



# Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study

Patricia Mucci-LoRusso<sup>a</sup>, Barry S. Berman<sup>b</sup>, Peter T. Silberstein<sup>c</sup>, Marc L. Citron<sup>d</sup>, Linda Bressler<sup>e</sup>, Sharon M. Weinstein<sup>f</sup>, Robert F. Kaiko<sup>g</sup>, Barbara J. Buckley<sup>g</sup> and Robert F. Reder<sup>g</sup>

<sup>a</sup>Harper Hospital and Karmanos Cancer Institute, Detroit, MI; <sup>b</sup>Treatment Centers for Cancers and Blood Disorders, P.A., Kissimmee, FL; <sup>c</sup>Mercy Cancer Center, North Iowa Mercy Health Center, Mason City, IA; <sup>d</sup>Long Island Jewish Medical Center, New Hyde Park, NY; <sup>e</sup>University of Illinois Hospital and West Side VA Medical Center, Chicago, IL; <sup>f</sup>The University of Texas, M.D. Anderson Cancer Center, Houston, TX; <sup>g</sup>Purdue Pharma L.P. Norwalk, CT, USA

Controlled-release oral formulations of oxycodone and morphine are both suitable analgesics for moderate to severe pain. They were compared in cancer-pain patients randomized to double-blind treatment with controlled-release oxycodone ( $n=48$ ) or controlled-release morphine ( $n=52$ ) every 12 h for up to 12 days. Stable analgesia was achieved by 83% of controlled-release oxycodone and 81% of controlled-release morphine patients in 2 days (median). Following titration to stable analgesia, pain intensity (0 = none to 3 = severe) decreased from baseline within each group ( $p \leq 0.005$ ), from 1.9 (0.1) to 1.3 (0.1), mean (SE), with controlled-release oxycodone, and from 1.6 (0.1) to 1.0 (0.1) with controlled-release morphine (no significant between-group differences). Typical opioid adverse experiences were reported in both groups. Hallucinations were reported only with controlled-release morphine ( $n=2$ ). Visual analog scores (VAS) for 'itchy' and 'scratching' were lower with controlled-release oxycodone ( $p \leq 0.044$ ), as was peak-to-trough fluctuation in steady-state plasma concentration ( $p=0.004$ ). The correlation between plasma concentration and dose was stronger ( $p=0.026$ ) for oxycodone (0.7) than morphine (0.3). The relationship between pain intensity (VAS) and plasma concentration was more positive for oxycodone ( $p=0.046$ ). There was a positive relationship between morphine-6-glucuronide concentrations and urea nitrogen and creatinine levels ( $p=0.0001$ ). Controlled-release oxycodone was as effective as controlled-release morphine in relieving chronic cancer-related pain, and as easily titrated to the individual's need for pain control. While adverse experiences were similar, controlled-release oxycodone was associated with less itching and no hallucinations. Controlled-release oxycodone provides a rational alternative to controlled-release morphine for the management of moderate to severe cancer-related pain.

## INTRODUCTION

The clinical use of oxycodone was first reported in 1917 (Falk, 1917). Like morphine and other

pure agonists, there is no known ceiling to the analgesic effects of oxycodone (Jacox *et al.*, 1994), allowing dose titration to an acceptable balance between pain control and side effects. Oxycodone is an effective analgesic for chronic cancer pain (Kalso & Vainio, 1990; Glare & Walsh, 1993; Heiskanen & Kalso, 1997), and may be associated with a lower incidence of central nervous system (CNS) side effects than morphine (Kalso & Vainio, 1990; Maddocks *et al.*, 1996).

Paper received 12 December 1997, revised 5 June 1998 and accepted in revised form 3 July 1998.

Correspondence to: Patricia Mucci-LoRusso, Harper Hospital, Division of Hematology and Oncology, 3990 John R - 5 Hudson, Detroit, MI, USA 48201.

While oxycodone's analgesic effects are similar to those of morphine, other pharmacological characteristics distinguish these two opioids. Oxycodone has a rapid onset of action (O'Brien, 1996), and its oral bioavailability (Leow *et al.*, 1992; Pöyhiä *et al.*, 1992b) is approximately twice that of morphine. A metabolite of morphine, morphine-6-glucuronide, appears to contribute substantially to analgesia (Wolff *et al.*, 1995; Faura *et al.*, 1996). While a metabolite of oxycodone, oxymorphone, has analgesic properties (Kalso *et al.*, 1990; Chen *et al.*, 1991; Otton *et al.*, 1993), pharmacokinetic-pharmacodynamic studies suggest that oxycodone rather than oxymorphone is primarily responsible for pharmacological effects in man (Kaiko *et al.*, 1996; Heiskanen *et al.*, 1997; Kaiko, 1997). Significant relationships between plasma oxycodone concentrations and pharmacological effects have been reported (Kaiko, 1997), while the relationships between plasma morphine concentrations and pharmacological effects are not as clearly defined (Glare & Walsh, 1991).

Over the last 15 years, controlled-release (CR) oral morphine has become a standard therapy for moderate to severe cancer pain. However, individual differences in response or preference make it desirable to have a selection of opioids available for the treatment of moderate to severe pain. An oral, CR formulation of oxycodone that allows dosing every 12 h (q12h) is available in several countries, including Finland, Denmark, and the USA. Because CR oxycodone appeared similar if not identical to CR morphine in its analgesic efficacy, these two products were compared directly in patients with chronic cancer-related pain.

