphonates in bone pain, anticonvulsants and antidepressants in neuropathic pain) [56]. The use of an analgesic ladder should be individualized with the appropriate application of supportive drugs (laxatives and antiemetics) for the prevention and treatment of opioid adverse effects [19, 51] and non-pharmacological measures such as radiotherapy and invasive procedures (nerve blockades and neurolytic blocks) [20].

* Currently not available in Poland

Oxycodone

Oxycodone (6-deoxy-7,8-dehydro-14-hydroxy-3-O-methyl-6-oxomorphine) is a semi synthetic thebaine derivative that was derived from thebaine in 1916 and was used for the first time in 1917 in Germany [21]. The presence of a CH_3 group at position 3 instead of OH group in the oxycodone molecule in comparison to morphine is responsible for reduced first pass metabolism (Fig. 1). Oxycodone was originally available in one formulation with paracetamol or NSAIDs, which was erroneously classified as a weak opioid [15]. Oxycodone is now available as a single agent, and thus, it is appropriately placed at the third step of the WHO analgesic ladder. Depending on the country, oxycodone is available in oral immediate- and controlled-release formulations and in ampoules for parenteral administration. In Poland, oxycodone is available in oral controlled-release tablets and ampoules for parenteral administration; oral immediate-release formulations are not yet available.

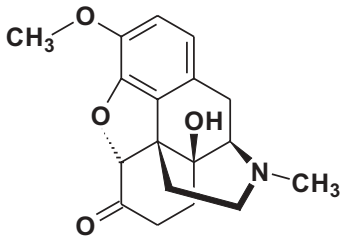

Fig. 1. Chemical structure of oxycodone

Pharmacodynamics and pharmacokinetics

Oxycodone is a strong opioid that as opposed to morphine may display a significant affinity to κ opioid receptors, along with agonistic effect mediated by μ opioid receptors [83]. The activation of κ opioid receptors activates the μ and δ receptors (cross-talk), which may be responsible for the effective oxycodone analgesia [42]. However, the concept of κ opioid receptor mediated analgesia was challenged by Lemberg et al. who suggest only μ opioid receptors involvement in oxycodone analgesic effects with possible metabolites contribution [47]. Interestingly, treatment with a combination of morphine and oxycodone produces antinociceptive synergy with less sedation in rats than equivalent doses of either opioid alone [84]. Limited cross-tolerance is observed between oxycodone and morphine in rats [66], which has also been observed in clinical studies [57]. In comparison to morphine (1.2 nmol), the inhibitory constant (Ki) for oxycodone is 47.4 nmol; thus, oxycodone possesses lower affinity to μ opioid receptors in comparison to morphine [12]. However, apart from affinity, intrinsic activity may be responsible for the analgesic effects of a given opioid. Oxycodone possesses similar lipid solubility to morphine – the partition coefficients are 0.7 and 0.5 or 1.7 and 1 for oxycodone and morphine, respectively [75,76]. However, in rats oxycodone permeates the blood-brain barrier very rapidly and its concentrations in brain are three times higher than in blood, which may explain its analgesic potency [10]. Oxycodone increases prolactin expression; however, its effect on testosterone expression is not clear. In animal studies, oxycodone treatment causes degranulation of mast cells and histamine release, but this effect is less intense than that of morphine [15]. In contrast to morphine, oxycodone does not display immunosuppressive effects in experimental studies due to a different chemical structure [85]. However, in contrast to morphine and tramadol, oxycodone is associated with dose-dependent QTc prolongation and it is capable of inhibiting hERG (human ether-a-go-go related gene) channels *in vitro*, although with very low affinity [22].

Oxycodone possesses high oral bioavailability (60–87%), which is caused by reduced first pass hepatic clearance and is not due to increased absorption [77]. High oral bioavailability is the most prominent pharmacokinetic difference between oxycodone and morphine; morphine displays significantly lower oral bioavailability (about 20–30%) [88]. High-fat meals, in contrast to non-fat meals, delay the absorption but increase the bioavailability of immediate-release oxycodone elixir. This delay in absorption is not the case with controlled-release oxycodone tablets [5]. The clinical relevance of these differences is probably not significant. The volume of distribution of oxycodone (2–3 l/kg) is comparable to that of morphine. The $T_{1/2}$ is approximately 2–3 h after intravenous administration, 3 h after administration with an immediate release (IR) oral solution and approximately 8 h after treatment with controlled-release (CR) oxycodone tablets. The maximum plasma concentration is reached within 25 min after intravenous (*iv*) injection, 1.3 h

after IR administration and 2.6 h after administration of a CR formulation [38]. The maximum plasma concentration after IR oxycodone administration is twice as high as an equivalent dose of CR oxycodone [58]. In a study with young and old volunteers, the absorption of oxycodone was greatest in elderly women and lowest in young men. The mean area under the curve (AUC) was 41% greater and the mean c_{max} was 35% higher in women compared with men. On a weight-adjusted basis, women cleared oxycodone about 25% more slowly than men [37]. However, oxymorphone levels are lower in women and elderly patients due to reduced CYP2D6 activity and first pass metabolism [36, 37]. A single-dose, analytically blinded, randomized, crossover study demonstrated bioequivalence of two 10 mg and one 20 mg CR oxycodone tablet, with significant correlation between plasma oxycodone concentrations and pharmacodynamic effects in young healthy volunteers [6].

