Eur J Clin Pharmacol (1999) 55: 425–429

PHARMACODYNAMICS

G. B. Curtis · G. H. Johnson · P. Clark
R. Taylor · J. Brown · R. O'Callaghan
M. Shi · P. G. Lacouture

Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model

Received: 10 August 1998 / Accepted in revised form: 9 March 1999

Abstract *Objective*: The relative analgesic potency of single doses of oral controlled-release oxycodone and oral controlled-release morphine were compared in a randomized, double-blind trial using a postoperative pain model.
Methods: Women (n = 169) with moderate to severe pain following abdominal hysterectomy received single oral doses of controlled-release oxycodone, 20 mg or 40 mg, or controlled-release morphine, 45 mg or 90 mg. Assessments were made at 30 min, 60 min, then hourly after dosing for 12 h or until remedication.
Results: The most precise estimates of relative potency showed that controlled-release oxycodone was 1.8 times more potent than controlled-release morphine for total effect (95% confidence limits 1.09–2.42; lambda 0.44) and 2.2 times more potent for peak effect (95% confidence limits 0.96–4.59; lambda 0.71). Controlled-release oxycodone at doses of 20 mg or 40 mg was comparable with controlled-release morphine at doses of 45 mg or 90 mg, respectively, for total and peak analgesic effects. For the two higher doses, time to peak relief was approximately 1 h shorter with controlled-release oxycodone than with controlled-release morphine. Most patients reported onset of analgesia within 1 h with all doses. Side effects were similar with the two opioids.
Conclusion: Oral controlled-release oxycodone was twice as potent as oral controlled-release morphine in this single-dose, relative potency assay. When converting patients from oral morphine to oral oxycodone, an initial oral oxycodone dose of one-half the oral morphine dose is recommended.

Key words Oxycodone · Morphine · Controlled-release formulation

G.B. Curtis · R. Taylor
Alta View Hospital, 9600 South 1300 East,
Sandy, Utah 84094, USA

G.H. Johnson
LDS Hospital, 8th Avenue and C Street,
Salt Lake City, Utah 84143, USA

P. Clark
Cottonwood Hospital, 5770 South 250 East,
Murray, Utah 84107, USA

J. Brown · R. O'Callaghan
Jean Brown Associates, Inc., Consultants in Clinical Research,
Governor's Plaza, 560 East South Temple,
Suite 1102, Salt Lake City, Utah 84151, USA

M. Shi · P.G. Lacouture (✉)
Purdue Pharma L.P., 100 Connecticut Avenue,
Norwalk, Connecticut 06850-3590, USA
Tel.: +1-203-8547215; Fax: +1-203-8515296

Introduction

Oxycodone and morphine are pure opioid agonists available as controlled-release (CR) oral formulations. Based on the oral bioavailability and on previous reports of the relative potency of oral oxycodone versus oral morphine [1, 2], one would expect the analgesic potency of CR oxycodone to be higher than that of CR morphine. Because CR oxycodone is an alternative to CR morphine for the control of moderate to severe pain of more than a few days duration, it is important to know the relative potency of these two formulations to facilitate substitution of one for the other. Both CR products have similar times to maximum concentration. Following a single dose of 20 mg CR oxycodone in healthy men, the area under the concentration–time curve from zero to infinity ($AUC_{0-\infty}$) was 208 ± 75 ng/ml·h, mean ± SD, peak concentration (C_{max}) was 18.6 ± 6.1 ng/ml, time to reach peak concentration (t_{max}) was 2.62 ± 1.07 h, and the elimination half-life ($t_{1/2elim}$) was 7.99 ± 2.96 h [3]. Following a single dose of 20 mg CR morphine in healthy men and women, $AUC_{0-8\,h}$ was 86.9 ± 26.9 ng/ml·h, mean ± SEM, C_{max} was 14.83 ± 1.44 ng/ml, t_{max} was 2.4 ± 0.5 h, and $t_{1/2elim}$ was 4.1 ± 0.6 h [4]. The present study directly compared the relative potency of single doses of oral CR oxycodone and oral CR morphine in patients

with pain following major surgery, a model commonly used for comparing potent analgesics [5] such as oxycodone and morphine.

