

Original Article

The Use of Controlled-Release Oxycodone for the Treatment of Chronic Cancer Pain: A Randomized, Double-Blind Study

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Abstract

To compare the effectiveness and safety of controlled-release (CR) oxycodone tablets with immediate-release (IR) oxycodone in patients with chronic cancer pain, a multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain. Patients were treated with 6 to 12 tablets or capsules of fixed-combination opioid/nonopioid analgesics per day at study entry. Patients received 30 mg of CR oxycodone tablets every 12 hr or 15 mg of IR oxycodone four times daily for 5 days. No titration or supplemental analgesic medications were permitted. The mean (\pm SE) baseline pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) was 1.5 ± 0.1 for the CR oxycodone-treated group and 1.3 ± 0.1 for the group given IR oxycodone ($P > 0.05$). The 5-day mean pain intensity was 1.4 ± 0.1 and 1.1 ± 0.1 for the CR and IR groups, respectively ($P > 0.05$). Discontinuation rates were equivalent (33%). There was no significant difference between treatment groups in the incidence of adverse events. This study demonstrates that cancer pain patients given 6 to 12 tablets or capsules of fixed-dose combination analgesics can be equally well treated with CR oxycodone administered every 12 hr or IR oxycodone four times daily at the same total daily dose. CR oxycodone offers the benefits of twice daily dosing. *J Pain Symptom Manage* 1998;16:205-211. © U.S. Cancer Pain Relief Committee, 1998.

Introduction

Oxycodone is a well-known opioid agonist similar to morphine in its efficacy. Compared with morphine, oxycodone has a higher oral-

to-parenteral bioavailability^{1,2} and is about twice as potent on a milligram basis.³⁻⁶ Immediate-release (IR) oxycodone is available as a single agent or in combinations with acetaminophen or aspirin. Oxycodone alone and in combination is used extensively in the treatment of a variety of pain syndromes.

A controlled-release (CR) oxycodone hydrochloride tablet has been developed to extend the duration of action of oral oxycodone and

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to provide the benefits of twice-daily dosing. These tablets provide an onset of analgesic action comparable to that of IR oxycodone.⁷ The CR dosage form allows the independent selection and titration of nonopioid coanalgesics, a treatment not possible using fixed-combination products.

The purpose of this study was to compare the effectiveness and safety of CR oxycodone tablets with marketed IR oxycodone in patients with chronic cancer pain previously treated with fixed-combination opioid/nonopioid analgesics.

Methods

Study Population

The study included adult patients recruited from 15 centers in the United States who were receiving 6 to 12 tablets or capsules per day of fixed-combination analgesics for cancer-related pain. Patients were of either gender and had stable coexistent disease. Patients were excluded if their pain was not already acceptably controlled; if they had surgery or radiotherapy within 10 days prior to study or anticipated these procedures during study; if they had compromised function of a major organ system; or if they were receiving nonopioid analgesics (before the protocol was amended). Of course, concomitant nonanalgesic therapies were allowed during the study.

To encourage participation and to lower the discontinuation rate, the protocol was modified during the study to include patients undergoing or recently given radiotherapy and those receiving stable doses of nonopioid analgesics or analgesic adjuvants. In addition, patients receiving ten or more tablets or capsules of fixed-combination analgesics were no longer permitted to enter the study, but could be enrolled in a companion study intended for patients with greater opioid requirements.

All patients gave written informed consent; the study received institutional review board approval at each site.

Study Design and Drug Treatment

This was a randomized, double-blind, parallel-group study. Patients received 30 mg of CR oxycodone (OxyContin® Tablets, Purdue Pharma L.P., Norwalk, Conn) every 12 hr or 15 mg of IR oxycodone (Roxicodone™, Rox-

ane Laboratories, Inc., Columbus, Ohio) four times daily for 5 days using a double-dummy technique. The total daily oxycodone dosage was 60 mg for each treatment group. Patients needing titration of analgesic or supplemental medication were required to discontinue from the study.