## MATERIALS AND METHODS

### Patients

One-hundred-and-one adult patients who required around-the-clock treatment with opioid analgesics for chronic, cancer-related pain were enrolled from the general cancer patient population presenting at nine centers in the USA. Patients were eligible if they required the equivalent of 30–340 mg of oral oxycodone daily.

Patients whose pain was not controlled by maximum recommended doses of non-opioid analgesics were also eligible if they would require at least 30 mg. This minimum oxycodone requirement, equivalent to six tablets per day of a widely used fixed-dose combination (5 mg oxycodone/325 mg acetaminophen), ensured that patients required opioid analgesia for their cancer pain and could potentially benefit from the minimum daily dose of 40 mg used in this study. The maximum oxycodone requirement of 340 mg was set to allow patients to titrate, if necessary, up to the maximum 400-mg dose accommodated in the blister packaging.

Patients were excluded if they had a history of sensitivity to oxycodone or morphine, any contra-indication for opioid therapy (such as paralytic ileus or severe pulmonary disease), or severely compromised organ function that could obscure efficacy or adversely affect safety. Patients whose pain control was so fragile they could not switch opioids were also excluded.

All patients provided written, informed consent before enrolling in the study. The protocol received institutional review board approval at each center before the study was initiated. The study was conducted in accordance with ethical principles originating from the Declaration of Helsinki.

### Study design

Patients with chronic cancer-related pain were randomly assigned to oxycodone hydrochloride controlled-release tablets (OxyContin<sup>®</sup>, Purdue Pharma L.P., Norwalk, CT, USA; multiples of 20-mg tablets) or morphine sulfate controlled-release tablets (MS Contin<sup>®</sup>, The Purdue Frederick Co., Norwalk, CT, USA; known as MST Continus<sup>®</sup> in Europe; multiples of 30-mg tablets). Block randomization was used to ensure that all centers had a comparable number of patients in each treatment group. The double-dummy technique was used to blind the study medications. Supplemental analgesics were immediate-release (IR) oxycodone (multiples of two 5-mg tablets) for patients receiving CR oxycodone and IR morphine (MSIR<sup>®</sup>, The Purdue Frederick Co.; multiples of 15-mg tablets) for

TABLE 1. Equianalgesic dose conversion factors for converting to oral oxycodone<sup>a</sup>.

Pre-study opioid	Parenteral	Oral
Hydromorphone	20	4
Levorphanol	15	7.5
Meperidine	0.4	0.1
Methadone	3	1.5
Morphine	3	0.5 <sup>b</sup>
Oxycodone	2	1
Codeine	0.23	0.15
Hydrocodone	—	0.9
Transdermal fentanyl ( $\mu\text{g/h}$ ): 1.8		

<sup>a</sup>Based on tables of equianalgesic doses reported in reviews by Houde (1974) and Foley (1985).

Total daily dose prior opioid  $\times$  conversion factor = total daily oral oxycodone equivalent.

<sup>b</sup>In this study, a factor of 0.67 was used: for every 1.5 mg of oral morphine, the equivalent dose of oral oxycodone was 1 mg due to the tablet strengths available.

patients receiving CR morphine. They were blinded by enclosing the tablets in green capsules filled with lactose.

The q12h and supplemental analgesics were prepackaged for up to 12 days of dosing on blister cards marked with randomization numbers. Each supplemental analgesic dose was one-fourth to one-third of the q12h scheduled dose. Various dose levels were marked on the cards, and patients were instructed by the study site staff on the appropriate number of tablets or capsules to be taken for each q12h scheduled or supplemental dose, respectively.

Study medications were taken at 8.00 am and 8.00 pm. Patients were instructed to take a supplemental dose as needed for breakthrough pain, but not more frequently than once every 2–4 h, or 1 h before activity associated with incident pain. Non-opioid analgesics and adjuvant medications were allowed during the study provided they had been given on a regular basis (not as needed) before the study.

The initial daily dose of study medication (oral oxycodone equivalent dose) was calculated from the patient's prestudy daily opioid dose using a table of standard conversion factors (Table 1), and could be adjusted based on the investigator's judgment. The dose was titrated until stable pain control was achieved. Pain control was considered stable when, over a 48-h period, the

q12h dose was unchanged,  $\leq$  two supplemental analgesic doses were taken per day, the dosing regimen for any non-opioids or adjuvants was unchanged, and the patient reported that pain control was acceptable and any side effects were tolerable. Common opioid-related side effects were treated appropriately. Assessments were made for 48 h after stable pain control was achieved. Patients who could not be stabilized within 10 days were discontinued.

## Assessments

Patients recorded medication use, pain intensity, and adverse experiences in a daily diary. Pain intensity was assessed using a categorical scale (0 = none, 1 = slight, 2 = moderate, 3 = severe) because it is easy for patients to complete, has consistently demonstrated its validity as an indicator of pain intensity, and correlates well with other measures of pain intensity (Jensen & Karoly, 1992). Pain was assessed at the time of enrollment (baseline) and before each q12h dose (reflecting average pain since the previous evaluation). Pain scores and adverse experiences were reviewed daily to assess whether pain control was stable or dose titration was required. Acceptability of therapy was assessed at baseline and the end of the study using a categorical scale (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent). Quality of life was also assessed at baseline and the end of the study, using the Functional Assessment of Cancer Therapy-General (FACT-G), a 28-item questionnaire consisting of five subscales measuring different aspects of quality of life: physical, social/family, relationship with physician, emotional, and functional (Cella, 1993; Cella *et al.*, 1993).