Patients and methods

Patients

One hundred and sixty-nine women who had undergone abdominal hysterectomy were enrolled in the study when they were free of anesthesia, showed no signs of paralytic ileus, were able to take oral medication, and were experiencing moderate to severe pain. Since patients were randomly assigned to the four treatment groups, any differences among individuals in stage of recovery are expected to be evenly distributed among the treatments and would therefore not affect the estimate of their relative effects. Patients who had received long-acting opioid analgesics, such as methadone or buprenorphine, for postoperative pain were excluded. Morphine, Demerol (meperidine, Sanofi Pharmaceuticals, Inc., N.Y.), and Toradol (ketorolac, Roche Laboratories Inc., Nutley, N.J.) were used for parenteral analgesia, which was discontinued at least 1 h before administration of study drug. Other analgesics were discontinued at least 3 h before administration of study drug. Seventeen patients received only oral analgesics (an opioid or a nonsteroidal anti-inflammatory drug) before the study. Each of the three participating hospitals received Institutional Review Board approval before the study was initiated, and all patients gave written informed consent before entering the trial. The study was conducted according to the ethics principles that have their origin in the Declaration of Helsinki.

Study design

This double-blind, parallel-group, single-dose study assessed the relative potency of oral CR oxycodone (OxyContin tablets, Purdue Pharma L.P., Norwalk, Conn.) in doses of 20 mg and 40 mg and oral CR morphine (MS Contin tablets, The Purdue Frederick Company, Norwalk, Conn.) in doses of 45 mg and 90 mg using a standard study design [6] in a postoperative pain model. Eligible patients post-abdominal hysterectomy were assigned to one of the four study treatments, based on a computer-generated randomization code, when they reported moderate or severe pain. Active and placebo tablets of identical appearance were packaged in blister cards labeled with the patient number for each dosing unit; dosing units for all four groups contained six tablets.

At the time of dosing, patients were given a diary and instructions on reporting pain intensity, pain relief, and adverse events. Assessments were made before dosing (baseline), and at 30 min, 60 min, and then hourly after dosing for 12 h or until patients requested remedication. Pain intensity was rated using a categorical (CAT) scale of 0 = none; 1 = slight; 2 = moderate; or 3 = severe and a 100-mm visual analog scale (VAS) ranging from 0 = least possible pain to 100 = worst possible pain. Pain relief was rated using a CAT scale of 0 = none; 1 = a little; 2 = moderate; 3 = a lot; or 4 = complete and a VAS ranging from 0 = none to 100 = complete relief. Adverse events were recorded when reported spontaneously by the patient or observed by the research staff. Vital signs were measured before study medication dosing and at the end of the study.

Measures of analgesia

Total analgesic effects were assessed by the sum of the pain intensity differences (SPIDs) and total pain relief (TOTPAR). Pain intensity differences (PIDs) were calculated by subtracting the hourly pain intensity ratings from the baseline pain intensity rating; these scores were added over the 12-h study period to obtain the SPID. The observed pain relief scores (PARs) were added to calculate TOTPAR. Both SPID and TOTPAR were weighted for the length of time between observations. Peak analgesic effects were assessed by peak pain intensity difference (PPID) and peak pain relief (PPAR), which were calculated as the maximum observed PID and PAR, respectively. The time to reach peak effects, measured by time to PPID (TPPID) and time to PPAR (TPPAR), was determined for patients who had differences in pain intensity or who achieved pain relief, respectively. The time to onset of pain relief was defined as the midpoint of the time interval during which patients first reported an improvement in pain relief of at least 1 unit from baseline on the CAT scale.

Statistical and relative potency analyses

A two-way analysis of variance (ANOVA) procedure was used to assess measures of analgesia. Pairwise comparisons of treatments were made using Tukey studentized range test procedures. For patients who required remedication before completion of the 12-h observation period, the remaining pain intensity scores were set to baseline and PARs to 0. Time to onset of pain relief was analyzed using survival analysis procedures (SAS software). Survival functions were estimated using the Kaplan-Meier estimator [7] based on data of only those patients who had onset of relief. The Cochran-Mantel-Haenszel test (SAS software) controlling for center effect was used to test the null hypothesis that the treatments did not differ in the proportion of patients who obtained onset. All analgesic treatment effects were tested using a two-sided hypothesis with $\alpha = 0.05$.

To obtain estimates of the relative potency of CR oxycodone to CR morphine with 95% confidence interval (CI), ANOVA techniques were applied to bioassay analyses for total (SPID and TOTPAR) and peak (PPID and PPAR) effects. The assumptions of (i) a statistically significant positive common slope of the log dose–response line, (ii) parallelism of the log dose–response lines, and (iii) insignificant differences in analgesic effects [6] between corresponding dose levels of CR oxycodone and CR morphine were tested using ANOVA. Assay precision was measured with lambda (λ), which was calculated by dividing the square root of the ANOVA error mean square hy the common slope [6].