Oxycodone predominantly binds to albumin (45%) in a non-dose dependent manner; this binding is slightly higher than morphine (35%) [50]. Oxycodone in addition to oral, subcutaneous (*sc*) and *iv* administration, may be given rectally. The bioavailability of rectal administration is similar to the oral route (61%), but greater individual variability exists. Analgesia occurs in 30 min, and peak plasma concentration appears 2.8 h after administration of oxycodone in a pectinate suppository [48]. In addition, oxycodone may be administered by an epidural route, when it is approximately 9-fold less potent than morphine, probably due to relative lack of κ receptors expression in dorsal horns [2]. Other routes of administration include the nasal passage, which has a bioavailability of 46 ± 34% [95]. Sublingually administered oxycodone is poorly absorbed (15%) [29]. Buccal administration is comparable to oral bioavailability [73]. Oxycodone administration by the transdermal route was also tested in animals [97].

Oxycodone is metabolized in the liver primarily to noroxycodone through CYP3A4 and, to a much less extent, to oxymorphone *via* CYP2D6. Noroxycodone is metabolized to noroxymorphone through CYP2D6, and oxymoprhone is metabolized to noroxymorphone by CYP3A4 (Fig. 2). However, analgesia observed after oxycodone administration seems to rely primarily on the parent compound. The primary oxycodone metabolites (noroxycodone and oxymorphone) also display affinity for μ opioid receptors. However, noroxycodone possesses only 17% of the potency of the parent compound. Oxymorphone, in spite of high affinity for μ opioid receptors (8.7 fold more potent analgesia than morphine after intramuscular administration), is produced in very small amounts [49]. Noroxymorphone is produced in a significant amount and possesses significant affinity for opioid receptors. However, the blood-brain barrier is extremely impermeable to noroxymorphone in comparison to the parent compound; thus, its role in analgesia seems to be negligible [45]. Low blood-brain barrier permeability is also characteristic of noroxycodone, oxymorphone and morphine [62].

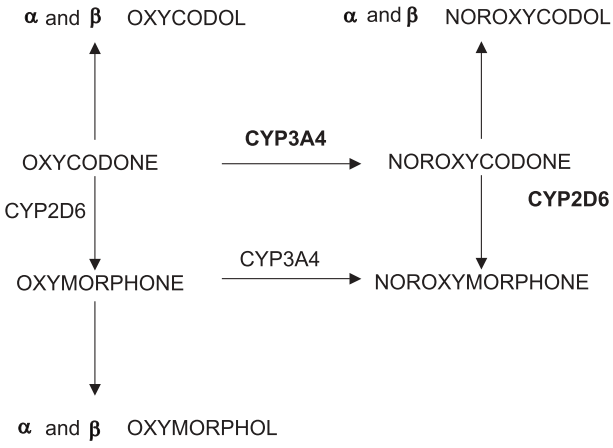

Fig. 2. Oxycodone metabolic pathways, adapted from [8,16], modified

Even though oxycodone has lower first pass hepatic clearance than morphine, oxycodone elimination is significantly influenced by the hepatic blood flow. In patients with hepatic impairment, the maximum plasma concentration of oxycodone is 40% higher, and the AUC is 90% higher in comparison to patients with normal liver function. Therefore, in patients with liver cirrhosis or other hepatic diseases, the oxycodone dose should be reduced [36]. Oxycodone is excreted through the kidneys. In patients with renal insufficiency, the oxycodone dose should also be decreased. Oxycodone concentrations in uremic patients are higher than in subjects with normal renal function. In patients with renal failure, the oxycodone half-life is prolonged but it can range from 1.8 to 26 h. The elimination of oxycodone metabolites (noroxycodone and oxymorphone) is also impaired in patients with renal failure [43].

CYP2D6 polymorphism probably does not influence oxycodone analgesia and adverse effects [77]. Sertraline, which minimally inhibits CYP2D6, intensifies adverse effects of oxycodone (hallucinations,

tremors), whereas fluoxetine and quinidine treatments significantly inhibit CYP2D6 and do not intensify oxycodone adverse effects [8]. Oxycodone does not interact with amitriptyline, ciprofloxacin and levoquin but does reduce the oral bioavailability of cyclosporin by half [15]. In healthy subjects a CYP3A4 inducer rifampin decreased greatly oral and intravenous oxycodone AUC by 86% and 53%, respectively ($p < 0.001$), and modestly reduced analgesic effects with an increase of the plasma metabolite-to-parent compound ratios for noroxycodone and noroxymorphone ($p < 0.001$) [68]. In a study conducted in volunteers St John's wort reduced AUC of oral oxycodone by 50% ($p < 0.001$) and its elimination half-life from 3.8 ± 0.7 to 3.0 ± 0.4 h ($p < 0.001$) but did not influence analgesia [67]. Although no clinical studies have been conducted CYP3A4 inhibitors may cause decreased clearance of oxycodone and an increase of its plasma concentrations with a greater risk of toxicity; this may also be the case when discontinuing CYP3A4 inducers. A pharmacodynamic interaction of oxycodone with other drugs acting on CNS, such as benzodiazepines, neuroleptics and antidepressants, may intensify oxycodone adverse effects, especially sedation, and in patients that are more sensitive to opioids, respiratory depression [71].