Pharmacokinetic–pharmacodynamic (PK–PD) assessments were made after stable analgesia had been maintained for at least 48 h. Steady-state plasma opioid concentrations were measured in blood samples taken just before (0 h, trough) and 3 h after (peak) the last 8.00 am dose. At the same time, patients assessed current pain intensity using the categorical scale and a visual analog scale (VAS) (0 mm = no pain to 100 mm = worst possible pain). Drug effects were rated using 10 items from the Specific Drug Effect

Questionnaire (SDEQ) (Preston *et al.*, 1991; Kaiko *et al.*, 1996); patients' VAS ratings ranged from 0 mm ('not at all') to 100 mm ('an awful lot') and observers' from 0 mm ('not at all') to 100 mm ('extremely'). Patients assessed drowsiness and nausea using a categorical scale (0 = none, 1 = slight, 2 = moderate, 3 = severe) and a VAS (from 0 mm = none to 100 mm = worst possible). The relationship between plasma opioid concentrations and laboratory measures of liver [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels] and kidney [blood urea nitrogen (BUN) and serum creatinine levels] function was assessed at the end of the study.

### Analytical methodology

Blinded plasma samples were analysed for oxycodone, oxymorphone, and noroxycodone concentrations using a validated gas chromatographic-mass spectrometric procedure with a lower limit of detection of 0.2 ng/ml for all analytes (Kaiko *et al.*, 1996). Blinded plasma samples were analysed for intact morphine and morphine-6-glucuronide using a validated high performance liquid chromatographic method (Rotshteyn & Weingarten, 1996). The lower limit of detection was 1.0 ng/ml for morphine and 5.0 ng/ml for morphine-6-glucuronide.

### Statistical analysis

Sample size estimates indicated that 80 patients, 40 in each treatment group, would be adequate to detect a 20% difference in mean pain intensity scores with 80% power and 5% significance level. Statistical analyses were performed using the SAS system (Cary, NC, USA). All statistical tests and confidence intervals were constructed at the 0.05 level.

Pain scores and supplemental analgesic use during the period of stable pain control, i.e. the last 48 h of the study, were used in the efficacy analyses. Mean pain intensity during the last 48 h of the study was analysed using two-way analysis of variance (ANOVA). Number of supplemental analgesic doses over the last 48 h, acceptability

of therapy, and FACT-G scores were analysed using ANOVA. The time to achieve a stable dosing regimen was analysed using Kaplan-Meier estimate of the distribution for each treatment group and log-rank test of the treatment difference in distributions. The percentage of patients who achieved a stable dosing regimen was analysed using Fisher's exact test. Linear regression analysis was used to examine the relationships between study assessments and plasma opioid concentrations.

Trough ( $C_{\min}$ ) and approximate peak ( $C_{\max}$ ) plasma opioid concentrations were determined from blood samples taken at 0 and 3 h (Savarese *et al.*, 1986; Thirlwell *et al.*, 1989; Reder *et al.*, 1996) after the last dose, respectively. Peak-to-trough fluctuation in plasma concentrations was calculated using the scaled difference,  $(C_{\max} - C_{\min})/C_t$ , where  $C_t$  is the average of the 0- and 3-h concentration values. A two-way ANOVA was used to test differences between treatments for  $C_{\max}$ ,  $C_{\min}$ , and the scaled difference.

## RESULTS

### Patient disposition and characteristics

Of the 101 patients enrolled, 100 received at least one dose of study medication: 48 in the CR oxycodone group and 52 in the CR morphine group. Fifty-five percent of the patients were male. The mean (range) age was 59 (30–83) years; weight, 71 (38–110) kg; and height, 170 (145–198) cm. Bone and viscera were the most common pain sites. Nerve pain was the primary pain type in 10/48 (21%) CR oxycodone patients and 9/52 (17%) CR morphine patients. At the time of enrolment (baseline), mean pain intensity was 'moderate' in both treatment groups.

The most common prestudy pain medication was a fixed-dose combination of oxycodone-acetaminophen [paracetamol] (22 patients in each treatment group), followed by single-entity morphine (13 patients in the CR oxycodone group and 17 patients in the CR morphine group). Other pre-study opioids included: fixed-dose combinations of acetaminophen with codeine,

hydrocodone, or propoxyphene; oxycodone-aspirin; and single-entity oxycodone, fentanyl, levorphanol, codeine, and meperidine. Non-steroidal anti-inflammatory drugs and adjuvants such as tricyclic antidepressants were also used. Most patients were receiving more than one pain medication prior to the study, and all but three patients (in the CR oxycodone group) were receiving opioids prior to enrolment. The oral oxycodone equivalent dose of the prestudy analgesics, mean (range), was 64 mg (14–280 mg) in the CR oxycodone group and 70 mg (14–235 mg) in the CR morphine group.

Seven patients in the CR oxycodone group and nine in the CR morphine group discontinued from the study before achieving stable pain control, for the following reasons: adverse experience (two patients in the CR oxycodone group and six in the CR morphine group), intercurrent illness (three in the CR oxycodone group), ineffective treatment (one in each treatment group), patient request (one in each treatment group), and protocol violation (one in the CR morphine group). An additional four patients discontinued from the study after achieving stable pain control, for the following reasons: adverse experience (CR oxycodone), protocol violation (CR oxycodone), intercurrent illness (CR morphine), or worsening of pre-existing condition (CR morphine).