Patients evaluated pain intensity and acceptability of current therapy at baseline and over the past day. During the double-blind period, patients rated pain intensity in a diary four times daily: morning (overnight pain rating), midday (morning pain rating), evening (afternoon pain rating), and bedtime (evening pain rating). A four-point categorical (CAT) scale of 0 = none, 1 = slight, 2 = moderate, and 3 = severe was used for these ratings. Patients also assessed acceptability of therapy considering pain intensity and side effects for both day and night. Acceptability of therapy was rated on a five-point CAT scale of 1 = very poor, 2 = poor, 3 = fair, 4 = good, and 5 = excellent. Observers contacted patients by telephone daily throughout the 5-day study period and recorded information about adverse events and changes in the patients' condition.

Outcomes

The primary efficacy measures were mean pain intensity by day (the average of the four CAT scale ratings for pain intensity for each study day) and mean acceptability of therapy by day (the average of the two CAT scale ratings for acceptability of therapy for each study day). Other efficacy measures included mean pain intensity and mean acceptability of therapy by time of day, overall mean daily pain intensity and acceptability of therapy, and discontinuation rates both overall and by reason.

Safety was evaluated by adverse events obtained by questioning and/or examining the patients. Discontinuation rates because of adverse events were determined.

Statistical Methods

The sample size was sufficient to detect a 40% difference in pain intensity between treatments with a statistical power equal to 0.80. Baseline comparisons were made using Fisher's Exact Test⁸ for categorical variables and a two-way analysis of variance (ANOVA) model⁹ for continuous variables. For the intent-to-treat population, that is, patients who

were randomized to the study and took at least one dose of the study drug, scores for mean pain intensity and acceptability of therapy by day, by time of day, and overall were compared across treatment groups using a two-way analysis of covariance (ANCOVA).⁹ The ANCOVA model included effects for treatment, center, baseline pain (covariate), and the interaction between treatment and center. A repeated measures ANOVA model was used to evaluate treatment effects over the 5-day study period in the subset of patients who completed the study. Discontinuation rates were compared using Fisher's exact test. Fisher's exact test also was used to assess differences between treatments for the number of patients reporting at least one adverse event related to the study drug. All analyses used two-sided tests with a critical alpha level of 0.05. Interactions were tested at an alpha level of 0.10.

Results

Patient Demographics and Disposition

Of the 111 cancer patients who entered the study, 50% were women and 77% were white. The average age was 57 years (range, 31–80 years). The most common cancer diagnoses were breast, gastrointestinal, lung, and gynecologic; the primary pain types were bone (45%) and viscera (28%).

Of the 111 patients entered, 103 (93%) (52 CR oxycodone and 51 IR oxycodone) were evaluable for intent-to-treat analyses. Eight patients were excluded for administrative reasons. Sixty-six (59%) patients (33 in each group) completed the 5-day study period; 37 (33%) patients (19 CR oxycodone and 18 IR oxycodone) discontinued. Reasons for discontinuation included ineffective treatment (ten CR oxycodone and four IR oxycodone), adverse events (four CR oxycodone and seven IR oxycodone), unrelated illness (one in each group), protocol violations (four CR oxycodone and five IR oxycodone), and other (one IR oxycodone).

Oxycodone Dosage

Single-entity CR oxycodone or IR oxycodone were substituted for 6–12 tablets or capsules of fixed-combination analgesics per day containing 30–60 mg of oxycodone or its equivalent plus acetaminophen. The majority of patients

(79%) had received six to nine tablets or capsules per day. In 71% of patients, the prestudy combination analgesic was oxycodone/acetaminophen. Most lower-dose (six to nine tablets or capsules) patients received a total daily prestudy oxycodone dosage ranging from 30 to 45 mg with 2.0–2.9 g of acetaminophen; higher-dose (ten to 12 tablets or capsules) patients received a daily oxycodone dosage of 50–60 mg with 3.2–3.9 g of acetaminophen. Other prior opioids included codeine/acetaminophen (17%), hydrocodone/acetaminophen (10%), propoxyphene napsylate/acetaminophen (2%), and transdermal fentanyl (1%) (protocol violation).