Tab. 1. A relative potency of oral oxycodone to other opioids (oral route unless indicated), adapted from [3, 4, 8, 16, 25, 26, 40, 77, 89, 98], modified

Analgesic	Potency ratio to oxycodone	Duration of action[1] (h)
Tramadol	10 : 1	5–6
Codeine	10 : 1	3–6
Dihydrocodeine (DHC)	6 : 1	3–6
Pethidine*	10 : 1	2–4
Morphine	1.5-2 : 1 (oral) 3 : 4 (*sc*, *iv*)	3–6
Methadone**	1 : 2	8–12
Hydromorphone***	1 : 4	4–5
Oxymorphone***	1 : 2	3–6
Buprenorphine (sublingual)	1 : 40	6–12
Buprenorphine (transdermal)	1 : 50	72–96
Fentanyl (transdermal)	1 : 50	48–72

[1]Duration of action of immediate-release oral preparations (IR). Opioids available in Poland in controlled-release oral formulations (CR): DHC and oxycodone (both CR only), tramadol and morphine (both IR and CR), methadone (only oral syrup available, long and changeable plasma half-life, a possibility of QT interval prolongation). * Not recommended for chronic cancer and non-malignant pain. ** For equivalent daily doses of oral morphine to 100 mg; with higher doses the ratio is greater i.e., methadone analgesic effect is stronger. *** Opioids currently unavailable in Poland. *sc* – subcutaneous route; *iv* – intravenous route

Oxycodone formulations and dosing guidelines

In Poland oxycodone hydrochloride is available in CR tablets at 5, 10, 20, 40 and 80 mg and in ampoules containing 10 mg/1 ml and 20 mg/1 ml for parenteral (subcutaneous and intravenous) administration. Immediate-release tablets are currently unavailable in Poland. CR oxycodone (CRO) formulation provides analgesia for 12 h with a plasma half-life of 37 min (38% of the dose) and an immediate analgesic effect for 1 h followed by a prolonged phase with the plasma half-life of 6.2 h (62% of the dose) [16].

CRO may be administered as the first strong opioid, typically at an initial dose of 5–10 mg every 12 h in opioid-naive patients [44, 93, 101] or at an initial dose of 10–20 mg every 12 h in opioid-tolerant patients, when weak opioids (tramadol, codeine, dihydrocodeine) are ineffective [52, 90]. In opioid-naive patients the initial dose may depend on pain intensity; 5 mg every 12 h for patients with pain intensity 4–6 and 10 mg every 12 h for patients with pain intensity 7 or more on a numerical rating scale (NRS: 0 – no pain, 10 – the worst pain imaginable) [72]. Oxycodone may be used when switching from other strong opioids [65]; in this situation the initial dose depends on the dose of the previous opioid that was administered as well as analgesia, adverse effects, comorbidities and the patient comprehensive clinical evaluation (equianalgesic dose ratio of oxycodone and other opioids for the oral route is shown in Tab. 1). When changing from oral to parenteral route of oxycodone administration the dose should be halved. When oral morphine is changed to oral oxycodone, the morphine dose should be halved [3]. When oral oxycodone is switched to morphine the dose is increased by 1.5-fold. When switching drugs, a parenteral route oxycodone dose is equal to approximately 70% of the morphine dose although significant differences in this re-

gard were found; therefore, an individual dose adjustment is necessary [4].

Adverse effects

In general, adverse effects of oxycodone are similar to other opioids and include dry mouth, constipation, nausea and vomiting, pruritus, dizziness, somnolence and confusion [15]. However, in several studies fewer CNS adverse effects were found with oxycodone than with other opioids treatment. In a study, where morphine was substituted with a continuous *sc* infusion of oxycodone in 13 patients suffering acute delirium symptoms, a significant improvement in mental state, nausea and vomiting was observed [57]. In another study of 38 patients that switched from morphine or hydromorphone to *sc* oxycodone due to delirium, the symptom disappeared in 34% of patients. Local toxicity was apparent in 2 of the 63 patients treated with subcutaneous oxycodone; in both cases, the oxycodone concentration was high (50 or 60 mg/ml). Pallor of the skin at the needle site with surrounding erythema was present in one patient; however, oxycodone treatment was continued using different infusion site. In another patient, in addition to mentioned symptoms ecchymosis appeared; this patient discontinued oxycodone infusion [26].

In a retrospective, observational, cohort study using Medicaid administrative claims, the time until first adverse outcome was examined among 5684 subjects [32]. Patients prescribed CRO were 35% less likely to be admitted to the emergency department or hospital for opioid-related adverse event (adjusted hazard ratio (HR) 0.45; 95% confidence interval (CI) 0.26 to 0.77), had a 23% lower risk of hospitalization (adjusted HR 0.77; 95% CI 0.66 to 0.91), had a 41% lower risk of constipation (adjusted HR 0.59; 95% CI 0.35 to 1.00) and had a 29% lower risk of death (adjusted HR 0.71; 95% CI 0.54 to 0.94) compared with those prescribed controlled-release morphine (CRM).