All 100 patients who received study medication were analysed for safety. Seventy-nine patients (39 in the CR oxycodone group and 40 in the CR morphine group) who achieved stable pain control and had simultaneous PK and PD assessments were analysed for efficacy. Sixty-six patients (35 in the CR oxycodone group and 31 in the CR morphine group) who had plasma opioid concentrations determined at both 0 and 3 h after the last dose and complied with the protocol were included in the PK analysis. These evaluability groups were defined after the study was completed and before the treatment code was unblinded.

## Analgesia

Pain intensity scores were similar in the CR oxycodone and CR morphine groups during the period of stable analgesia, i.e. the last 48 h of

the study. Mean (SE) pain intensity decreased significantly from baseline in both groups ( $p \leq 0.005$ ): from 1.9 (0.1) to 1.3 (0.1) in the CR oxycodone group and from 1.6 (0.1) to 1.0 (0.1) in the CR morphine group. Differences between treatments were not statistically significant.

Dose titration to effect was similar with the two treatments (Table 2). The mean final daily doses of q12h study medication were 101 mg (range: 40–360 mg) in the CR oxycodone group and 140 mg (range: 60–300 mg) in the CR morphine group. Compliance was good, with 83% of the patients in each group taking all of their scheduled q12h doses. The use of supplemental analgesic was similar in the two treatment groups during the period of stable analgesia. CR oxycodone patients used a median of 1 (range, 0–4) dose on the next to the last day and 1 (range, 0–3) dose on the last day of the study. CR morphine patients used a median of 1 (range, 0–3) dose on both days.

## Acceptability of therapy and quality of life

Mean (SE) acceptability of therapy at the final visit increased significantly from baseline in both treatment groups, from 3.1 (0.1) to 4.0 (0.1) in the CR oxycodone group ( $p = 0.0001$ ) and 3.3 (0.2) to 3.9 (0.1) in the CR morphine group ( $p = 0.0061$ ). At the end of the study, 74% of patients in the CR oxycodone group and 77% in the CR morphine group rated therapy good to excellent, with no statistically significant differences between treatments. Quality of life, assessed by the FACT-G questionnaire, showed no clinically significant changes during the study in either treatment group (results not shown).

## Side effects

Forty patients (83%) in the CR oxycodone group and 39 (75%) in the CR morphine group reported adverse experiences. Those reported most frequently were typical opioid side effects (Table 3), and most were mild-to-moderate in severity. Two patients in the CR morphine group experienced hallucinations, which were considered possibly related to study drug. This adverse experience

TABLE 2. Titration to stable analgesia.

	CR oxycodone	CR morphine
Patients achieving stable analgesia <sup>a</sup>	40/48 (83%)	42/52 (81%)
Time to stable analgesia, median (range)	2 (1–10) days	2 (1–9) days
Number of dose adjustments, median (range)	0 (0–8)	0 (0–3)
Patients requiring no dose adjustments <sup>b</sup>	26/39 (67%)	29/40 (73%)

<sup>a</sup> Calculated for all patients who received study medication.

<sup>b</sup> Calculated for patients who achieved stable analgesia and had pharmacokinetic–pharmacodynamic assessments.

There were no statistically significant differences between treatments.

TABLE 3. Adverse experiences reported by  $\geq 10\%$  of patients: probably or definitely related to study medication<sup>a</sup>.

Adverse experience	CR oxycodone ( <i>n</i> = 48)		CR morphine ( <i>n</i> = 52)	
	<i>n</i> (%)	No. reports	<i>n</i> (%)	No. reports
Constipation	10 (21)	13	10 (19)	12
Somnolence	7 (15)	13	10 (19)	14
Nausea	6 (13)	8	8 (15)	14
Vomiting	6 (13)	10	5 (10)	8
Dizziness	4 (8)	5	7 (13)	7
Pruritus	4 (8)	4	5 (10)	7
Dry mouth	1 (2)	2	7 (13)	7

<sup>a</sup> Adverse experiences spontaneously reported by patients or observed by investigators were judged by the investigators to be possibly, probably, or definitely related to study medication.

was not reported in the CR oxycodone group. Overall, the adverse experience profiles of CR oxycodone and CR morphine were similar.

Three patients in the CR oxycodone group and six in the CR morphine group discontinued because of adverse experiences, most commonly gastrointestinal complaints. Two patients died during the study; both deaths were due to disease progression, and the investigators did not consider them to be related to the study medication.

#### Pharmacokinetics–pharmacodynamics

Plasma opioid and metabolite concentrations at 0 and 3 h after the last dose are reported in Table

4. Peak-to-trough fluctuation in plasma opioid concentrations was less with CR oxycodone than with CR morphine, based on a significantly smaller scaled difference in the CR oxycodone group than in the CR morphine group (Table 4). Pain intensity scores at 0 and 3 h after the last dose confirmed that pain was well controlled in both treatment groups (Table 5). Mean elicited scores for nausea and drowsiness were 'slight' on the categorical scale and  $\leq 24$  mm on the VAS. Scores for most SDEQ items were very low ( $<20$  mm); both patients and observers rated 'relaxed' the highest (mean scores ranging from 46–68 mm). At 3 h, scores for 'itchy' (rated by patients) and 'scratching' (rated by observers) were significantly lower in the CR oxycodone

TABLE 4. Plasma concentrations and pharmacokinetic parameters<sup>a</sup>.

