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Oxycodone

Pharmacological profile and clinical data in chronic pain management

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Opioids are widely used as effective analgesic therapy for cancer pain. Despite years of controversy, their use has been also accepted in chronic non-cancer pain. Oxycodone alone and in combination has been used for over 80 years in the treatment of a variety of pain syndromes. As single agent, the controlled release (CR) oxycodone's market in the USA grew from 10% in 1996 to 53% in 2000 and it has become a leading opioid in the United States. Recent data showed that the fixed-combination oxycodone/acetaminophen (5 mg/325 mg) is the most often prescribed opioid across all the different chronic pain diagnoses. Compared with morphine, oxycodone has a higher oral bioavailability and is about twice as potent. Pharmacokinetic-pharmacodynamic data support oxycodone as a pharmacologically active opiod that does not require conversion to oxymoprhone for pharmacological activity. Seven studies addressed the safety and efficacy of oxycodone for the treatment of non-cancer pain (low back pain, osteoarthritis pain, and painful diabetic neuropathy). Both immediate release (IR) and CR oxycodone are equally effective and safe. Along these trials, mean daily dosage of oxycodone was approximately 40 mg, with a low incidence of intolerable typical opiate side effects. In cancer pain, oxycodone can be considered a valid alternative to oral morphine to be used for opioid rotation. No difference in analgesic efficacy between CR oxycodone and CR morphine was found. Controlled-release preparations, with a long duration of action, are attractive because they offer the advantage of longer dosing intervals and sustained analgesic effect.

Key words: **Oxycodone - Acetaminophen - Oxymorphone - Non malignat pain - Cancer pain.**

Oxycodone is a strong, semisynthetic, opioid analgesic, derivative of the opium alkaloid thebaine. The chemical formula is 14-hydroxy-7,8 dihydrocodeinone. It has been in use for over 80 years, mainly as the hydrochloride or terephthalate salt.[1]

Oxycodone was first introduced in the United States in fixed combination with acetaminophen (APAP), acetylsalicylic acid, or nonsteroidal anti-inflammatory drugs (NSAIDs). Thus, for a long time, it has been classified as a "weak" opioid for mild and moderate pain, with the same indications as codeine. The most common formulation have combined 5 mg of oxycodone with 325 mg of APAP. This formulation has been used for over 20 years with proven efficacy and safety. A recent American survey, based on record audits from 12 family medicine practitioners, assessed the current medical management of a general population with chronic pain. The

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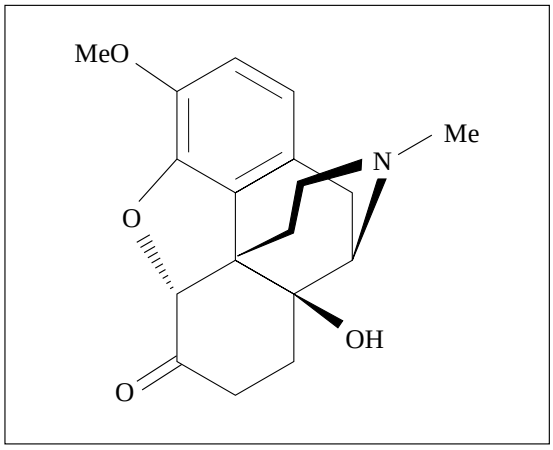

Figure 1.—The chemical structure of oxycodone.

oxycodone/acetaminophen fixed combination resulted the most prescribed opioid (31%) across all the pain diagnoses, whose most were low back pain.[2]

However, the fixed combination with acetaminophen has limited its use in cancer pain due to the potential toxicity of the nonopioid component. Acetaminophen, when administrated for long intervals at high doses, has the potential to result in hepatotoxicity.[3] Thus, the maximum recommended dose of acetaminophen is 4 000 mg daily. In fixed combinations, 4 000 mg daily of acetaminophen corresponds to no more than 60 mg daily of oxycodone.

However, new oxycodone/acetaminophen formulations with higher amount of oxycodone (7.5 mg and 10 mg) and lower amount of acetaminophen (325 mg) has been recently introduced. These new formulations have been shown to be more effective and safer than the old one by maintaining the benefit of dual analgesic mechanisms, while reducing the total daily dose of acetaminophen.[4]

Oxycodone is also available as single agent, in controlled release (CR) and immediate release (IR) formulations. Many clinical trials proved the efficacy and safe of these formulation in both acute and chronic pain. Single-agent oxycodone can be titrated to analgesic effective dose, as other opioids, without ceiling effects. Moreover, its potency is consistently higher than that of morphine. For these reasons, oxycodone is better classified as a "strong" opioid analgesic agent.