Using a meta-analysis [79], oxycodone tolerability was similar to morphine. However, when the meta-analysis was repeated using only data from the trials with morphine as the control treatment, the pooled odds ratio (OR) favored oxycodone for dry mouth (OR 0.56; 95% CI, 0.38–0.83) and drowsiness (OR 0.72; 95% CI, 0.47–1.1). CRO renders fewer adverse effects in the CNS in comparison to morphine. In a study comparing CRM and CRO, hallucinations occurred only in the CRM group, whereas itching and scratching was less intense in CRO group ($p = 0.044$) [61]. In another study comparing morphine and oxycodone, morphine caused significantly more nausea; hallucinations occurred only in patients treated with morphine [39]. Comparison of the effect of a combination of morphine and oxycodone with the standard morphine administration alone on cancer pain, determined that patients receiving oxycodone experienced less nausea and vomiting [46]. In two comparative studies with morphine, no difference [11] or similar adverse effects were found: more intense vomiting in the morphine group and more intense constipation in the oxycodone group with similar effects on nausea were observed [33]. In a study comparing CRO with CRM, 11 patients on oxycodone and 7 patients on morphine dropped out [34]. In a study comparing CRO and hydromorphone, hallucinations were found only in patients treated with hydromorphone [30]. In a study comparing CRO with extended release oxymorphone no differences in adverse effects were found [25].

Nausea was more common in females and in patients younger than 50 years old among the 24 patients treated with an oxycodone IR solution when weak opioids were ineffective [28]. Nausea and vomiting occurred during oxycodone treatment more frequently in women than in men (30% *vs*. 19% in cancer and 52% *vs*. 31% in non-cancer patients); however, due to a relatively small number of patients, these differences were not statistically analyzed [86]. Less vomiting was reported in patients on CRO than in patients treated with immediate-release oxycodone (IRO) [41]. Oxycodone abuse during pregnancy causes neonatal withdrawal syndromes because of transplacental absorption of the drug [78]. In three studies of CRO treatment, a decrease in adverse effects was observed during the course of the trials [13, 23, 72]. In an open study of 390 patients, 10 (2.6%) patients discontinued treatment with CRO due to adverse effects, which appeared in 4% of treated patients and were usually of mild or moderate intensity; nausea, vomiting and constipation were the most common [90]. In a large, post-marketing surveillance study that comprised 1824 patients treated with CRO tablets, the most common adverse effects were constipation (25.5%), nausea (13.3%), vomiting (6.2%), lethargy (3.7%) and dysuria (2.1%). All adverse effects were decreased with preventive medications [101].

Oxycodone overdose symptoms are drowsiness, stupor, miosis, muscle flaccidity, seizures, bradycardia, respiratory depression and hypotonia. In severe cases of oxycodone intoxication coma, pulmonary edema and circulatory failure appear; these effects may cause death. In this situation, naloxone should be administered intravenously either as repeated bolus injections or as a continuous infusion. In the case of cardiac shock due to oxycodone overdose, artificial respiration, oxygen and intravenous fluids should be administered [71].

Overview of oxycodone clinical studies in cancer pain

Open studies of oxycodone controlled-release formulations

Numerous clinical studies indicate that oxycodone is effective for treating patients with cancer and chronic non-malignant pain [81]. Studies confirmed high analgesic efficacy of CRO [14]. Immediate and controlled-release formulations of oxycodone are equally effective and safe [41, 74, 86, 92] with dose titration possible using CRO [86]. CRO was evaluated in several open clinical studies [13, 70, 72, 90, 101]; in these studies, high CRO doses were used [7, 23].

Bercovitch and Adunsky [7] retrospectively compared high and low CRO doses in 97 consecutive patients with cancer pain. Only 18 (18.55%) patients were treated with a high dose of CRO (mean 231.1 mg per day). The daily mean CRO 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 CRO doses. Survival was not related with CRO doses. However, patients that were treated with higher CRO doses maintained Karnofsky scores higher than 40 points most of the time in comparison to patients receiving low dose CRO. The use of high dose CRO is safe and efficient and unrelated with shorter survival.

Ferrarese et al. [23] investigated the role and tolerability of high-dose (over 160 mg per day) CRO 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 CRO 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 CRO 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 CRO and diminished after the first week of treatment and did not cause withdrawal from the study. High-dose CRO effectively treated moderate to severe cancer and non-cancer pain.

Oxycodone comparative studies with other opioids

In a meta-analysis, a similar analgesic and adverse effects of oxycodone, morphine and hydromorphone were observed [79]. In several studies, analgesia and adverse effects of oxycodone were assessed in comparison to other opioids, predominantly morphine (Tab. 2).

Morphine

Mucci-LoRusso et al. [61] compared controlled-release morphine (CRM) with CRO in a randomized, double-blind, parallel-group study of patients with cancer pain. CRO was administered to 48 patients and CRM was administered to 52 patients for 12 days. Stable analgesia was achieved in 83% of the patients on CRO and 81% of the patients on CRM in a median of two days. After titration, the pain intensity (0 – none, 3 – severe) decreased from baseline ($p = 0.005$) in both groups; from 1.9 ± 0.1 (the mean ± SE) to 1.3 ± 0.1 in patients administered CRO and from 1.6 (0.1) to 1.0 (0.1) in the CRM group (no significant differences). Although adverse effects were reported in both groups, hallucinations were observed only in two patients in the CRM group. Itching and scratching were less intense in the CRO group ($p = 0.044$). CRO treatment provided more smooth steady-state plasma concentration ($p = 0.004$) and there was a stronger ($p = 0.026$) correlation between plasma concentration and dose of oxycodone (0.7) than for morphine (0.3). The rela-

