

Steady-State Bioavailability of Controlled-Release Oxycodone in Normal Subjects

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ABSTRACT

The steady-state bioavailability of a controlled-release (CR) oxycodone tablet was compared with that of an immediate-release (IR) oxycodone solution in a randomized, analytically masked, multiple-dose, crossover study in 24 normal subjects. Each subject received either one 10-mg CR oxycodone tablet every 12 hours for 4 days or 5 mL of a 1-mg/mL IR oxycodone solution every 6 hours for 4 days. Steady state was achieved after approximately 1 day of dosing. The mean (\pm SD) maximum plasma oxycodone concentrations for CR oxycodone and IR oxycodone were 15.1 ± 4.7 ng/mL and 15.6 ± 4.4 ng/mL, respectively. The time to maximum concentration (T_{\max}) was approximately twice as long for CR oxycodone (3.2 ± 2.2 hours) as for IR oxycodone (1.4

± 0.7 hours) ($P = 0.005$). The area under the plasma concentration-time curve from 0 to 12 hours at steady state was 103.6 ± 40.0 ng \cdot h/mL for CR oxycodone and 99.0 ± 35.8 ng \cdot h/mL for IR oxycodone. Except for T_{\max} , there were no significant differences in pharmacokinetic parameters between treatments. Approximately twice as many adverse experiences, several of longer duration than noted with CR oxycodone, were reported with IR oxycodone. The bioavailability of the CR tablet was equal to that of the IR solution; however, the rate of oxycodone absorption from the CR tablet was slower than that from the IR solution, as shown by the T_{\max} value. The use of CR oxycodone will allow selection of the most clinically appropriate nonopioid analgesic, as well as independent titration and dosing, thereby enhancing therapeutic flexibility.

INTRODUCTION

Oxycodone is a semisynthetic opioid agonist that has been used clinically since 1917. Oral oxycodone has approximately twice the analgesic potency of oral morphine on a per-milligram basis.^{1,2} Its oral bioavailability, estimated at 60% or more, is higher than that of morphine.³⁻⁵ Oxycodone may also be associated with fewer side effects than morphine^{6,7}; however, comparative studies are few and patient numbers small. The usual oral formulations combine oxycodone with aspirin or acetaminophen. Oxycodone is also available as an immediate-release (IR) single agent. The usual oral starting dose for opioid-naive adults is 5 mg every 6 hours.

An oral controlled-release (CR) oxycodone hydrochloride tablet has been developed using a patented delivery system (Acrocontin™, The Purdue Frederick Company, Norwalk, Connecticut). This system combines two polymers to control the release of the drug into the gastrointestinal tract by both dissolution and diffusion. Three tablet strengths—10, 20, and 40 mg—of oxycodone hydrochloride have been developed. All have similar *in vitro* oxycodone release profiles.

By reducing dosing frequency, CR (modified- or extended-release) dosage forms should enhance patient convenience and compliance while maintaining similar efficacy and the same or better safety than IR products. Compliance is a particularly important issue in chronic drug therapy, especially in patients with complex diseases who receive multiple therapies administered on different dosing schedules over long periods of time.

CR oxycodone tablets were developed for patients who require opioid therapy and for whom independent titration of

opioid and nonopioid analgesics may be appropriate. Unlike therapy with fixed-combination analgesics containing oxycodone and aspirin or acetaminophen, the use of CR oxycodone allows selection of the nonopioid that is most favorable in a particular clinical setting. Independent titration of opioid and nonopioid drugs should allow analgesic therapy to be adjusted with greater precision, especially as the pain state changes.

In patients with pain syndromes requiring around-the-clock opioid therapy, the development of oral CR morphine signaled a breakthrough in convenient, effective analgesic therapy. Like morphine, oxycodone is an opioid agonist that has no "ceiling" effect for analgesia; therapy with oxycodone can be initiated when an opioid is first indicated and continued as the pain syndrome progresses. Oxycodone has less of the opioid stigma associated with morphine therapy, which can be a significant factor in patient/caregiver resistance to adequate pain therapy.

The purpose of this study was to compare the bioavailability and other pharmacokinetic characteristics of the CR oxycodone tablet with those of an IR oxycodone solution at steady state when given in repeated oral doses to normal volunteers.

SUBJECTS AND METHODS

Subjects

Twenty-four normal, healthy male volunteers entered this study. The body weights of all participants were within $\pm 10\%$ of optimal weight. All subjects were free of significant abnormal findings on baseline physical examination and clinical laboratory tests, and none had a history of frequent nausea or emesis of any etiology.