Recently, oxycodone has been recognized as an alternative to oral morphine for the management of acute postoperative and chronic, malignant and non-malignant, pain.

In the last decade, it has become the leading opioid in the United States, where the medical use of opioids increased 400% from 1996 through 2000. Four opioids share the market: CR and IR morphine, normal release (NR) hydromorphone, transdermal fentanyl and CR and IR oxycodone. CR oxycodone's market share grew from 10% in 1996 to 53% in 2000.[5] However, the monthly cost of CR oxycodone regimen, calculated from average wholesale prices, is slightly higher than transdermal fentanyl and consistently higher than CR morphine or methadone.[6]

In Italy, oxycodone will be available in the next months as combined formulation oxycodone/acetaminophen with fixed dose of acetaminophen (325 mg) and variable doses of oxycodone (from 5 mg to 20 mg).

Pharmacological profile

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Like all pure opioid agonists, with increasing doses there is increasing analgesia. There is no defined maximum dose and the ceiling to analgesic effectiveness is imposed only by side effects, such as somnolence and respiratory depression. The precise mechanism of the analgesic action is unknown. However, specific central nervous system opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of oxycodone. Pharmacological effects of oxycodone include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia.

The chemical structure of oxycodone (14-hydroxy-7,8 dihydrocodeinone) differs from that of codeine as oxymorphone differs from morphine [1] (Figure 1).

Oxycodone is a weak base, with a pKa of 8.5. Its liposolubility and the serum protein binding (38-48%) is similar to that of morphine, significantly lower than that of Fentanyl (85%).[7]

Oxycodone is well absorbed, when orally administered. Compared with morphine, it has a higher oral bioavailability. In humans, about 60% of an oral dose of oxycodone (range from 50% to 87%) reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to the 3-methoxy substituent (group CH3 at position 3) that prevents extensive first-pass glucuronidation.[8] The relative oral bioavailability of controlled-release to immediate-release oral dosage forms is 100%.

In normal volunteers, the t1/2 of absorption is 0.4 h for immediate-release oral oxycodone, whereas controlled release oxycodone exhibits a biphasic absorption pattern with 2 apparent absorption half-times of 0.6 and 6.9 h, which describes the initial release of oxycodone from the tablet followed by a prolonged release. Indeed, with the controlled-release oxycodone tablets, 38% of the available dose is rapidly absorbed with a mean half-life of 37 min, providing a fast onset of analgesia, within 1 h.[9]

Food has no significant effect on the extent of absorption of oxycodone. However, the peak plasma concentration of oxycodone increased by 25% when administered with a high-fat meal.[8]

Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites.

A high portion of oxycodone is metabolized to noroxycodone by way of N-demethylation during the first pass. Noroxycodone is its major circulating metabolite, with a considerably weaker analgesic effect than oxycodone. Oxycodone is also O-demethylated to oxymorphone, whose potency has been estimated to be approximately 14 times that of oxycodone. Indeed, oxymorphone is a known analgesic that is marketed in parenteral form in the United States. However, although possessing analgesic activity, oxymorphone is present in the plasma only in low concentrations, after oral administration of oxycodone. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. Correlations indicate that oxycodone, not oxymorphone, is the principal pharmacologically active agent after oral oxycodone administration.[10] The extent of oxymorphone-mediated analgesia could vary because of genetic differences in cytochrome P450 activity. Indeed, the formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6.[11] Oxymorphone represents less than 15% of the total administered dose. However, this route of elimination may be blocked by a variety of drugs (*e.g.*, certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants).

Further metabolism of oxycodone proceeds by the way of 6-ketoreduction to 6-oxycodol, and conjugation with glucuronid acid.

Oxycodone and its metabolites are excreted primarily via the kidney. Approximately 8%-14% of the dose is excreted as free oxycodone, up to 50% as conjugated oxycodone, 0% as free oxymorphone, 14% as conjugated oxymorphone, whereas both free and conjugated noroxycodone have been found in the urine but not quantified.[1]

Elimination half time is independent of dose and route of administration.