Tab. 2. Oxycodone comparative studies in cancer pain, adapted from [11, 25, 30, 33, 34, 39, 46, 61], modified

Author / ref. / study design	No. of pts	Daily doses (mg)	Duration	Analgesic efficacy	Adverse effects
Mucci-LoRusso et al. [61] randomized, double blind, parallel	O 48 M 52	Final doses, the means (range): CRO 101 (40–360) CRM 140 (60–300)	12 days	Stable analgesia within 2 days: CRO 83%, CRM 81%. No difference in VS:CRO 1.9 ± 0.1 (baseline) to 1.3 ± 0.1 CRM 1.6 ± 0.1 (baseline) to 1.0 ± 0.1	Hallucinations only with CRM. Less itching and scratching with CRO. Less plasma level fluctuations during steady-state with CRO
Kalso and Vainio [39] randomized, double blind, crossover	O 20 M 20	Oral, median doses: O first 130, O second 162. M first 168, M second 228	4 days, no wash-out	No difference in VAS	Sedation most frequent in both groups. Hallucinations only with M, more nausea in M group
Lauretti et al. [46] randomized, double blind, crossover	O 22 M 22	Range: CRM 20–90 CRO 20–60 DR (O/M), means, assessed weakly: 1:1.80 1:1.83 1:1.76 1:1.84	14 days, no wash-out	No difference in VAS. 38% less rescue IRM consumption in the CRO group	Less nausea and vomiting in CRO group
Bruera et al. [11] randomized, double blind, crossover	O 23 M 23	The mean (SD) CRO 93 ±114 CRM 145.2 ± 204 DR O/M, median (range):1:1.5 (1:1–2.3)	7 days, no wash-out	No difference in VAS and VS: CRO 23 ± 21 and 1.2 ± 0.8 CRM 24 ± 20 and 1.3 ± 0.7 Number of daily rescue doses: CRO 2.3 ± 2.3 CRM 1.7 ± 2.1 (p = 0.01)	No differences in adverse effects
Heiskanen and Kalso [33] randomized, double blind, crossover	O 27 M 27	End of titration (the means):CRO 123 CRM 180 DR (O/M): 2:3[1] 3:4[2]	3–6 days no wash-out	CRM better analgesia (VS) (0.77 ± 0.07) than CRO (0.99 ± 0.12); p < 0.05. More daily rescue analgesic consumption with CRO	Nightmares only in CRM group. More constipation with CRO, more vomiting with CRM
Heiskanen et al. [34] randomized, double blind, crossover	O 20 M 20	Stable phase (the means ± SD): CRO 148 ± 18 CRM 204 ± 24	3–6 days, no wash-out	No difference (CRO vs. CRM) in VAS	Higher variation of morphine plasma concentrations than oxycodone. From 18 patients withdrawn 11 on oxycodone, 7 on morphine
Hagen and Babul [30] randomized, double blind, crossover	O 31 H 31	Final doses (the mean ± SD) CRO 124 ± 22 CRH 30 ± 6 DR (O/H):4:1	7 days, no wash-out	No difference (CRO *vs.* CRH) in VAS (28 ± 4 *vs.* 31 ± 4), VS (1.4 ± 0.1 *vs.* 1.5 ± 0.1), More daily rescue analgesic consumption (1.4 ± 0.3 *vs.* 1.6 ± 0.3)	Hallucinations only with CRH. No difference in VAS (CRO *vs.* CRH) sedation (24 ± 4 *vs.* 18 ± 3), nausea (15 ± 3 *vs.* 13 ± 3) and patient preference
Gabrail et al. [25] randomized, double blind, crossover	O 20 OXY 20	Final doses (the means) CRO 91.9 OXY 45.9 DR (O/OXY): 2:1	7–10 days, no wash-out	No difference in analgesia (Brief Pain Inventory)	No difference in adverse effects

ref. – reference number, pts – patients, O – oxycodone, M – morphine, H – hydromorphone, OXY – oxymorphone, CRO – controlled-release oxycodone, CRM – controlled-release morphine, CRH – controlled-release hydromorphone, VAS – visual analogue scale, VS – verbal scale, DR (O/M) – dose ratio of oxycodone to morphine, DR (O/H) – dose ratio of oxycodone to hydromorphone, DR (O/OXY) – dose ratio of oxycodone to oxymorphone. [1]When oxycodone is administered first. [2]When oxycodone is administered after morphine

tionship between pain intensity (VAS) and plasma drug concentration was more positive for oxycodone ($p = 0.046$). CRO was as effective as CRM in the treatment of moderate to severe cancer pain and induced less itching and no hallucinations.