	Plasma concentration (ng/ml) after last dose		C <sub>max</sub> (ng/ml)	C <sub>min</sub> (ng/ml)	Scaled difference <sup>b</sup>
	Hour 0	Hour 3			
CR oxycodone (n=35)					
Oxycodone	33.3 (4.2)	58.5 (6.9)	58.1 (7.5)	29.2 (3.0) <sup>c</sup>	0.6 (0.1) <sup>d</sup>
Oxymorphone	1.0 (0.1)	1.4 (0.2)	—	—	—
Noroxycodone	64.0 (13.4)	83.3 (18.5)	—	—	—
CR morphine (n=31)					
Morphine	21.3 (2.8)	57.0 (9.7)	47.2 (5.7)	16.0 (1.8) <sup>c</sup>	0.9 (0.1) <sup>d</sup>
Morphine-6-glucuronide	134.2 (10.2)	278.7 (26.8)	—	—	—

<sup>a</sup> Mean (SE); pharmacokinetic parameters calculated only for oxycodone and morphine.

<sup>b</sup> Scaled Difference = (C<sub>max</sub> - C<sub>min</sub>) / C<sub>t</sub>, where C<sub>t</sub> is the average of 0-h and 3-h concentration values.

<sup>c</sup> Statistically significant difference between groups, p=0.001.

<sup>d</sup> Statistically significant difference between groups, p=0.004.

TABLE 5. Pain intensity scores<sup>a</sup> at 0 and 3 h after last dose of study medication.

	CR oxycodone (n=39)	CR morphine (n=40)
Categorical scale <sup>b</sup>		
Hour 0	1.2 (0.1)	1.1 (0.1)
Hour 3	0.8 (0.1) <sup>c</sup>	0.9 (0.1)
Visual analog scale <sup>d</sup>		
Hour 0	29 (4)	26 (4)
Hour 3	19 (4)	20 (4)

<sup>a</sup> Mean (SE).

<sup>b</sup> 0 = none, 1 = slight, 2 = moderate, 3 = severe.

<sup>c</sup> Significant difference between Hour 0 and Hour 3, p=0.03.

<sup>d</sup> From 0 mm = no pain to 100 mm = worst possible pain.

There were no statistically significant differences between treatment groups.

group than in the CR morphine group (p ≤ 0.044).

Linear regression analysis revealed a significant correlation between trough plasma opioid concentrations and total daily dose of q12h medication plus supplemental analgesic (Fig. 1), with a significantly stronger correlation (p = 0.026) for oxycodone (0.7; r<sup>2</sup> = 0.5) than for morphine (0.3; r<sup>2</sup> = 0.1). Correlation coefficients for the relationships between PD variables and plasma opioid concentrations were low. However, the relationship between the decrease in pain intensity measured by VAS and plasma opioid concentration was significantly more positive for oxycodone than for morphine (p = 0.046).

Five patients in the CR oxycodone group and

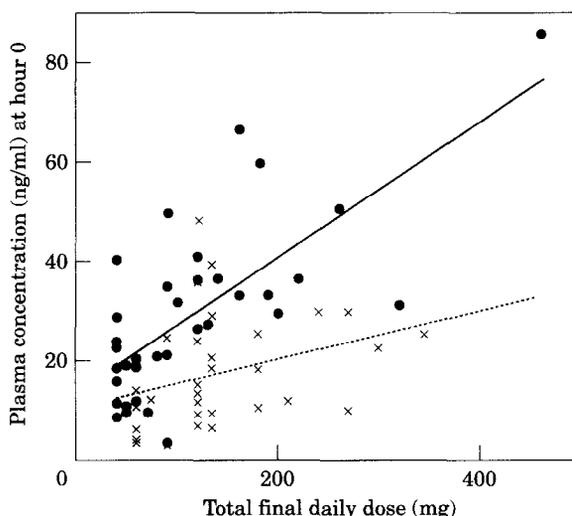


FIG. 1. Effect of total final daily dose (q12h study medication plus rescue medication) on trough (hour 0) plasma opioid concentration. The correlation was significantly higher for CR oxycodone (0.7) (●) than for CR morphine (0.3) (X) (p=0.026). CR oxycodone (n=35): solid line; CR morphine (n=31): dashed line.

four in the CR morphine group had elevated BUN or creatinine levels. Six patients in the CR oxycodone group and 16 in the CR morphine group had relatively mild hepatocellular abnormalities evidenced by elevated AST, ALT, or bilirubin levels. A significant relationship was found between morphine-6-glucuronide concentrations and BUN and creatinine (Fig. 2) levels (p=0.0001). r<sup>2</sup> values for BUN vs morphine-6-glucuronide were 0.46 at 0 h and 0.52 at 3 h. The r<sup>2</sup> value for creatinine vs morphine-6-glucuronide was 0.63 at both time points. There

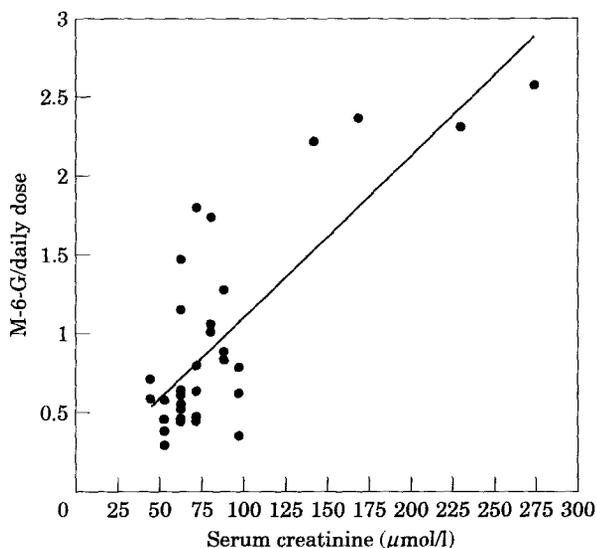


FIG. 2. Linear regression analysis showing significant ( $p=0.0001$ ) relationship between trough plasma morphine-6-glucuronide (M-6-G) concentrations (ng/ml) adjusted for daily opioid dose (dependent variables) and serum creatinine levels (independent variables).

were no other significant relationships between plasma opioid or metabolite concentrations and the measures of liver or kidney function used in this study.