The elimination half-life of controlled-release oxycodone is 4,5 h compared to 3,2 h for immediate-release oxycodone. Given the shortness of its half-life of elimination, steady-state of plasma concentrations are achieved within 24-36 h of initiation of dosing with oxycodone controlled-release. A study comparing controlled-release and immediate-release oxycodone showed that the 2 treatments are equivalent for AUC and C_{max}. During titration to obtain stable analgesia, the absorption profile of CR oxycodone suggests that it may be used as readily as IR oxycodone in patients with chronic, moderate to severe pain.[12]

Oxycodone has been found in breast milk. Precautions should be taken for special populations. The plasma concentrations are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Oxycodone elimination is impaired with renal failure due to an increased volume of distribution and reduced clearance. Patients with impaired renal function (creatinine clearance <60 mL/min) [13] and patients with mild to moderate hepatic dysfunction [14] show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. This is accompanied by an increase in sedation but not by differences in respiratory rate. Both CR and IR oxycodone doses theoretically need to be reduced in patients with renal and end-stage liver diseases.

Oxycodone is a mu- and kappa-opioid receptor agonist, whereas its metabolite oxymorphone is a pure mu-opioid receptor agonist.

The affinity of oxycodone for mu-opioid receptors is 1/10 -1/40 that of morphine.[1] Studies on rats demonstrated that part of the antinociceptive effects of oxycodone is mediated by kappa-opioid receptors. Coadministration of sub-antinociceptive doses of oxycodone plus morphine to rats resulted in high levels of antinociceptive synergy. This synergistic interaction seems to require both mu and kappa opioid receptors, although the exact cellular mechanism is still unclear.[15]

The parenteral potency of oxycodone is approximately 0.75 that of parenteral morphine. In contrast, the relative potency of oral oxycodone is approximately twice that of oral morphine.[16] Oral equianalgesic ratio of oxycodone to morphine range from 1:1 to 1:2.3 as result of significant inter-individual differences. The higher oral-intravenous ratio of oxycodone (0.70) compared with that of morphine (0.31) reflects the greater oral bioavailability of oxycodone compared to morphine.[17]

Linear relationships have been detected between oxycodone concentration and pharmacodynamic parameters, such as pupil diameter, respiratory rate, and sedation. Changes in pupil diameter are the most strongly correlated pharmacodynamic parameter with oxycodone concentration.[16] Conversely, no concentration-effect relationship has been detected between the active metabolite oxymorphone and the incidence of typical opioid adverse effects. Moreover, drugs that block CYP2D6, such as quinidine, inhibit oxymorphone synthesis, but does not alter oxycodone analgesia.[5]

In summary, pharmacokinetic-pharmacodynamic data support oxycodone as a pharmacologically active opiod that does not require conversion to oxymoprhone for pharmacological activity.[10]

Side effects of oxycodone are typical of opioids and similar to those of morphine except for fewer oxycodone-induced hallucinations. The most common side effects are nausea, constipation, dizziness, pruritus, and somnolence. Some reports suggest that morphine causes more nausea, while oxycodone more constipation.[5]

Oxycodone in chronic non-malignant pain

For a long time, physicians have resisted using opioid therapy for chronic pain because of the concerns of addiction, physical dependence, and tolerance.[18] Moreover, in the past, neuropathic pain has been considered intrinsically refractory to opioid analgesics.

After years of controversies, opioids have been recognised to have a role also in chronic non-malignant pain to control severe pain when all the other medical therapies have been ineffective. Controlled clinical trials demonstrated that opioids may be effective in both nociceptive and neuropathic non-cancer pain.[19]

In the last years, in the United States, the use of long-acting opioid analgesics has consistently increased and oxycodone has become the most prescribed opioid for chronic non-malignant pain, particularly for the treatment of osteoarthritis pain and chronic low back pain. In the year 2000 over 6.5 million prescriptions of oxycodone were written and it ranked as the eleventh most prescribed drug that year.[20]