Adverse events were summarized by treatment group. Differences between treatment groups in vital signs were tested using ANOVA; within-group changes from baseline were assessed using the Student's paired t test.

Results

Patients' characteristics

Fifteen of the 169 patients prematurely discontinued from the study for the following reasons: took prohibited medications ($n = 8$), vomited the study medication ($n = 3$), chewed the study medication ($n = 1$), had additional surgical procedures ($n = 1$), lost the diary ($n = 1$), or withdrew consent ($n = 1$). There were no significant differences among treatment groups for the number of patients who discontinued from the study. Among the 154 patients evaluated for analgesic effects, there were no significant differences among treatment groups for age, height, weight, or baseline pain intensity (Table 1).

Relative potency

Estimates of the relative potency of CR oxycodone to CR morphine were similar for total analgesic effects

Table 1 Patients' characteristics. *CR* controlled-release

	CR oxycodone		CR morphine	
	20 mg (n = 36)	40 mg (n = 38)	45 mg (n = 39)	90 mg (n = 41)
Age (years), mean (range)	40 (24–73)	43 (29–73)	39 (23–56)	42 (27–68)
Height (cm), mean (range)	165 (140–185)	165 (150–183)	164 (142–185)	166 (153–180)
Weight (kg), mean (range)	75 (52–117)	77 (46–146)	79 (40–136)	74 (53–104)
Baseline pain:				
CAT,[a] mean (SE)	2.19 (0.07)	2.24 (0.07)	2.23 (0.07)	2.22 (0.07)
VAS,[b] mean (SE)	65.9 (2.3)	66.1 (2.5)	62.8 (2.1)	63.8 (2.4)

[a] Categorical scale of 0 = none, = slight, 2 = moderate, 3 = severe

[b] Visual analog scale ranging from 0 mm = least possible pain to 100 mm = worst possible pain

(SPID and TOTPAR) measured using the CAT scale or VAS (Table 2). A significantly positive common slope ($P < 0.05$) was observed for all variables except PPAR measured using the CAT scale and PPID measured using the VAS. There were no significant deviations from parallelism of dose–response lines. Total analgesic effects of the two drugs were similar, as demonstrated by no significant differences between CR oxycodone 20 mg and CR morphine 45 mg, nor between CR oxycodone 40 mg and CR morphine 90 mg for SPID and TOTPAR. An example of the graphic display of summary measures of analgesia as a function of the log dose is shown in Fig. 1.

Analgesic effects

Total analgesic effects were significantly greater with the high dose than the low dose of each drug (Table 3). There were no significant differences between the low doses of the two drugs, nor between the high doses, indicating that the total analgesic effects of the two drugs were similar.

Although there were no significant differences among treatment groups in peak drug effects, mean PPID and PPAR values were numerically higher in the higher dose groups for both drugs (Table 3). The peak effects of the two drugs were similar, as shown by no significant differences between the low doses of the two drugs, nor between the high doses. TPPAR assessed using the CAT scale was significantly shorter in the CR oxycodone 40-mg group than in the CR morphine 90-mg group (Table 4). No other between-group differences in time to peak effect were statistically significant.

More than 90% of the patients in each group experienced onset of relief, with no significant differences between treatments in the percentage of patients experiencing onset. Derived onset of relief was related to dose, with 75% of the patients reporting onset by 15 min with the high doses and 45 min with the low doses.

Adverse events and vital signs

The most common adverse events were those typically seen with opioids. Those reported by 5% or more of the 169 patients and judged by the investigator to be related to study medication were somnolence (reported by 37% of patients), nausea (32%), dizziness (12%), vomiting (8%), headache (7%), pruritus (5%), and postural

Table 2 Relative potency of controlled-release (CR) oxycodone to CR morphine. *CI* confidence interval; *SPID* sum of the pain intensity differences; *TOTPAR* total pain relief; *PPAR* peak pain relief; *PPID* peak pain intensity difference; *CAT* categorical; *VAS* visual analog scale