## DISCUSSION

Oral CR oxycodone was as effective as oral CR morphine for controlling chronic cancer pain in this double-blind, parallel-group study. When well-accepted principles of pharmacologic management of chronic cancer pain (Jacox *et al.*, 1994; World Health Organization, 1996) were applied in the present study, mean pain intensity decreased from 'moderate' to 'slight' during treatment with both CR oxycodone and CR morphine, even though all but three patients had been receiving opioid analgesics before the study. Acceptability of therapy was similar for the two treatments, with more than 70% of patients rating therapy as good to excellent. Despite better pain control after dose titration with CR oxycodone or CR morphine, FACT-G scores measuring quality of life remained stable during the study. The duration of this trial may have been too short to show an effect of better pain control on

quality of life. In addition, pain is only one of the many dimensions of quality of life measured by the FACT-G.

Oral CR morphine has become a standard therapy for moderate to severe cancer pain over the last 15 years. An alternative opioid agonist, such as CR oxycodone, is needed for some patients because of individual differences in sensitivity to the analgesic or side effects of different opioids (Galer *et al.*, 1992; Lawlor *et al.*, 1997; Derby *et al.*, 1998). A study of oral oxycodone in cancer patients no longer responding to weaker analgesics demonstrated that the oxycodone dose could be titrated to control pain in the majority (20/24) of patients (Glare & Walsh, 1993). In a cross-over comparison in cancer patients with severe pain, oxycodone was as effective as morphine when the dose was titrated to effect using a patient-controlled analgesia device and then given orally at the appropriate dose (Kalso & Vainio, 1990). A two-period cross-over study, comparing oral CR oxycodone and oral CR morphine in cancer pain found that pain was well controlled with both treatments (Heiskanen & Kalso, 1997). Because there was a significant period effect, mean pain scores (4-point scale) for the first period were examined, as well as scores for both periods combined. There were no significant differences between treatments for the first period, while scores were higher with CR oxycodone (0.99) than with CR morphine (0.77) ( $p<0.05$ ) for both periods combined. The clinical significance of this difference is open to interpretation; the authors noted that the two opioids were comparable when the period effect was taken into account. In the present parallel-group study, which eliminates the possibility of a period effect, oral CR oxycodone was as effective as oral CR morphine for the treatment of cancer pain.

Steady-state is reached in approximately 1 day with both formulations (Savarese *et al.*, 1986; Reder *et al.*, 1996), allowing dose titration every 1 to 2 days if necessary. Dose titration was accomplished with equal facility with both oral CR formulations. Stable analgesia was achieved in 2 days (median) in both treatment groups. The percentage of patients achieving stable analgesia and the number of dose adjustments required

were also similar, demonstrating that dose titration is as efficient with CR oxycodone as CR morphine.

The side-effect profiles of CR oxycodone and CR morphine were similar overall in this trial. However, there were small differences which could be significant for individual patients. For example, no patients in the CR oxycodone group reported hallucinations, compared with two patients in the CR morphine group. Hallucinations occurred only during morphine treatment in a cross-over trial comparing oxycodone and morphine in cancer pain (Kalso & Vainio, 1990). An open-label trial showed significant improvement in mental state when subcutaneous oxycodone was substituted for morphine in cancer patients experiencing acute delirium (Maddocks *et al.*, 1996). Although spontaneous reports of pruritus were similar in both treatment groups in the present study, the SDEQ scores for 'itchy' rated by patients and 'scratching' rated by observers were statistically significantly lower with CR oxycodone than with CR morphine. This is consistent with findings that oxycodone may have less propensity to stimulate histamine liberation (Pöyhiä *et al.*, 1992a) than morphine (Flacke *et al.*, 1987).

While oxycodone and morphine have similar analgesic efficacy, there are pharmacokinetic and pharmacodynamic distinctions between them. Oxycodone does not undergo as extensive first-pass metabolism (Pöyhiä *et al.*, 1993) as does morphine, and its oral bioavailability of 60% (Pöyhiä *et al.*, 1992b) to 87% (Leow *et al.*, 1992) is approximately twice that of oral morphine (Glare & Walsh, 1991). As a result of its higher bioavailability, among other factors, oral oxycodone has twice the potency of oral morphine on a milligram basis, with equivalent analgesic efficacy. In the present study, there was less peak-to-trough fluctuation in plasma opioid concentrations with CR oxycodone than with CR morphine. At steady-state, the time to  $C_{\max}$  ( $T_{\max}$ ) for CR oxycodone in normal volunteers is  $3.2 \pm 2.2$  h (Reder *et al.*, 1996). For CR morphine,  $T_{\max}$  at steady-state is  $2.3 \pm 0.2$  h in normal volunteers (Savarese *et al.*, 1986) and  $3.4 \pm 2.1$  h in cancer patients (Thirlwell *et al.*, 1989). Thus, the 3-h blood sample approximated  $T_{\max}$  for both CR

opioids. One-half of the variation in oxycodone concentrations could be explained by the variation in dose, compared with only one-tenth of the variation in morphine concentrations. While the clinical relevance of these differences is unclear at present, they show that therapeutic plasma opioid concentrations were more stable and predictable with CR oxycodone than with CR morphine.