No subject had a history of drug (including alcohol) abuse or had received an opioid for at least 3 months before the study. None had recently donated blood or taken any medication or nutritional supplement.

The subjects provided written informed consent before participation. The study received institutional review board approval and was performed according to the principles of the Declaration of Helsinki.

Test Medications

The test medications were oxycodone hydrochloride CR tablets* each containing 10 mg of oxycodone hydrochloride, and oxycodone hydrochloride IR oral solution† (1 mg/1 mL).

Study Design

This study was a randomized, analytically masked, multiple-dose, crossover comparison of the steady-state pharmacokinetics of CR oxycodone and IR oxycodone. The two crossover phases were separated by a 4-day period.

Drug Treatment

The subjects entered the testing facility the evening before each crossover phase began and remained there until the 36-hour sampling period after the last dose was completed (8 AM on day 4 for CR oxycodone and 2 PM on day 4 for IR oxycodone). The subjects fasted 2 hours before and after each dose. To ensure proper stomach emptying, subjects were encour-

aged to remain in a sitting position for the first 4 hours after dosing.

Phase 1

On days 1 through 3, the subjects were given one 10-mg CR oxycodone tablet every 12 hours (8 AM and 8 PM) or 5 mL of a 1-mg/1 mL IR oxycodone solution orally every 6 hours (8 AM, 2 PM, 8 PM, and 2 AM). Assignment to receive the tablet or the liquid form was determined by a randomization code. On day 4, subjects receiving the oxycodone tablet were given one 10-mg CR oxycodone tablet at 8 AM only. Subjects receiving oxycodone liquid were given 5 mL of a 1-mg/1 mL IR oxycodone solution at 8 AM and 2 PM only. Subjects received a maximum of 7 doses (total, 70 mg) of CR oxycodone or 14 doses (total, 70 mg) of IR oxycodone.

Phase 2

After a 4-day period, the subjects were crossed over to the other medication. The dose and schedule of administration for each medication were the same as those during phase 1. The duration of the clinical portion of the study was approximately 13 days.

Blood Sample Collection

During both phases, blood samples for determination of plasma oxycodone concentration were collected just before the 8 AM dose (trough) on days 2 through 4. On day 4, blood samples were taken at the following times after the 8 AM dose: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 6.25, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 13, 14, 16, 18, 20, 24, and 36 hours.

The blood samples were collected in 10-mL silicone-coated tubes containing ethylenediaminetetraacetic acid and centrifuged. The plasma was separated and

*Trademark: OxyContin™ tablets (Purdue Pharma L.P., Norwalk, Connecticut).

†Trademark: Roxicodone™ Oral Solution USP (Roxane Laboratories, Inc., Columbus, Ohio).

stored frozen at -20°C until analyzed. The samples were blind coded for analysis.

Safety Evaluations

Routine physical examinations, complete blood cell counts, clinical chemistry analyses, and urinalyses were performed before and after the study. Vital signs, including oral body temperature, respiratory rate, sitting radial pulse, and blood pressure, were monitored at screening, predose, and every 12 hours on days 1 to 5 of each study phase.

Adverse experiences were recorded and promptly evaluated to determine severity and duration. Subjects reporting adverse experiences were followed up until they returned to normal.

Plasma Oxycodone Analyses

Plasma oxycodone analyses were conducted using some modifications of a validated gas chromatography/mass spectrophotometry procedure described previously by Kaiko et al.⁸ Naltrexone 100 ng (100 μL) was used as the internal standard. After elution from the solid-phase extraction column, the eluent was dried and derivatized with 100 μL of N,O-bis(trimethylsilyl) trifluoroacetamide with 1% trimethylchlorosilane (RegisilTM, Regis Chemicals, Morton Grove, Illinois) at 90°C for 1 hour. Three microliters of an ethyl acetate solution were injected into a Hewlett Packard gas chromatograph (HP5890)/mass spectrophotometer (HP5988A) equipped with a 30 m \times 0.32 mm 0.25- μm film DB5-5% column (J & W Scientific, Folsom, California). After an initial hold at 100°C for 1 minute, the temperature was increased to 290°C at a rate of 40°C per minute. The assay had a quantitation limit

of 0.2 ng/mL and was linear over the range of 0.2 to 100 ng/mL, with an accuracy of 4.0% to 0.3%. The mean coefficients of variation for low (0.2 ng/mL) and high (100 ng/mL) quality controls in this study were 10% and 4.8%, respectively.