TABLE I.—*Oxycodone in chronic non-malignant pain.*

Author (year)	Study design	Population	Comparison	Mean daily dose	Results
Jamison RN 1998 [23]	Randomized Open-label Long-term Randomized	Chronic back pain (36 patients)	NSAID *vs* (A) IR oxycodone *vs* (B) CR morphine + IR oxycodone	(B) 41.1mg morphine equivalent	Opioids superior to NSAID CR morphine + IR oxycodone superior to IR oxycodone
Hale ME 1999 [24]	Active-controlled Double-blind Crossover	Chronic back pain (47 patients)	CR *vs* IR oxycodone	≤40 mg	CR and IR comparable in efficacy and safety Typical opiate side effects
Salzman RT 1999 [12]	Randomized	Chronic low back pain (57 patients)	CR *vs* IR oxycodone	40 mg	CR and IR comparable in efficacy, safety, and ease of titration
Caldwell JR 1999 [25]	Randomized Double-blind Placebo-controlled	Osteoarthritis pain (107 pts)	CR oxycodone *vs* IR oxycodone + APAP *vs* placebo	40 mg	CR oxycodone or IR oxycodone + APAP superior to placebo
Roth SH 2000 [26]	Randomized Double-blind Placebo-controlled	Osteoarthritis pain (133 patients)	CR oxycodone *vs* placebo	40 mg	CR oxycodone 20 mg superior to placebo
Watson CP 2003 [27]	Randomized Double-blind Placebo-controlled Crossover	Neuropathic pain (45 patients)	CR oxycodone *vs* placebo	40±18.5 mg	Typical opiate side effects CR oxycodone is effective and safe
Gammaitoni AR 200 [34]	Prospective Open-label	Chronic low back pain (33 patients)	Fixed-dose combination Oxy/APAP 2.5-10/325 mg	Oxy/APAP 24.6/975mg	Fixed-dose combination Oxy/APAP is effective in pain relief Safe and well tolerated

A recent survey on 690 patients suffering from chronic non-malignant pain, in treatment with long-term opioids (oxycodone hydrochloride or fentanyl transdermal system), revealed that more than 60% of patients received oxycodone and the median daily dose was 80 mg. Interestingly, most of patients used long-acting opioids in a manner that is inconsistent with the standard recommendation in the manufacturers' prescribing information. CR oxycodone HCl was taken a median of 3 tablets per day, whereas transdermal fentanyl was kept on the skin, on average, for 2.5 days.[21]

One of the concerns about chronic opioid therapy is the risk of adverse cognitive and psychomotor effects. The performance of everyday tasks, such as routine work duties and safe car driving, could be worsened by opioid effects. Recent findings suggested that nor oxycodone with acetaminophen neither transdermal fentanyl impair cognitive ability or psychomotor function, in patients under long-term treatment.[22]

Beside the concerns about their safety, also the efficacy of long-term opioids in chronic non-malignant pain has been quested.

Seven studies are currently available in the literature that addressed the safety and efficacy of oxycodone for the treatment of non-cancer pain (Table I).[4, 12, 23-27]

All of these studies demonstrated that oxycodone was effective in relieving chronic non-malignant pain.

Four of these studies [4, 12, 23, 24] have been conducted on patients suffering from low back pain. This is one of the most common pain complaints that has disabled an estimated 7 million Americans and accounts for more than 8 million physician visits yearly in the US.[2]

In chronic low back pain, oxycodone, at mean daily dose of 40 mg, was shown to be superior to NSAIDs.[23] CR oxycodone q12h was comparable to IR oxycodone qid in efficacy and safety in patients with chronic low back pain; 91% of patients were titrated to stable pain control with an average daily oxycodone dose of 40 mg. Typical opioids side effects were reported in 89% of patients during titration. The most common side effects were constipation, nausea, pruritus, somnolence, and dizziness. The incidence of side effects was similar in both CR and IR oxycodone group, and declined over the time.[24] Another study was conducted on 57 patients with stable chronic moderate-to severe low back pain to evaluate the efficacy of CR oxycodone *vs* IR oxycodone during titration to stable pain. Usually, IR formulations are suggested during titration to stable analgesia. However, this study did not show statistically significant differences in percentage of patients successfully titrated and mean time to obtain stable pain control between the two groups. The results suggest that CR oxycodone can be used as readily as IR oxycodone during titration phase.[12] Finally, a recent study of Gammaitoni *et al.*[4] evaluated the analgesic efficacy of the new combinations oxycodone/acetaminophen with increased dose of oxycodone (7.5 and 10 mg) and stable dose of acetaminophen (325 mg). These formulations reduce the risk of hepatotoxicity acetaminophen-related, but maintain the double-analgesic mechanism of the combination therapy. These new formulations were effective in the treatment of moderate-to-severe chronic low back pain, with a mean daily dose of 24.6 mg oxycodone/975 mg APAP. A total of 67% of patients were titrated to optimal pain using *t.i.d.* dosing. These results suggest that combination of an optimum dose of APAP with oxycodone can produce additive analgesic effect.[4]