Kalso and Vainio [39] compared morphine and oxycodone in 20 patients who suffered from severe cancer pain in a double-blind crossover study. During the first two days, patients received each drug intravenously to titrate the dose and for the next two days analgesics were given orally. Then drugs were switched, and the above procedure was repeated. The assumed oral bioavailability for the first 10 patients and the last 10 patients were 44% and 33%, respectively, for patients treated with morphine and 66% and 50%, respectively, for patients receiving oxycodone. Patients were able to readjust the oral dosing. Equally effective analgesia was achieved with both drugs, but the dose of intravenous oxycodone was 30% higher than morphine. The median calculated oral/intravenous ratios that rendered comparable analgesia were 0.31 for morphine and 0.70 for oxycodone. The most common adverse effect in both groups was sedation. Morphine caused significantly more nausea; hallucinations occurred only in patients treated with morphine, and the occurrence of other adverse effects was similar in both groups.

Lauretti et al. [46] evaluated analgesic effects induced by a combination of morphine and oxycodone on cancer pain in comparison to the standard morphine administration alone. CRO and CRM were compared in 26 patients. The study started with an open-label, randomized titration phase to achieve stable pain control for 7 days, followed by a double-blind, randomized crossover phase in two periods, 14 days each. Patients were provided with oral immediate-release morphine (IRM) as needed. A total of 22 patients were evaluated. The weekly upload consumption ratio of morphine/oxycodone was 1:1.8. Patients that received oxycodone experienced less nausea and vomiting. The rescue morphine analgesic consumption was 38% higher ($p < 0.05$) in patients receiving only morphine in comparison to patients receiving both morphine and oxycodone. The morphine/oxycodone combination is a useful alternative to morphine alone; treatment with the combination rendered better analgesia and less nausea and vomiting.

Bruera et al. [11] performed a double-blind, crossover trial comparing CRO and CRM. Thirty two patients on a stable dose of oral opioids were randomized and administered CRO or CRM for 7 days, and then the drugs were switched. The dose ratio of oxycodone to morphine was set at 1:1.5. Pain was assessed by VAS (0–100 mm) and CAT (categorical, 0–4) scales. Patients and investigators were blinded to global ratings of efficacy and treatment preferences. Twenty three patients completed the study. VAS and CAT pain scores were 23 ± 21 and 1.2 ± 0.8, respectively, for patients administered CRO and 24 ± 20 ($p = 0.43$) and 1.3 ± 0.7 ($p = 0.36$), respectively, for patients administered CRM (the mean ± SD). There were no differences in adverse effects ($p = 0.40$), analgesic efficacy and drug preferences. The median oxycodone/morphine dose ratio was 1.5, and the maximum was 2.3.

Heiskanen and Kalso [33] compared CRO and CRM in 45 patients with cancer pain. The study started with an open-label, randomized titration phase to achieve analgesia within 48 h, followed by two double-blind, randomized crossover phases in two periods that last for 3–6 days each. The dose ratio of oxycodone to morphine was set at 2:3. Twenty seven patients were evaluated. Pain was effectively relieved during both of the stable phases, and both analgesics were equally effective. More escape doses were used and the mean pain intensity was greater in the CRO treated group. The ratio of total opioid consumption of oxycodone to morphine was 2:3, when oxycodone was administered first and 3:4 when oxycodone was administered after morphine. Nightmares appeared only in the CRM group; a more intense vomiting in the morphine group and a more intense constipation in the oxycodone group were observed.

Heiskanen et al. [34] compared CRO with CRM in 45 patients with cancer pain and stable pain after open-label titration in a randomized, double-blind, cross-over trial. Twenty patients were evaluated. Seven were excluded due to escape medication use after the 0 h time point; 18 patients were excluded from different reasons: adverse events during titration (7), insufficient pain relief (3), inappropriate use of escape analgesics (3), sudden deterioration (2), non-compliance (2), and incomplete absorption of drugs (1). Both opioids provided adequate analgesia. The variation of plasma morphine concentration was higher than that of oxycodone, which was consistent with the lower morphine bioavailability. Liver dysfunction selectively affected oxycodone and morphine metabolism. There were three patients with markedly aberrant plasma opioid concentrations.

Hydromorphone

Hagen and Babul [30] compared CRO with controlled-release hydromorphone (CRH) in a double-blind crossover study of 44 patients with stable cancer pain. Each analgesic was administered for 7 days; the drugs were then switched and administered for 7 days. Thirty one patients completed the study and received either a final CRO daily dose 124 ± 22 or a final CRH daily dose 30 ± 6 mg. No differences were noted in pain intensity, as assessed by the VAS (28 ± 4 *vs*. 31 ± 4) and categorical scale (1.4 ± 0.1 and 1.5 ± 0.1), daily rescue analgesic consumption (1.4 ± 0.3 *vs*. 1.6 ± 0.3), sedation scores (24 ± 4 mm *vs*. 18 ± 3 mm), nausea scores (15 ± 3 mm *vs*. 13 ± 3 mm) and patient preference. Two patients had hallucinations during CRH treatment; however, no patients experienced hallucinations during CRO therapy.

Gagnon et al. [26] assessed the effects of intermittent oxycodone *sc* injections *via* the Edmonton Injector in 63 advanced cancer patients. Local tolerance and systemic toxicity were monitored. Only two patients developed injection site intolerance, and in both cases, a dose of 50 mg/ml and higher was administered. Most of patients were switched to oxycodone treatment due to opioid toxicity, and in 34% of these patients, the delirium intensity decreased. A subgroup of 19 patients who were switched from morphine and hydromorphone to oxycodone *sc* was studied for equianalgesic ratio with oxycodone. Ratios (the mean ± SD) of 1.2 ± 0.4 for morphine *sc* to oxycodone *sc* and 0.5 ± 0.4 for hydromorphone *sc* to oxycodone *sc* were found. When hydromorphone *sc* was converted to a morphine *sc* equivalent dose and the results for these patients were added to those for morphine *sc* group, the mean and median overall ratios of morphine *sc* equivalent dose to oxycodone were 1.9 ± 1.5 and 1.4, respectively. The cost of oxycodone *sc* was found to be comparable to morphine *sc* and lower than hydromorphone *sc*.