Further pharmacokinetic differences in the two opioids suggest that oxycodone could offer advantages over morphine in renally-impaired patients. There is only a 1-h increase in the half-life of elimination of oxycodone and nor-oxycodone in these patients (Benziger *et al.*, 1996); in contrast, there is marked prolongation of the elimination half-life of the morphine glucuronides (Glare & Walsh, 1991). The present study showed a significant relationship between blood urea nitrogen and serum creatinine levels and morphine-6-glucuronide concentrations, but not concentrations of oxycodone or its metabolites. Oxycodone may also have advantages over morphine in elderly patients because, unlike morphine pharmacokinetics (Baillie *et al.*, 1989), age has little influence on the pharmacokinetics of oxycodone (Benziger *et al.*, 1996).

The role of metabolites in analgesia may also be different for oxycodone and morphine. While reports in the literature suggest that the oxycodone metabolite, oxymorphone, has analgesic properties (Kalso *et al.*, 1990; Chen *et al.*, 1991; Otton *et al.*, 1993), its plasma concentration in man is very low. Pharmacokinetic-pharmacodynamic studies suggest that oxycodone, rather than oxymorphone, is responsible for the pharmacological effects in man (Kaiko *et al.*, 1996; Heiskanen *et al.*, 1997; Kaiko, 1997), and significant correlations were observed between plasma oxycodone concentrations and PD variables (Kaiko, 1997). In contrast, the relationship between plasma morphine concentrations and pharmacological effects is not clearly defined, and the metabolite, morphine-6-glucuronide, appears to contribute to analgesic effects in man (Wolff *et al.*, 1995; Faura *et al.*, 1996). In the present study, the decrease in pain intensity (measured by VAS) correlated more strongly with oxycodone concentrations than with morphine concentrations.

The results of the present study show that CR oxycodone was as effective as CR morphine in relieving chronic cancer-related pain. CR oxycodone was as easily titrated to the individual's need for pain control as CR morphine. While the adverse experience profiles were similar, itching was less severe and no hallucinations were reported with CR oxycodone. CR oxycodone provides a rational alternative to CR morphine for the management of moderate-to-severe cancer-related pain.

## ACKNOWLEDGMENTS

The authors wish to acknowledge the following principal investigators, study co-ordinators, and their staffs who participated in this study: Michael Mullane, MD, University of Illinois Hospital, Chicago, IL; Dannette Clemens-Schutjer, RN, Mercy Cancer Center, North Iowa Mercy Health Center, Mason City, IA; Anne Marie Ferris, RN, Harper Hospital, Detroit, MI; Ronald Kaplan, MD, Jack D. Weiler, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY; Guadalupe Palos, LMSW, RN, OCN, The University of Texas, M.D. Anderson Cancer Center, Houston, TX; Winston C.-V. Parris, MD, FACPM, Vanderbilt Pain Control Center, Vanderbilt University Medical Center, Nashville, TN; Valda Pascall, RN, Long Island Jewish Medical Center, New Hyde Park, NY; Susan Rabinowe, MD, St Francis Hospital and Medical Center, Hartford, CT; Michael S. Roberts, MD and Vicky Rochford, RN, Treatment Centers for Cancers and Blood Disorders, P.A., Kissimmee, FL, USA.

This study was sponsored by Purdue Pharma L.P., Norwalk, CT, USA.

Declaration of Interests: Drs Mucci-LoRusso, Berman, Silberstein, Citron, Bressler, and Weinstein were investigators in this trial and financially compensated for their efforts. Dr Kaiko, Ms Buckley, and Dr Reder are employed by Purdue Pharma L.P.

## REFERENCES

Baillie SP, Bateman DN, Coates PE, Woodhouse KW. Age and the pharmacokinetics of morphine. *Age Ageing* 1989; **18**: 258-262.