CR and IR oxycodone formulations have been studied also in osteoarthritis pain.[25, 26] Osteoarthritis is one of the most common joint disorders. Radiographic evidences of disease are present in 80% of the population by age 75 years. More than 20 million Americans with osteoarthritis experience pain from the disease.[28]

Both CR oxycodone q12h and IR oxycodone/acetaminophen qid seem to be effective and safe for patients with osteoarthritis pain. Both forms provide better analgesia than placebo and improved quality of sleep. Mean daily dosage of oxycodone was about 40 mg.[25]

CR oxycodone therapy has been studied also for long-term therapy (6 months). It provided sustained analgesia, with a typical opioid side effect profile, during both short- and long-term treatment of moderate to severe osteoarthritis pain. Pain relief was accompanied by significant reduction in the interference of pain with mood, sleep, and enjoinment of life, and by significant improvement in quality of sleep. During long-term treatment, the mean daily dose remained stable at approximately 40 mg and also the discontinuation rate was similar (52.6% in the double-blind *vs* 56.6% in the long-term trial).[26]

The only randomized controlled trial on neuropathic pain has been conducted on 45 patients with painful diabetic symmetrical distal sensory neuropathy.[27] Up to 50% of patients with diabetes mellitus develop peripheral neuropathy of whom 10% experience pain. CR oxycodone, at mean daily dose of 40 mg, was effective and safe for the management of patients with diabetic neuropathic pain and improved their quality of life. Oxycodone was superior to placebo and significantly affected most of the SF-36 items, by showing favourable outcomes for all domains. In this study, acetaminophen 325-650 mg q4-6h has been used as rescue medication for breakthrough pain.[27]

In conclusion, the evidence support the use of oxycodone for the management of chronic non-malignant pain, especially when pain has not responded adequately to other interventions. Along all these studies, total daily dose of 40 mg provided adequate anal-

gesia in most of treated patients, with a low incidence of intolerable typical opiate side effects.

Oxycodone in cancer pain

Opioids are frequently used in the treatment of moderate and severe cancer pain, according to the World Health Organization (WHO) analgesic stepladder. Morphine is the opioid of first choice. It is the standard opioid analgesic against which others are compared. It is the most widely available opioid in a variety of formulations. Oral medication should be used as the first line approach in most patients when initiating analgesic therapy. Titration is required at the beginning of the opioid therapy to individualize the dose for the single patient, and may be required periodically because of the natural history of the primary disease or the development of tolerance. Two types of formulation are required: normal release for dose titration and slow release for maintenance treatment. According to the European Association Palliative Care (EAPC) recommendations, oxycodone, if available in both normal and modified release, is an effective alternative to morphine.[29]

Four studies [12, 30-32] compared the safety and efficacy of CR oxycodone with IR oxycodone in cancer pain. All these studies showed no significant differences in analgesic effect and patient acceptance between IR and CR oxycodone. Patients were easily converted from IR to CR oxycodone and viceversa.[32] Adverse effects such as nausea, somnolence, dizziness, constipation, pruritus, and headache were reported in both treatment groups without statistically significant differences. However, in the a trial conducted in 164 cancer patients, fewer adverse events were reported with CR than with IR oxycodone. The frequency of headache and gastrointestinal adverse effects was significantly lower with CR oxycodone than with IR oxycodone.[30]

Mean daily oxycodone dosage was similar between CR (104 to 114 mg) and IR (113 to 127 mg) formulations, but consistently higher than that in non-malignant pain trials.[12-30] One patient discontinued treatment while taking IR oxycodone 360 mg/day, due to unacceptable delirium with upward titration.[12]

Time to obtain stable analgesia was not significantly different in patients receiving the CR and IR formulations of oxycodone (1.6 *vs* 1.7 days), confirming the idea that the convention of determining CR opioids dosages by first using IR formulations to titrate to stable pain may be unnecessary when CR oxycodone is used.[12]

