

COMBINED USE OF STRONG OPIOIDS FOR PAIN RELIEF IN CANCER PATIENTS-A PROSPECTIVE RANDOMIZED COMPARATIVE STUDY

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Key words: Cancer, opioids, Oxycodone; k-Opioid receptors.

Abstract

Background: Long-term clinical use of opioids in cancer patients can cause a wide range of severe adverse effects such as respiratory depression and tolerance. Different pharmacological techniques, such as rotation or switching from one opioid to another have been introduced during the last decades, proposed for restoring the opioid response, in an effort to improve the balance between analgesia and adverse effects. Although not advocated by the WHO, recent experimental and clinical data suggest the possible use of an opioid combination to improve analgesia.

Objectives: Our primary outcome was to evaluate the possible analgesic efficacy of the combination of transdermal fentanyl and oral oxycodone and secondary to assess the central nervous system adverse events (mainly sedation) in patients suffering from moderate cancer pain.

Methods: We conducted a prospective, randomized, comparative study in 32 patients suffering from moderate cancer pain. The patients continued the existing treatment and were randomly allocated into two groups. Patients in the group A received an additional dose of 25 µg/h transdermal fentanyl, while patients in the group B received an additional dose of 40 mg/d oral oxycodone.

Results: We demonstrated that both treatments appeared to improve pain relief. However, the patients who received the combination of transdermal fentanyl and oral oxycodone presented significantly less sedation.

Conclusions: The present study demonstrated that the combination of potent opioids may improve the pain relief in patients with moderate cancer pain. We addressed the possible advantages of the use of oxycodone in future combinations within strong opioids. Since no opioid combination regimen is evidence-based treatment, further appropriately designed studies are needed to clarify the benefits and safety of combination opioid therapy and improve our therapeutic strategies against cancer pain.

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Introduction

Opioid analgesics are the most frequently used drugs and remain the mainstay of cancer pain treatment¹. The use of a single strong opioid in cancer pain management has been common practice for a long time¹. However, in some patients, long-term clinical use of opioids can cause a wide range of adverse effects such as respiratory depression, constipation, and tolerance^{2,3}. Therefore, strong opioids with non-opioids and adjuvant analgesics are in use during the last decades for providing symptomatic relief in cancer patients according to the WHO pain ladder¹. However, in a recent systematic review emphasis is given to drug-drug interactions⁴. Drug-drug interactions are reported to lead to serious adverse drug reactions in patients treated with opioids for cancer pain^{4,5}. The authors addressed that the combined use of an opioid and another drug with CNS depressant effect increases the risk of acute opioid toxicity and may lead to severe CNS adverse effects such as severe sedation and respiratory depression⁴.

Switching or rotation from one opioid to another has been introduced about 20 years ago. This pharmacological technique has been proposed for restoring the opioid response, in an effort to improve the balance between analgesia and adverse effects, although not always successfully^{6,7}. This is based on the different biochemical characteristics and receptor activity of opioids, presenting asymmetric tolerance among them⁸. According to published reports, equianalgesic doses with a second opioid lower than the one being used may produce a better analgesia and a reduction of the intensity of adverse effects in about 80% of patients⁹⁻¹¹.

Clinical and experimental data are nowadays in favor of co-administration of low doses of different opioids, and claim that may produce marked antinociceptive synergy with reduced central nervous system (CNS) adverse effects¹²⁻¹⁴. The European Association of Palliative Care (EAPC) recommendations on opioids in cancer pain have identified the practice of combination opioid therapy as an important area¹⁵. A systematic review, literature appraisal and recommendations for combination of opioid therapy have been conducted¹⁶. In a recent clinical

study compared opioid rotation versus combination for cancer patients with chronic uncontrolled pain, both techniques appeared to provide significant relief of pain and improved patient satisfaction¹⁷.

Based on this rationales, and after using this approach in several patients, an open-label, prospective, randomized, comparative study was designed with the aim of evaluating the possible advantages of the combination of transdermal fentanyl and oral oxycodone, concerning the analgesic efficacy and CNS adverse events (mainly sedation) in patients suffering from moderate cancer pain.

Patients and Methods

A sample of 53 cancer patients with moderate pain was examined. Our study protocol, conformed to the provisions of in accordance with the Helsinki Declaration, was approved by the Scientific and Ethics Committee of our institution. Patients, aged 60-75 years old, were admitted to our palliative cancer care unit for a period of 6 months. A written informed consent was obtained from all patients before participating in the study. The patients visited the palliative cancer care unit requiring a change in the analgesic treatment that they were already receiving because they were still suffering from moderate pain [Numerical Rating Scale (NRS): 4-7]. Initial screening performed and excluded patients if they were suspected to be abused with opioids, had cardiac failure, respiratory failure, hepatic or renal failure, impaired cognitive function and uncontrolled central nervous system involvement. The analgesic treatment that they were already receiving included transdermal fentanyl (50-175 µg/h) or sublingual fentanyl (200-600 µg). Additional adjuvants included gabapentin (900-2400 mg/d) or pregabalin (75-375 mg/d), paracetamol (3 g/d), lornoxicam (8 mg/d). The patients continued the existing treatment and were randomly allocated using sealed envelopes into two groups. Patients in the group A received an additional dose of 25 µg/h transdermal fentanyl, while patients in the group B received an additional dose of 40 mg/d oral oxycodone. According to the equianalgesic dose table of opioids, 25 µg/h transdermal fentanyl is equianalgesic with 40 mg/d oral oxycodone.