During the study, patients received 60 mg of CR or IR oxycodone (or 0.9 mg/kg oxycodone on average) every 24 hr. Ninety-four percent of the patients treated were at least 95% compliant.

Efficacy

Pain intensity. Mean (\pm SE) baseline pain scores were slight to moderate prior to randomization: 1.5 ± 0.1 for the CR oxycodone-treated group and 1.3 ± 0.1 for the group given IR oxycodone ($P > 0.05$).

Mean pain intensity scores (least squares) by study day shown in Figure 1 were slight to moderate in both groups throughout the study period with some tendency toward decreased scores by day 5. No significant treatment differences in mean pain intensity scores were detected for any of the 5 study days. The mean

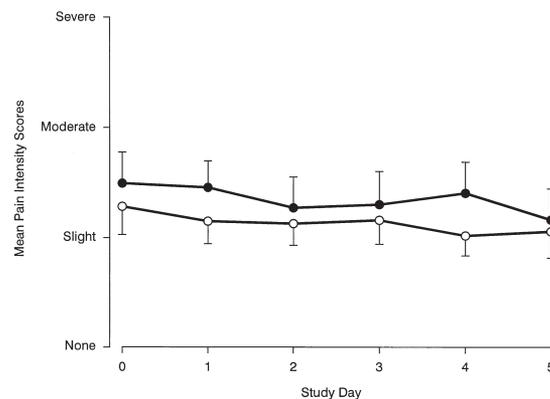


Fig. 1. Mean (\pm two SE) daily pain intensity scores over the 5-day study period in cancer pain patients treated with CR oxycodone (●) and IR oxycodone (○). Categorical scale of 0 = none, 1 = slight, 2 = moderate, and 3 = severe.

pain intensity scores for patients who completed the study also showed no significant treatment differences. There were no significant differences between treatments in the mean pain scores either by time of day or overall. The overall mean pain intensity scores were 1.4 ± 0.1 and 1.1 ± 0.1 for patients given CR and IR oxycodone, respectively.

Eleven patients with neuropathic pain reported significantly higher baseline pain intensity scores for both current pain ($P = 0.03$) and pain over the past day ($P = 0.01$) than patients with other pain types. Although the overall pain scores achieved following treatment with oxycodone were not as low as in patients without neuropathic pain, neuropathic pain patients were opioid responsive. Overall pain intensity scores in this group decreased from 2.0 at baseline to 1.6 compared with a decrease from 1.3 at baseline to 1.2 in patients with other pain types.

Acceptability of therapy. Mean baseline acceptability of therapy scores for both current acceptability (CR oxycodone 3.6 ± 0.1 ; IR oxycodone 3.4 ± 0.2) and acceptability over the past day (CR oxycodone 3.6 ± 0.1 ; IR oxycodone 3.3 ± 0.2) were fair to good and comparable for both treatment groups ($P > 0.05$).

Mean acceptability of therapy scores (least squares) by day were fair to good throughout the study period (Figure 2). There were no significant treatment differences in mean acceptability of therapy scores for any of the 5 study

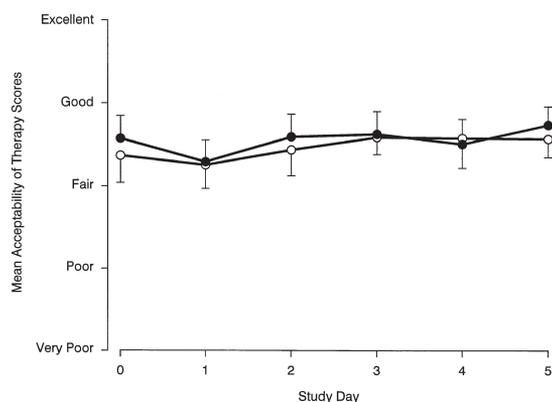


Fig. 2. Mean (\pm two SE) acceptability of therapy scores over the 5-day study period in cancer pain patients treated with CR oxycodone (●) and IR oxycodone (○). Categorical scale of 1 = very poor, 2 = poor, 3 = fair, 4 = good, and 5 = excellent.

days. There were also no significant differences between treatment groups in mean acceptability of therapy scores by time of day or in overall scores.