Pharmacometric and Statistical Methods

The following pharmacokinetic parameters were calculated for each subject and treatment: maximum plasma oxycodone concentration (C_{max}), minimum plasma oxycodone concentration (C_{min}), and time after administration at which the C_{max} occurred (T_{max}). The area under the plasma concentration-time curve over the 12-hour dosing interval (AUC_{0-12}) was calculated using the trapezoidal rule. The oscillation of the plasma oxycodone concentration curve in the 12-hour dosing interval was determined by percent swing:

$$\% \text{ Swing} = 100 \times (C_{\text{max}} - C_{\text{min}})/C_{\text{min}}$$

The oscillation of the plasma oxycodone concentration curve in the 12-hour dosing interval in relation to the mean plasma concentration was determined by percent fluctuation:

$$\% \text{ Fluctuation} = 100 \times (C_{\text{max}} - C_{\text{min}})/(\text{AUC}/12)$$

The mean bioavailability ratios were calculated for all parameters as 100% (CR oxycodone mean/IR oxycodone mean). Ninety percent confidence limits were set on the ratio as:

$$t \times s/m(\text{IR oxy})$$

where t is the value of Student's t test for $P = 0.10$, s is the standard error of the dif-

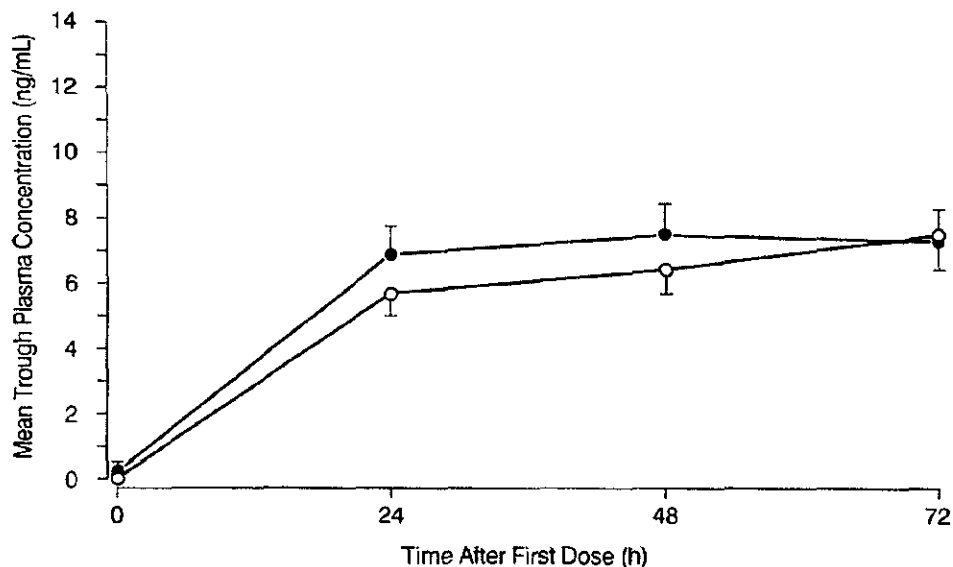


Figure 1. Trough plasma oxycodone concentrations (mean \pm SE) by time after first dose of controlled-release oxycodone (●) and immediate-release oxycodone (○).

ference between the means based on the error mean square for the analysis of variance, and $m(\text{IR oxy})$ is the mean value of IR oxycodone.

RESULTS

Subjects had a mean age of 34.5 years (range, 21 to 50 years) and a mean body weight of 74.7 kg (range, 61.4 to 85.4 kg). Six subjects were white; 18 were black.

Three subjects receiving IR oxycodone withdrew because of adverse experiences (ie, itching, rash, and sternomastoid muscle pain). Twenty-one subjects were available for the bioavailability analyses; all 24 subjects were included in the safety evaluation.

Pharmacokinetics

Both treatment groups reached steady state in approximately 1 day of dosing (Figure 1). Steady state was maintained through

day 4. On day 4, the mean (\pm SE) oxycodone plasma concentrations at trough or 0 hour (just before the 8 AM dose) were 7.2 ± 0.8 ng/mL for the group receiving CR oxycodone and 7.4 ± 0.8 ng/mL for the group receiving IR oxycodone.