- Benziger DP, Cheng C, Miotto J, Grandy R. Comparative pharmacokinetics of controlled-release oxycodone (Oxy-Contin) in special populations. In: International Association for the Study of Pain, 8th World Congress on Pain Abstracts, 1996 Aug 17-22, Vancouver, BC, Canada. Seattle (WA): IASP Press, 1996: 285 [abstract].
- Cella DF. *Manual: Functional Assessment of Cancer Therapy (FACT) Scales and the Functional Assessment of HIV Infection (FAHI) Scale*. 3rd ed. Chicago (IL): Rush-Presbyterian-St. Luke's Medical Center, April 9, 1993.
- Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, Eckberg K, Lloyd S, Purl S, Blendowski C, Goodman M, Barnicle M, Stewart I, McHale M, Bonomi P, Kaplan E, Taylor S, Thomas CR, Harris J. The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol* 1993; **11**: 570-579.
- Chen ZR, Irvine RJ, Somogyi AA, Bochner F. Mu receptor binding of some commonly used opioids and their metabolites. *Life Sci* 1991; **48**: 2165-2171.
- Derby S, Chin J, Portenoy RK. Systemic opioid therapy for chronic cancer pain: practical guidelines for converting drugs and routes of administration. *CNS Drugs* 1998; **9**: 99-109.
- Falk E. Eukodal, ein neues narkotikum. *Muenchener Medizinische Wochenschrift* 1917; 20 March: 381-384.
- Faura CC, Moore RA, Horga JF, Hand CW, McQuay HJ. Morphine and morphine-6-glucuronide plasma concentrations and effect in cancer pain. *J Pain Symptom Manage* 1996; **11**: 95-102.
- Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg* 1987; **66**: 723-730.
- Foley KM. The treatment of cancer pain. *N Engl J Med* 1985; **313**: 84-95.
- Galer BS, Coyle N, Pasternak GW, Portenoy RK. Individual variability in the response to different opioids: report of five cases. *Pain* 1992; **49**: 87-91.
- Glare PA, Walsh TD. Clinical pharmacokinetics of morphine. *Ther Drug Monit* 1991; **13**: 1-23.
- Glare PA, Walsh TD. Dose-ranging study of oxycodone for chronic pain in advanced cancer. *J Clin Oncol* 1993; **11**: 973-978.
- Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* 1997; **73**: 37-45.
- Heiskanen T, Olkkola KT, Kalso E. The effect of quinidine on the metabolism and pharmacodynamics of oxycodone. In: Scandinavian Association for the Study of Pain, 20th Annual Meeting Programme and Abstracts, Apr 17-20. Aarhus, Denmark, 1997: 81 [Abstract].
- Houde RW. The use and misuse of narcotics in the treatment of chronic pain. *Adv Neurol* 1974; **4**: 527-536.
- Jacox A, Carr DB, Payne R, Berde CB, Brietbart W, Cain JM, Chapman CR, Cleeland CS, Ferrell BR, Finley RS, Hester NO, Hill CS, Leak WD, Lipman AG, Logan CL, McGarvey CL, Miaskowski CA, Mulder DS, Paice JA, Shapiro BS, Silberstein EB, Smith RS, Stover J, Tsou CV, Vecchiarelli L, Weissman DE. *Management of Cancer Pain*. Clinical Practice Guideline No. 9. AHCPR Publication No. 94-0592. Rockville, MD. Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, Public Health Service, March 1994: 39-74.
- Jensen MP, Karoly P. Self-report scales and procedures for

- assessing pain in adults. In: Turk DC, Melzack R, editors. *Handbook of Pain Assessment*. New York: The Guilford Press, 1992: 135–151.
- Kaiko RF. Pharmacokinetics and pharmacodynamics of controlled-release opioids. *Acta Anaesthesiol Scand* 1997; **41**: 166–174.
- Kaiko RF, Benziger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD. Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Ther* 1996; **59**: 52–61.
- Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther* 1990; **47**: 639–646.
- Kalso E, Vainio A, Mattila MJ, Rosenberg PH, Seppälä T. Morphine and oxycodone in the management of cancer pain: plasma levels determined by chemical and radio-receptor assays. *Pharmacol Toxicol* 1990; **67**: 322–328.
- Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. *Pain* 1997; **72**: 79–85.
- Leow KP, Smith MT, Williams B, Cramond T. Single-dose and steady-state pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. *Clin Pharmacol Ther* 1992; **52**: 487–495.
- Maddocks I, Somogyi A, Abbott F, Hayball P, Parker D. Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. *J Pain Symptom Manage* 1996; **12**: 182–189.
- O'Brien CP. Drug addiction and drug abuse. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill, 1996: 557–577.
- Otton SV, Wu D, Joffe RT, Cheung SW, Sellers EM. Inhibition by fluoxetine of cytochrome P450 2D6 activity. *Clin Pharmacol Ther* 1993; **53**: 401–409.
- Pöyhkä R, Kalso E, Seppälä T. Pharmacodynamic interactions of oxycodone and amitriptyline in healthy volunteers. *Current Therapeutic Research* 1992a; **51**: 739–749.
- Pöyhkä R, Seppälä T, Olkkola KT, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* 1992b; **33**: 617–621.
- Pöyhkä R, Vainio A, Kalso E. A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. *J Pain Symptom Manage* 1993; **8**: 63–67.
- Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. *Drug Alcohol Dependence* 1991; **27**: 7–17.
- Reder RF, Oshlack B, Miotto JB, Benziger DD, Kaiko RF. Steady-state bioavailability of controlled-release oxycodone in normal subjects. *Clin Ther* 1996; **18**: 95–105.
- Rotshteyn Y, Weingarten B. A highly sensitive assay for the simultaneous determination of morphine, morphine-3-glucuronide, and morphine-6-glucuronide in human plasma by high-performance liquid chromatography with electrochemical and fluorescence detection. *Ther Drug Monit* 1996; **18**: 179–188.
- Savarese JJ, Goldenheim PD, Thomas GB, Kaiko RF. Steady-state pharmacokinetics of controlled release oral morphine sulphate in healthy subjects. *Clin Pharmacokinet* 1986; **11**: 505–510.
- Thirlwell MP, Sloan PA, Maroun JA, Boos GJ, Besner J-G, Stewart JH, Mount BM. Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; **63**: 2275–2283.
- Wolff T, Samuelsson H, Hedner T. Morphine and morphine metabolite concentrations in cerebrospinal fluid and plasma in cancer pain patients after slow-release oral morphine administration. *Pain* 1995; **62**: 147–154.
- World Health Organization. *Cancer Pain Relief: with a Guide to Opioid Availability*. 2nd ed. Geneva: World Health Organization, 1996: 14–37.