Discontinuation rates. Sixty-six (59%) patients completed the five-day study period; 37 (33%) patients discontinued. Discontinuation rates for both treatment groups were equivalent. There were no significant differences between treatments in patients discontinuing for lack of adequate pain control or adverse events. The majority of patients who discontinued for ineffective treatment withdrew during the first 24 hr. By design, titration and rescue were not permitted.

When discontinuation rates of all patients enrolled in the study were examined by pre-study opioid/nonopioid analgesic dose, patients in the higher-dose group (ten to 12 tablets or capsules per day) had significantly higher discontinuation rates for lack of adequate pain control (29%) than patients given six to nine tablets or capsules per day (10%) ($P = 0.04$).

Safety

Of the 111 patients enrolled, 109 were evaluable for safety. Seventy-six patients (70%) (69% CR oxycodone and 70% IR oxycodone) reported at least one adverse event considered by the investigators to be at least possibly related to treatment. The 280 adverse events reported were about equally divided between groups (138 CR oxycodone and 142 IR oxycodone). The majority of these adverse events involved the gastrointestinal (43%) and nervous (33%) systems; the most commonly reported adverse events were typical of those seen during opioid therapy (Table 1). Confusion occurred in only two patients, both treated with IR oxycodone.

Eleven patients (four CR oxycodone and seven IR oxycodone) discontinued the study because of adverse events. While constipation was actively managed, less aggressive management of nausea and vomiting may have contributed to patients discontinuing because of adverse events (Table 2). There was no discernible pattern distinguishing patients who discontinued from those patients who developed adverse events but did not discontinue. All adverse events resolved. No patient died during the study.

Table 1
Most Commonly Reported Related Adverse Events^a

Adverse event	CR oxycodone		IR oxycodone	
	No. (%) patients	No. reports	No. (%) patients	No. reports
Nausea	11 (20)	17	13 (24)	25
Somnolence	13 (24)	18	12 (22)	22
Dizziness	8 (15)	16	10 (19)	13
Constipation	12 (22)	14	10 (19)	11
Vomiting	5 (9)	6	11 (20)	19
Pruritus	7 (13)	8	5 (9)	8
Headache	7 (13)	10	3 (6)	3
Dry mouth	4 (7)	6	3 (6)	4
Sweating	1 (2)	1	5 (9)	8
Abdominal pain	3 (6)	5	1 (2)	1
Insomnia	3 (6)	3	1 (2)	1

^aAdverse events at least possibly related to study drug in $\geq 5\%$ of patients. CR, controlled release; IR, immediate release.

Differences in the incidence of patients reporting adverse events were not significant between treatment groups, although there was a trend toward less nausea, vomiting, and sweating in patients receiving CR oxycodone (Table 1). When analyzed by prestudy fixed-combination opioid dose, more lower-dose patients (76%) reported at least one related adverse event than higher-dose patients (48%) ($P = 0.02$). A significant difference also was observed for nausea: 34% of lower-dose patients reported nausea compared with 9% of higher-dose patients ($P = 0.02$).