Oxymorphone

Gabrail et al. [25] compared the analgesic efficacy and safety of CRO to extended release oxymorphone (ERO) in a randomized, double-blind, crossover study of patients with moderate to severe cancer pain. For the first 7–10 days patients were titrated with open-label oxycodone or oxymorphone to achieve stable dose that provided adequate analgesia with tolerable adverse effects and no requirement for more than 2 doses of rescue medication per day. The subsequent double-blind treatment phase was a 7–10 day period of CRO or ERO treatment followed by crossing over to the alternate medication for another 7–10 days. Pain was assessed by the Brief Pain Inventory. Forty patients completed the second double-blind phase. The mean daily doses of CRO 91.9 mg was twice that of ERO 45.9 mg, an equianalgesic dose ratio of 2:1. Rescue medication use was low in both groups (15 mg oral morphine per day). No differences in analgesia and adverse events were observed between the groups.

Oxycodone combined with naloxone

A new oral formulation (oxycodone/naloxone, OXN) that combines prolonged-release oxycodone (PRO) and prolonged-release naloxone (PRN) was developed. The ratio of 2:1 PRO to PRN was chosen for the new tablets, which have different strengths: 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg [59, 63]. The aim of this formulation is to counteract opioid-induced constipation (OIC) development [17] through naloxone local antagonist effect on the opioid receptors in the gut wall [54] while maintain analgesia [16] due to the high systemic oxycodone availability after oral administration (60–87%) [38]. Naloxone possesses low bioavailability after oral administration (< 2%) [24], due to the extensive first pass metabolism, which accounts for the fact that withdrawal symptoms and the attenuation of oxycodone analgesia are normally not observed [94]. Because the mode of oral naloxone action depends on normal liver function any hepatic impairment should be of concern [80].

Initial OXN doses in opioid-naive patients are 5/2.5–10/5 mg b.i.d. In patients not responding to treatment with weak opioids an initial dose of 10/5 or 20/10 mg b.i.d. is usually effective. When switching from other strong opioids to OXN an initial dose should be individualized based on a previous opioid dose and complex clinical evaluation. The maximal daily dose is 40/20 mg b.i.d. Several clinical studies demonstrated that OXN rendered similar analgesic efficacy and reversed OIC in comparison to oxycodone administered alone in patients with chronic non-malignant and cancer pain [55, 59, 63, 64, 87, 91, 99]. The indication for the OXN administration is severe pain demanding strong opioid administration; the presence of an opioid receptor antagonist (naloxone)

counteracts OIC by blocking the oxycodone activation of opioid receptors in the gut wall [1].

Oxycodone/naloxone clinical studies

Meissner et al. [59] reported a randomized, double-blind study that assessed analgesic efficacy and, impact on the OIC of OXN and identified the optimal dose ratio of oxycodone and naloxone. Two hundred and two patients with chronic pain (most non-malignant, 2.5% cancer-related pain) and stable oxycodone dose (40, 60 or 80 mg per day) were randomized into groups that received 10, 20, and 40 mg per day naloxone or placebo. After 4 weeks of the maintenance phase, patients received oxycodone for two weeks. Pain intensity was evaluated by the NRS, and bowel function was assessed by the bowel function index (BFI). No loss of analgesia with naloxone was observed. Naloxone at doses of 20 and 40 mg improved bowel function in comparison to placebo ($p < 0.05$). The combination was well tolerated with no unexpected adverse effects. A trend towards an increase in diarrhea with the higher naloxone doses was observed. The 2:1 oxycodone/naloxone ratio was identified as the most suitable.

Müller-Lissner et al. [63] evaluated the impact of oral PRN treatment on opioid-induced bowel dysfunction (OIBD). OIBD was evaluated by the mean of the three components: ease of defecation, feeling of incomplete bowel evacuation and patient judgment of constipation – each assessed by 0–100 numerical analogue scale (NAS – the greater score, the worse OIBD). Bowel function improved with increasing PRN dose. At pre-randomization average scores of 48.0, 52.8, 49.4 and 46.2 were observed for placebo, 10 mg, 20 mg and 40 mg PRN groups, respectively, and at the end of maintenance the equivalent scores were 45.4, 40.3, 31.3 and 26.1 ($p < 0.05$ for 20 mg and 40 mg PRN *vs*. placebo). In a quadratic response surface model with PRN and PRO doses as factors, the improvement was observed with decreasing oxycodone/naloxone ratio and appeared to plateau at the 2:1 ratio, with the overall effect at 2:1 approximately 50% greater than at 4:1. No loss of analgesic efficacy with naloxone was observed [64]. Addition of up to 40 mg of oral PRN significantly reduced OIBD in patients with severe chronic pain who were established on oxycodone.