The mean plasma oxycodone concentration-time curves obtained during the 12-hour period that began with the 8 AM dose on day 4 are given in Figure 2. During that period, there was one peak/trough fluctuation associated with CR oxycodone, compared with two for the IR formulation, each after a 5-mg oral dose. Lower average peak and trough values also occurred after the afternoon (2 PM) dose of IR oxycodone compared with the morning (8 AM) dose.

The mean pharmacokinetic parameters for the two oxycodone formulations at steady state and 90% confidence limits of the various ratios are shown in Table 1. There were no significant differences be-

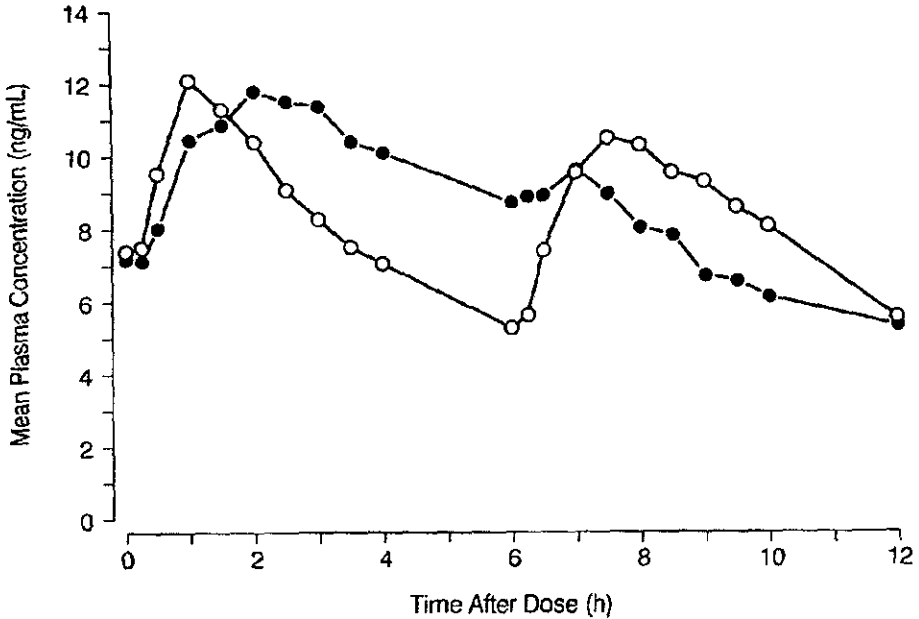


Figure 2. Mean plasma oxycodone concentrations during the 12 hours after administration of the last steady-state dose of controlled-release oxycodone (●) and the last two doses of immediate-release oxycodone (○) to 21 subjects. (Plasma oxycodone concentrations obtained from 13 through 36 hours are not shown.)

Table I. Mean pharmacokinetic parameters for oxycodone at steady state after administration of controlled-release (CR) oxycodone and immediate-release (IR) oxycodone. Data are given as mean \pm SD.

	CR Oxycodone (10 mg q 12 h)	IR Oxycodone (5 mg q 6 h)	CR Oxycodone/ IR Oxycodone* (%)	90% Confidence Limits
C_{max} (ng/mL)	15.1 \pm 4.7	15.6 \pm 4.4	97.1	85.5–108.7
C_{min} (ng/mL) [†]	6.2 \pm 2.6	6.5 \pm 3.1	96.4	81.0–111.6
T_{max} (h)	3.2 \pm 2.2 [‡]	1.4 \pm 0.7	230.2	160.0–300.9
AUC_{0-12} (ng \cdot h/mL)	103.6 \pm 40.0	99.0 \pm 35.8	104.4	91.0–117.9
% Swing	176.4 \pm 139.0	179.0 \pm 124.1	98.5	62.3–134.8
% Fluctuation	108.5 \pm 38.7	118.0 \pm 52.5	92.2	77.2–107.2

C_{max} = maximum plasma oxycodone concentration; C_{min} = minimum plasma oxycodone concentration; T_{max} = time after administration to maximum plasma oxycodone concentration; AUC_{0-12} = area under the plasma concentration–time curve over the 12-hour dosing interval.

*IR oxycodone = 100%.

[†]Average of the 0- and 12-hour plasma oxycodone concentrations for CR oxycodone and 0- and 6-hour plasma oxycodone concentrations for IR oxycodone.

[‡]Statistically significant ($P = 0.005$).