The primary aim of this study was to evaluate

Table 1
Pasero Opioid-induced Sedation Scale (POSS) with Interventions

Grade	Sedation level	Medical interventions
Grade 1	Awake and alert	Acceptable; no action necessary; may increase opioid dose if needed
Grade 2	Slightly drowsy, easily aroused	Acceptable; no action necessary; may increase opioid dose if needed
Grade 3	Frequently drowsy, arousable, drifts off to sleep during conversation	Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50% or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing non-opioid, such as acetaminophen or a NSAID, if not contraindicated.
Grade 4	Somnolent, minimal or no response to verbal and physical stimulation	Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

the analgesic profile of the combination and secondary outcome to investigate the CNS adverse effects (mainly sedation). A questionnaire that included items concerned the pain severity and sedation was completed. Pain was rated with the numerical rating scale (NRS) that ranged from 0 (no pain at all) to 10 (the worst pain that you can imagine) and was evaluated on the same day (D0), the third (D3) and sixth day (D6). Sedation was evaluated using the Pasero Opioid Sedation Scale (POSS) on the first and on sixth day (D0 vs D6)¹⁸. Table 1 shows the Pasero Opioid Sedation Scale with medical interventions required.

For the statistical analysis the Mann-Whitney U test was used to compare differences in NRS and sedation between the groups at D0, D3 and D6 time

intervals. The Friedman test was used to compare differences in the NRS in each group at D0, D3 and D6 time intervals. The results are presented as median and 1st (1stQ) and 3rd (3rdQ) quantiles. All p values were two-sided, and p values less than 0.05 were considered to indicate statistical significance.

Results

After initial screening a total of 32 patients, aged 60-75 (median 66) years old were included in the study. Male patients were predominantly more in both groups (10/16 in group A and 11/16 in group B). As shown in the table 2, the NRS was similar for the A and B groups at D0 (Mann-Whitney U test, W=-1,703,

Table 2
Statistical analysis for NRS between groups A and B, at D0, D3, D6

Day 0	Group	Min.	1stQ	Median	3rdQ	Max.
	A	4.00	6.00	6.00	6.00	7.00
	B	5.00	6.00	6.50	7.00	8.00
Day 3	A	3.00	4.00	4.00	4.25	5.00
	B	3.00	4.00	4.00	4.25	5.00
Day 6	A	3.00	4.00	4.00	4.00	5.00
	B	3.00	4.00	4.00	4.00	5.00

D0 vs D3 (p <0,01), D0 vs D6 (p <0,01), D3 vs D6 (p=0,558, NSS)

NSS = non statistical significance

$p=0,09$), T3 (Mann-Whitney U test, $W=0$, $p=1$) and D6 (Mann-Whitney U test, $W=1,123$, $p=0,371$). Using the Friedman test, there was statistically significant difference in the NRS at D0, D3 and D6 in each group ($\chi^2=57,226$, $p < 0,001$). Post hoc analysis (Wilcoxon-Nemenyi-McDonald Thompson test) showed that there was a statistically significant difference in the NRS at D0 and D3 ($p < 0,01$) and at D0 and D6 ($p < 0,01$) but not between D3 and D6 ($p=0,558$) between groups A and B.

In between groups statistical analysis (Table 3) showed significantly lower sedation levels ($p < 0.01$) in patients of group B, compared with patients of group A (D0 vs D6), both at POSS grades 2 and 3. Importantly, POSS grade 3 sedation is considered non acceptable and needs closed observation.

Table 3

Statistical analysis for Pasero Opioid-induced Sedation Scale (POSS) between both groups (D0 vs D6)

	Group A (n=16)	Group B (n=16)	P value
Grade 1	0	12	$P < 0.001$
Grade 2	14	4	$P < 0.01$
Grade 3	2	0	$P < 0.001$

Discussion

In our open-label clinical, prospective, randomized study we compared two different methods of treatment and combined two strong opioids (transdermal fentanyl and oral oxycodone) in patients with moderate cancer pain. We showed that both treatments appeared to improve pain relief. However, the patients who received the combination of transdermal fentanyl and oral oxycodone presented significantly less sedation. The Pasero Opioid-induced Sedation Scale (POSS), used in our study has been recommended as the superior sedation scale for the measurement of sedation during opioid administration for pain management¹⁹. In a comparative study among three different sedation scales the POSS scored higher in combined measures of ease of use, nursing confidence, and usefulness of information provided to

make clinical decisions¹⁹.