Moreover, when patients were switched from fixed-combination products (i.e. oxycodone/APAP 5 mg /325 mg) to single-entity therapy, without any supplemental medication, their discontinuation rate was directly proportional to the pre-trial doses of analgesics. These results suggest that the non-opioid component in fixed-combination products is an important consideration in the analgesic therapy of cancer patients when switching to single-entity dosage forms. Patients can be converted to CR oxycodone using a dose roughly equivalent to the previous opioids dose in the fixed-combination products. The non-opioid analgesic component can be continued regularly around the clock and independently titrated as necessary.[31]

Seven randomized clinical trials [17, 33-38] compared the efficacy of CR oxycodone with other long-acting opioids. Six of them compared CR oxycodone with CR morphine;[17, 33-37] one of them with hydromorphone [38] (Table II).[12, 17, 30-38]

Despite pharmacokinetic and pharmacodynamic distinctions, no differences in analgesic efficacy between CR oxycodone and CR morphine were found.[33-35] However, the decrease in pain intensity correlated more strongly with oxycodone concentrations than with morphine concentrations.[35]

When intravenously administered, the dose of oxycodone hydrochloride needed was 30% higher than that of morphine.[17] Instead, when orally administered, as result of its higher bioavailability, oxycodone has twice the potency of oral morphine on a milligram basis, with equivalent analgesic efficacy. The recommended conversion ratio for oral oxycodone to oral morphine is 1:2 mg. However,

TABLE II.—*Oxycodone in cancer pain.*

Author (year)	Study design	Population	Comparison	Results
Kaplan R 1998 [30]	Randomized Doule-blind Multicentre	Cancer pain (164 patients)	IR *vs* CR oxycodone	CR and IR oxycodone comparable in efficacy. Significantly fewer adverse events with CR
Parris WC 1998 [31]	Randomized Doule-blind Multicentre Parallel-group	Cancer pain (111 patients)	IR *vs* CR oxycodone	IR oxycodone slightly superior to CR oxycodone in efficacy. No difference in adverse events
Salzman RT 1999 [12]	Randomized controlled	Cancer pain (48 patients)	IR *vs* CR oxycodone	CR and IR comparable in efficacy, safety, and ease of titration
Stambaugh JE 2001 [32]	Randomized controlled Doble-blind	Cancer pain (30 patients)	IR *vs* CR oxycodone	CR and IR comparable in efficacy and safety
Kalso E 1990 [17]	Randomized controlled Double-blind	Cancer pain (20 patients)	Oxycodone *vs* morphine	No major differences in analgesia and side effects. Hallucinations only with morphine
Heiskanen T 1997 [33]	Crossover Randomized controlled Double-blind	Cancer pain (32 patients)	CR oxycodone *vs* CR morphine	Comparable analgesia Vomiting more frequent with morphine and constipation more common with oxycodone
Bruera E 1998 [34]	Randomized controlled	Cancer pain (101 patients)	CR oxycodone *vs* CR morphine	No significant differences in efficacy, preference, or adverse effects between CR oxycodone and CR morphine
Mucci-LoRusso P 1998 [35]	Randomized controlled Double-blind	Cancer pain (45 patients)	CR oxycodone *vs* CR morphine	Similar analgesic efficacy and adverse effects Hal-lucinations only with CR morphine Lower incidence of itching and scratching with CR oxycodone
Lauretti GR 2003 [36]	Randomized controlled	Cancer pain (26 patients)	CR oxycodone *vs* CR morphine	Combination of oxycodone and morphine resulted in less escape doses consumed
Heiskanen T 2000 [37]	Randomized controlled	Cancer pain (45 patients)	CR oxycodone *vs* CR morphine	Both opioids provide adequate analgesia
Hagen NA 1997 [38]	Doule-blind Crossover	Cancer pain (44 patients)	CR oxycodone *vs* CR hydromorphone	No significant differences in analgesia, sedation, nausea, or patient preference. Hallucinations only with CR hydromorphone

this ratio can not be considered a fixed rule. Some clinical experiences support the use of 2:3 ratio of oxycodone to morphine. In this study, indeed, the mean daily dose of CR oxycodone, at the end of titration to obtain stable analgesia, was 123 mg compared to 180 mg of CR morphine.[33] Others, instead, observed a median oral oxycodone/morphine dose ratio of 1.5 and a maximum of 2.3.[34] Finally, somebody supports the use of 1:1 mg conversion ratio for oral oxycodone and oral morphine, which represents a 3:1 potency ratio of oral oxycodone to parenteral morphine.[39]