Discussion

It is common practice to begin oral pharmacotherapy for chronic pain with acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). As the pain syndrome progresses, around-the-clock administration of a single-entity opioid for mild to moderate pain is recommended. The opioid can be combined with

a nonopioid analgesic as necessary. When this approach fails to acceptably relieve pain, a single-entity opioid for moderate to severe pain, often combined with a nonopioid analgesic and/or adjuvants, is substituted. The World Health Organization (WHO) has codified this therapeutic approach in a three-step analgesic ladder.¹⁰

Opioids in fixed combination with acetaminophen or aspirin are often used at the second step because these combinations provide additive analgesia;¹¹ however, the potential dose-limiting toxicity associated with the nonopioid analgesics can prevent upward titration as the disease and pain progress.¹² To minimize toxicity and to more effectively individualize therapy, around-the-clock dosing can be instituted using a suitable agonist opioid that has no ceiling effect for analgesia along with a nonopioid appropriate for the clinical setting. With this approach, the opioid can be titrated upward as much as needed throughout the course of the disease process. The nonopioid can be adjusted independently.

In this study, cancer pain patients who had been receiving fixed-dose combination analgesics for pain control at baseline were equally well controlled with CR oxycodone administered every 12 hr or IR oxycodone four times daily at the same total daily dose. Pain intensity and acceptability of therapy by day, by time of day, and overall were not different between treatments. Because the protocol did not permit titration to analgesic effect or supplemental medication, discontinuation rates for ineffective treatment were greater than would be

Table 2
Action Taken for Related Common Opioid Adverse Events (N = 109)

Adverse event	No. reports	No. (%) reports	
		Treated	Drug discontinued
Constipation	25	22 (88)	0
Vomiting	25	10 (40)	4 (16)
Nausea	42	11 (26)	7 (17)
Dizziness	29	0	6 (21)
Somnolence	40	1 (3)	3 (8)
Pruritus	16	0	1 (6)
Dry mouth	10	0	1 (10)

expected in actual clinical practice. When discontinuation rates for lack of adequate analgesia were examined by prestudy fixed-combination analgesic dose, the higher-dose group showed a greater discontinuation rate than the lower-dose group. These data suggest that the nonopioid components of the fixed-combination products are, not surprisingly, an important consideration in the analgesic therapy of cancer patients when switching to single-entity dosage forms.

The adverse event profile associated with CR oxycodone use was typical for opioids administered to patients with cancer pain. There was no significant difference in the incidence of adverse events between treatments, although there was a trend toward less nausea, vomiting, and sweating in patients receiving CR oxycodone. This finding might be expected based on the release characteristics of the two dosage forms; peak plasma oxycodone concentrations occur less rapidly and less frequently following dosing with CR oxycodone than with IR oxycodone.

When patients were analyzed by prestudy opioid dose, more patients given the lower dose of fixed-combination analgesics reported one or more related adverse events than higher-dose patients. A significant difference by prior opioid dose also was observed for nausea. These findings are expected because lower-dose patients had no opportunity to adapt to the increase in opioid dose administered (60 mg of oxycodone per day); they were switched directly to this study dose without titration.

The data from this study suggest that patients with chronic cancer pain can be converted from fixed-combination opioid/nonopioid analgesics to CR oxycodone using a dose roughly equivalent to the previous opioid dose. For example, CR oxycodone can be initiated at a dose of 10–20 mg every 12 hr in patients switching from one to five tablets or capsules of regular-strength, fixed-combination opioid/nonopioid analgesics per day. This approach should provide a conservative starting dose of CR oxycodone that can be titrated upward, if necessary. It should also help minimize the occurrence of typical opioid adverse events. After switching to CR oxycodone, the nonopioid analgesic component of therapy can be continued regularly around the clock, if indicated,

and independently titrated as necessary. Because this single-entity dosage form substitutes well for fixed-combination opioid/nonopioid analgesics, opioid therapy can be initiated with CR oxycodone instead of the combination products at the second step of the analgesic ladder in patients who may need ongoing opioid therapy.

In patients with cancer pain, CR oxycodone tablets provide the analgesic efficacy of a well-known opioid agonist as a convenient, oral tablet for every 12-hr dosing. CR oxycodone can be used relatively early in the chronic cancer pain disease process and then titrated upward as the pain progresses. Because it has no ceiling effect for analgesia, CR oxycodone can be used until oral tablets can no longer be swallowed.

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