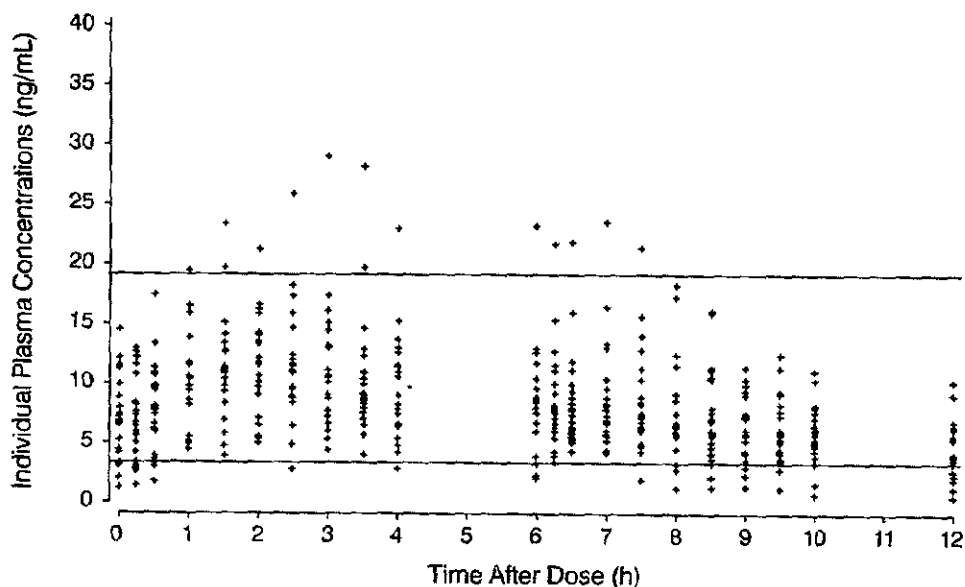


Figure 3. Individual plasma oxycodone concentrations in subjects receiving controlled-release oxycodone. Horizontal lines indicate 10th and 90th percentiles based on ranked maximum plasma oxycodone and minimum plasma oxycodone concentrations obtained with immediate-release oxycodone.

tween formulations in C_{\max} , C_{\min} , AUC_{0-12} , percent swing, and percent fluctuation. As expected, the T_{\max} for CR oxycodone was significantly longer than (ie, more than twice) that for IR oxycodone ($P = 0.005$). While statistically significant, the clinical relevance, if any, of the change in T_{\max} remains to be demonstrated. Because the 90% confidence interval for the ratio of the AUC_{0-12} values fell within 80% and 125%, the extent of absorption of CR oxycodone and IR oxycodone was considered equivalent. In addition, 88.4% of the individual plasma concentrations in subjects receiving CR oxycodone fell within the 10th and 90th percentiles based on ranked C_{\max} and C_{\min} values obtained from IR oxycodone administration (Figure 3).

Safety

Three subjects discontinued treatment because of adverse experiences: two because of itching and rash and one because of sternomastoid muscle pain. All three subjects were receiving IR oxycodone.

There were no significant differences between treatments in the number of subjects reporting adverse experiences. Five (20.8%) of 24 subjects given IR oxycodone and 4 (18.2%) of 22 subjects who received CR oxycodone reported one or more adverse experiences (Table II). All adverse experiences reported, except for chills, myalgia, bronchitis, fever, and flu syndrome, are commonly associated with opioid drugs.

Approximately twice as many adverse experiences were reported by subjects re-

Table II. Incidence and duration of adverse experiences reported after administration of controlled-release (CR) oxycodone and immediate-release (IR) oxycodone.

Adverse Experience	CR Oxycodone				IR Oxycodone			
	No. (%) of Subjects (n = 22)	Total Reports	Duration		No. (%) of Subjects (N = 24)	Total Reports	Duration	
			Days	Hours			Days	Hours
Abnormal dreams	1 (4.5)	1	-	22	0 (0)	0	-	-
Asthenia	0 (0)	0	-	-	1 (4.2)	1	3	-
Bronchitis	0 (0)	0	-	-	1 (4.2)	1	4	-
Chills	0 (0)	0	-	-	1 (4.2)	1	1	20
Confusion	0 (0)	0	-	-	1 (4.2)	1	1	18
Constipation	1 (4.5)	1	1	22	0 (0)	0	-	-
Emotional lability	0 (0)	0	-	-	1 (4.2)	1	4	-
Fever	0 (0)	0	-	-	1 (4.2)	1	-	20
Flu syndrome	0 (0)	0	-	-	1 (4.2)	1	3	-
Headache	1 (4.5)	1	-	10	1 (4.2)	1	-	13
Myalgia	0 (0)	0	-	-	1 (4.2)	1	4	-
Nausea	1 (4.5)	1	-	2	0 (0)	0	-	-
Pruritus	1 (4.5)	1	-	17	2 (8.3)	4	1-3	-
Somnolence	0 (0)	0	-	-	1 (4.2)	1	1	18
Vasodilation	0 (0)	0	-	-	1 (4.2)	1	1	10
Vomiting	1 (4.5)	2	-	<1	0 (0)	0	-	-
Total	4 (18.2)	7	-	-	5 (20.8)	15	-	-