The use of opioid combinations is not advocated by the World Health Organization (WHO). In the guidelines for the relief of chronic cancer pain, the WHO recommends that cancer pain may be managed by following the analgesic ladder¹. However, the effectiveness of these guidelines in clinical practice has been questioned²⁰. The EAPC assessed patients with cancer, on strong opioid analgesia in which two or more strong opioids were used simultaneously and analgesia and/or side effects were assessed as study outcomes¹⁵. A systematic review was conducted and concluded that the evidence to support this practice is limited and only a weak recommendation can be used to support combination opioid therapy¹⁶. This recommendation is also based on the caveat that the desirable effects of combination opioid therapy is outweighed by any disadvantages that this would confer. The authors suggested that prospective randomized trials are needed to clarify the benefits and safety of combination opioid therapy¹⁶.

The scientific basis for combination opioid therapy is complex and not well understood. The rationales for combination opioid therapy, in which two or more strong opioids were used simultaneously, are mainly to improve analgesia and secondary to limit the development of opioid tolerance and decrease opioid side effects^{12,13}. In recent years evidence has been evolving and basic scientific work is potentially supporting a role for combination opioid therapy. There is now adequate evidence showing clearly that multiple opioid receptors and subtypes of these receptor groups exist²¹. Additionally, pharmacological differences among mu-opioid analgesics have been observed in experimental studies, implying that all mu-opioids may not be working through the same mechanism of action²¹. These findings suggest in between-opioids differences indicating a complex pharmacology for opioid receptors¹⁰. However, in response to repeated administration of an agonist, opioid receptors undergo adaptations such as desensitization, down-regulation, and internalization, which may contribute to the development of tolerance and reducing eventually the use of opioids as analgesics²².

It has long been appreciated by clinicians the fact that individual patients may respond better to

one mu-opioid analgesic than another, improving tolerability and restoring satisfactory pain relief^{7,8}. Actually, this is the rationale for opioid switching^{7,8}. Additionally, evidence suggests the presence of functional interactions among mu-opioid analgesics, consistent with the involvement of multiple sub-populations of mu-opioid receptors²³. Interactions with other opioid receptors have also been recently reported in clinical-and experimental studies, showed that increased analgesia results with an improved side-effect profile^{12,14,16}. Accordingly, these data indicate the potential of synergistic effects when using opioids with different receptor characteristics²⁴. This may provide a scientific rationale for the use of combination opioid therapy.

In our study we combined transdermal fentanyl and oxycodone. The choice of oxycodone was based on adequate literature evidence, both in experimental and clinical studies^{14,16,25}. In contrast to mu-opioids, intrinsic antinociceptive effects of oxycodone seem to be principally mediated by putative kappa-receptors²⁶. It is possible that the synergistic analgesic effect may be the result of the simultaneous activation of both the mu-and kappa-opioid receptors. This synergistic interaction between mu-opioids and oxycodone appears to require both mu-and kappa-opioid receptors. Although the exact cellular mechanism mediating this synergistic effect is not clear, it may be attributed to up-regulation of G-protein activation leading to antinociception²⁷.

Co-administration of sub-antinociceptive doses of morphine and oxycodone in experimental studies produced unexpected antinociceptive synergy with a reduced incidence of CNS side effects relative to equi-antinociceptive doses of either opioid alone. These findings were observed irrespectively of the route the opioids were administered⁹.

In a clinical study, the rescue morphine

consumption was significantly reduced (38%) in patients receiving a combination of morphine and oxycodone as opposed to those receiving morphine alone²⁵. Of interest and similar to our results a synergistic effect between the two drugs was apparent during the first week of oxycodone treatment. The authors concluded that a combination of morphine and oxycodone may be a useful alternative to morphine alone, with a better analgesic profile and fewer CNS side effects (nausea, vomiting and sedation)²⁵.

Possible explanations for these findings may include that oxycodone has been shown to behave differently from other opioid agonists through varying effects on the G protein activation inwardly rectifying potassium currents (GIRK) in animal models²⁸. Additionally, oxycodone undergoes O-demethylation through the enzyme CYP2D1 and is metabolised to oxymorphone, a mu-opioid agonist with a potency 10-fold greater than that of morphine²⁹. Obvious limitation of our study is the lack of control group, as in most studies of cancer patients.

In conclusion the simultaneous use of two strong opioids is another clinical practice that seems to gradually gain more acceptance among patients with cancer pain. The present study demonstrated that the combination of potent opioids may improve pain relief in patients with moderate cancer pain. Additionally, the patients who received the specific combination of transdermal fentanyl and oral oxycodone presented significantly less sedation, highlighting the possible advantages of the use of oxycodone in future combinations within strong opioids. Since no opioid combination regimen is evidence-based treatment, further appropriately designed studies are needed to clarify the benefits and safety of combination opioid therapy and improve our therapeutic strategies against cancer pain.

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