Some reports suggest that oxycodone could offer advantages over morphine in renally-impaired patients. In these patients, the increase in the half-life elimination is lower with oxycodone than with morphine.[35]

Related to side effects, there were no major differences between these 2 opioids. Typical opioids adverse experiences were reported in both groups. One study reported a statistically significant ($P<0.04$) lower frequency of itching and scratching with CR oxycodone than with CR morphine.[35] In 2 studies, hallucinations were reported only with CR morphine.[17, 35] Another study showed a similar frequency of adverse effects with the 2 drugs, but vomiting was associated more frequently

(P<0.01) with CR morphine, and constipation was significantly (P<0.01) more common with CR oxycodone.[33] This finding about constipation has not been shown in other studies. According to other authors, incidence of nausea and vomiting were significantly (P<0,05) lower in patients receiving oxycodone, compared to those receiving morphine.[36]

The acceptability of therapy rated by the patients showed no differences between the 2 opioids.[33, 34, 36]

When co-administrated in rats, subantinociceptive doses of oxycodone and morphine resulted in synergistic levels of antinociception.[15] In cancer patients, the combination of morphine and oxycodone significantly reduced the number of escape doses of IR morphine, which was 38% higher in patients receiving morphine only.[36]

In conclusion, CR oxycodone is as safe and effective as CR morphine in the treatment of chronic cancer-related pain, and their combination may result in a better analgesia profile.

Finally, one double blind crossover study, comparing CR oxycodone and hydromorphone, showed no significant differences between treatments in analgesic efficacy or side effects. However, 2 patients in the CR hydromorphone group experienced hallucinations, but none did in the CR oxycodone group.[38]

Conclusions

IR and CR oxycodone are equally effective in the treatment of pain and have similar adverse effect profiles. CR preparations with a long duration of action are attractive because they offer the advantage of longer dosing intervals, which results in sustained analgesic effect and greater convenience. CR oxycodone provides a rational alternative to CR morphine for the management of moderate to severe chronic pain.

Mean limitations of the analyzed trials are the short duration of the studies and the subjectivity of the measures used for pain and daily activity levels.

Further studies are warranted to define the long-term impact of opioid therapy in cancer and non-cancer pain patients.

Riassunto

Ossicodone: profilo farmacologico e dati clinici nel trattamento del dolore cronico

Gli oppioidi sono ampiamente usati come efficace terapia analgesica nel dolore di tipo oncologico. Nonostante anni di controversie, il loro utilizzo è stato accettato anche nel trattamento del dolore non oncologico. L'ossicodone da solo o in combinazione è stato usato per oltre 80 anni per il trattamento di varie sindromi dolorose. Negli Stati Uniti, il mercato dell'ossicodone, come singolo agente, è passato dal 10% nel 1996 al 53% nel 2000, diventando così l'oppioide più venduto. Recenti dati hanno rilevato che la combinazione ossicodone/paracetamolo (5 mg/325 mg) è tra gli oppioidi la formulazione più prescritta in tutte le sindromi dolorose croniche. Rispetto alla morfina, l'ossicodone ha una maggiore biodisponibilità orale e una potenza doppia. I dati farmacocinetici e farmacodinamici supportano l'ipotesi che l'ossicodone sia esso stesso un oppioide farmacologicamente attivo, senza necessità di conversione in ossimorfone. Sette studi confermano la sicurezza e l'efficacia dell'ossicodone per il trattamento del dolore cronico non oncologico (low back pain, dolore osteoartritico, e neuropatia diabetica dolorosa). L'ossicodone a rilascio immediato (IR) e controllato (CR) sono egualmente efficaci e sicuri. In questi studi il dosaggio medio giornaliero di ossicodone è stato di circa 40 mg, con una bassa incidenza di effetti collaterali tipici degli oppioidi. Nel dolore da cancro l'ossicodone può essere considerato una valida alternativa alla morfina orale nella rotazione degli oppioidi. Non è stata riscontrata alcuna differenza tra CR ossicodone e CR morfina. Le preparazioni a rilascio controllato, con una lunga durata d'azione, sono interessanti perchè offrono il vantaggio di intervalli tra le dosi più lunghi e prolungato effetto analgesico.

Parole chiave: Ossicodone - Paracetamolo - Ossimorfone - Dolore cronico non oncologico - Dolore oncologico.

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