ceiving IR oxycodone than those receiving the CR formulation. Several of the IR-treated subjects had adverse experiences of longer duration than those reported by subjects given CR oxycodone (Table II). Most adverse experiences were mild.

Routine clinical laboratory screening tests were conducted at screening and at the end of the study. Statistically significant but clinically unimportant increases in blood urea nitrogen and serum triglyceride levels occurred in 10 subjects after completion of the two phases. Although a relationship to the study drug could not be excluded, these changes more likely resulted from the timing of the phlebotomies in relation to meals and to the diet consumed.

DISCUSSION

Under the conditions of this study, the bioavailability of CR oxycodone administered orally over 4 days as a 10-mg tablet every 12 hours was equal to that of 5 mg of IR oxycodone given as a 1-mg/1 mL solution every 6 hours. The values for C_{\max} , C_{\min} , and percent fluctuation were similar for the two dosage forms. As expected, T_{\max} was prolonged with CR oxycodone compared with IR oxycodone.

The CR characteristics of the dosage form are demonstrated not only by comparison of the standard bioavailability parameters, but also by comparison of the individual plasma oxycodone concentrations. Almost 90% of all the individual plasma concentrations measured during repeated-dose administration of CR oxycodone fell between the 10th and 90th percentiles established in the same subjects during administration of IR oxycodone at the same total daily oxycodone dose. This model presupposes that at least

80% of plasma concentration values fall within these limits. Values outside these limits would indicate that the drug was being released too quickly (values greater than the 90th percentile) or was not being released quickly enough (values less than the 10th percentile) to be considered comparable to the IR formulation in fluctuation of plasma oxycodone concentrations. Having almost 90% of plasma concentration values fall within the window further suggests the controlled-release nature of the CR oxycodone dosage form.

Steady state was reached with both formulations after approximately 1 day of dosing. Because steady state can be reached within 1 day and plasma oxycodone concentrations obtained with CR oxycodone exist in a narrow range relative to IR values, titration of dose to effect should be accomplished as readily with CR oxycodone as with IR oxycodone.

It is interesting to note that the afternoon peak/trough curve for the IR product was lower than the morning curve. This phenomenon has also been described following administration of morphine and codeine.^{9,10} Although the cause is unknown, it could be related to changes in posture or physical activity or to a diurnal variation in absorption or clearance.

In developing CR oxycodone, we intended to produce a formulation that, when administered according to the correct dosing guidelines, mimicked the C_{\max} , C_{\min} , and percent fluctuation in plasma oxycodone concentrations of IR oxycodone at steady state. In addition to providing benefits associated with less frequent dosing, our aim was to achieve a therapeutic profile comparable to that of the IR product. In contrast, others have suggested that CR opioids should have a lower C_{\max} and higher C_{\min} than the IR

version and a relatively flat plasma drug concentration–time curve.¹¹ We believe it is inappropriate to assume that less fluctuation in plasma concentrations necessarily results in a clinically superior sustained-release profile: There is insufficient knowledge about how these drugs interact with receptors, how their effects are mediated, and how fluctuations in plasma concentrations influence therapeutics to support this assumption.

CONCLUSIONS

The findings from this study suggest that, when applied to patients, CR oxycodone tablets will be able to be used as an alternative to IR oxycodone or other morphine-type opioids in around-the-clock therapy for patients with subacute and chronic pain syndromes. CR oxycodone should provide similar plasma concentrations and more convenient, less frequent dosing than IR oxycodone. This CR formulation will allow independent titration and dosing of oxycodone with any nonopioid analgesic that is clinically necessary, thereby enhancing therapeutic flexibility.

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