Nadstawek et al. [64] evaluated patient assessment of the efficacy and tolerability of oral PRO when co-administered with oral PRN. Two hundred and two patients with cancer and non-cancer pain who were on a stable PRO dose (40, 60 or 80 mg per day) were randomized into groups that received 10, 20, 40 mg of PRN or placebo. After 4 weeks of the maintenance phase patients were switched to PRO only for 2 weeks. Efficacy was good or very good in 50%, 67.4% and 72.5% of patients in the 10, 20 and 40 mg PRN group, respectively, compared to 43.5% of patients in the placebo group. Patient assessment of tolerability was ranked as good or very good by 83.3%, 79.1% and 82.5% of patients in the 10, 20 and 40 mg per day PRN dose group, respectively, compared with 71.7% of patients in the placebo group. The maintenance phase was preferred by patients in the PRN groups. Efficacy of a 2:1 dose ratio of oxycodone to naloxone was evaluated as good or very good by 70.4% of patients compared with 43.5% treated with placebo. Tolerability of the 2:1 dose ratio was ranked as good or very good by 81.5% of patients compared with 71.1% for the placebo group and patients preferred the maintenance phase.

Vondrackova et al. [99] in a randomized, double-blind, placebo- and active-controlled, parallel-group study demonstrated the superiority of an OXN combination over placebo with respect to analgesic efficacy in patients with moderate to severe chronic low back pain. The full analysis population consisted of 463 patients. The times to recurrent pain events were significantly longer for in the OXN group compared with placebo ($p < 0.0001$–0.0003). OXN reduced the risk of pain events by 42% ($p < 0.0001$). The appearance of pain events was comparable for OXN *vs.* OXY, which confirmed that the addition of PRN to PRO did not negatively influenced oxycodone analgesic efficacy. OXN provides patients with effective analgesia and improves OIBD. The safety profile of OXN is comparable to other opioids with the exception of OIC, which indicates that the addition of PRN improves tolerability.

Simpson et al. [91] conducted a double-blind, multicenter trial in 322 adult patients with moderate-to-severe, non-cancer pain who required opioids in a range of 20–50 mg per day of oxycodone. Patients were randomized to receive OXN or PRO for 12 weeks. The primary outcome was improvement in constipation (BFI), and the secondary assessments focused on pain intensity and additional bowel parameters. A significant improvement in BFI scores occurred with OXN compared with PRO after 4 weeks of double-blind treatment (–26.9 *vs*. –9.4, respectively; $p < 0.0001$), observed after only one week of treat-

ment and continued until study end. A significant increase in the number of complete spontaneous bowel movements and decrease in laxative use were also observed. The oxycodone analgesic efficacy was not compromised as pain intensity remained stable throughout the study period. The incidence of adverse events was comparable in both groups and typical for opioid analgesics. The fixed-ratio combination of OXN is superior to PRO alone and offers effective analgesia with significant improvement of OIC. Long-term analysis, over a period of up to 52 weeks of therapy, of the above two phase III studies [91, 99] conducted in patients with chronic pain demonstrated that the treatment with OXN in daily doses up to 80/40 mg was safe and effective [87].

Löwenstein et al. [55] in a randomized, double-blind, double dummy, parallel-group, multicenter study assessed the use of higher OXN doses (converted from PRO 60–80 mg per day and allowed to titrate the dose up to 120 mg/day) in patients with moderate-to-severe non-malignant pain and OIC. During pre-randomization period 265 patients receiving opioids for moderate-to-severe non-malignant pain were converted to PRO and titrated to an effective analgesic dose; then patients were randomized to be treated either with OXN or PRO alone. A significant improvement in bowel function assessed by BFI ($p < 0.0001$) after one week, increase in spontaneous bowel movements per one week (median 3.0 *vs*. 1.0) after 4 weeks of the treatment and lower laxative intake during the study period in OXN group comparing to PRO group were demonstrated. Pain intensity scores were comparable between the groups and consistent for duration of the study. No unexpected adverse effects attributable to OXN were observed. The treatment with OXN was superior to PRO administered alone in terms of bowel function, while providing equivalent analgesia.

Conclusions

Oxycodone is an important opioid analgesic, which may be successfully used as the first strong opioid in opioid-naive patients or non-responders to weak opioids (tramadol, codeine, dihydrocodeine) [96]. It is successfully (80% of patients) used in strong opioid-tolerant patients (opioid switch) when morphine or other opioids are ineffective [65, 81, 98]. Controlled-release oxycodone administered on a regular basis may be combined with immediate-release morphine formulations for breakthrough pain management, which provides additional analgesic benefits [9, 46, 60]. This combination will be probably the most frequent approach in cancer pain treatment in Poland until immediate-release oxycodone formulations are available. Controlled-release oxycodone is an effective and convenient opioid formulation for chronic cancer pain treatment. Recent reports of oxycodone use in visceral [53] and neuropathic cancer [69] and non-malignant chronic pain, especially in combination with pregabalin, are very promising [27]. Oxycodone/naloxone counteracts opioid-induced constipation and preserves oxycodone analgesia. Future research will assess analgesic effects of oxycodone in different types of pain [8, 27, 40, 53, 69, 89] with QL evaluation taken strongly into consideration in clinical studies and pharmacokinetic/pharmacodynamic analysis in experimental trials.

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