Variable	Scale	Ratio	95% CI	Lambda
TOTPAR	CAT	1.75	1.09–2.42	0.44
	VAS	1.76	1.02–2.55	0.49
PPAR[a]	CAT	1.70	1.03–2.37	0.45
	VAS	1.69	1.02–2.35	0.45
PPID[a]	VAS	2.18	0.96–4.59	0.71
	CAT	1.90	0.16–4.80	0.85

[a] Common slope not positive for PPAR measured using the CAT scale or PPID measured using the VAS (P = 0.064)

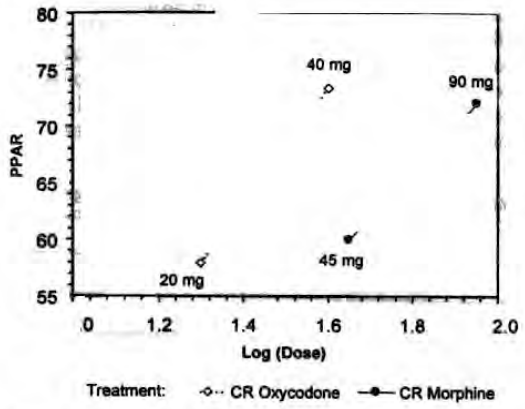

Fig. 1 Mean peak pain relief (*PPAR*; visual analog scale) versus $\log_{10}$ dose for 20-mg and 40-mg controlled-release (*CR*) oxycodone treatment groups (*diamonds*) and for 45-mg and 90-mg CR morphine treatment groups (*circles*)

Table 3 Summary measures of analgesia for controlled-release (CR) oxycodone and CR morphine. *SPID* sum of the pain intensity differences; *TOTPAR* total pain relief; *PPAR* peak pain relief; *PPID* peak pain intensity difference; *CAT* categorical; *VAS* visual analog scale

Variable	Scale	CR oxycodone		CR morphine	
		20 mg (n = 36)	40 mg (n = 38)	45 mg (n = 39)	90 mg (n = 41)
SPID	CAT	2.57 (0.56)	6.89 (1.26)*	4.19 (0.82)	8.40 (1.20)*
	VAS	120.2 (22.6)	260.9 (40.0)*	173.3 (33.7)	302.9 (41.4)*
TOTPAR	CAT	7.83 (1.29)	16.06 (2.21)*	10.99 (1.80)	19.72 (2.52)*
	VAS	196.0 (34.7)	402.2 (56.1)*	273.0 (48.2)	509.3 (66.5)*
PPID	CAT	0.92 (0.13)	1.24 (0.14)	1.03 (0.13)	1.27 (0.12)
	VAS	37.7 (4.2)	47.8 (3.8)	39.6 (3.8)	44.5 (4.0)
PPAR	CAT	2.33 (0.19)	2.79 (0.19)	2.44 (0.20)	2.71 (0.20)
	VAS	57.2 (5.4)	73.4 (4.9)	60.0 (5.7)	72.0 (5.3)

*For each drug, scores significantly higher with high dose compared with low dose ($P < 0.05$)

hypotension (5%). Patients receiving CR oxycodone had a higher incidence of headache (12–13%) than those receiving CR morphine (2%) ($P < 0.05$). Vital signs showed no significant differences among the four treatment groups, and there were no clinically significant changes from baseline within groups.

Discussion

The present study showed that oral CR oxycodone was 1.8 times more potent than oral CR morphine for total effect and 2.2 times more potent for peak effect, for an equianalgesic dose ratio of 1 mg of oral oxycodone to 2 mg of oral morphine. These were the most precise estimates of relative potency, as determined by the λ value. The variability around these estimates, as measured by the 95% CI, was approximately 2.5-fold. The CIs reported in the present study are orders of magnitude less than those reported previously for relative potency estimates of oral analgesics [8, 9]. While part of the variation is a result of true variation in potency, it is possible that differences among patients with respect to the first-pass hepatic metabolism and overall clearance rates of the two analgesics being compared is also operative.

The 1:2 ratio of oral oxycodone to oral morphine found in our study is consistent with reports by Houde [1] and Foley [2], also based on well-controlled, single-dose studies. However, different ratios have been reported in multiple-dose settings. In a multiple-dose, cross-over trial comparing oral CR oxycodone and oral CR morphine in patients with cancer pain, the total opioid consumption ratio of oxycodone to morphine was between 2:3 and 3:4 [10]. Reviews of cancer pain management indicate equianalgesic dose ratios of oral oxycodone to oral morphine ranging from 1:2, 2:3, and 1:1 [11, 12, 13]. Differences between equianalgesic doses derived from single-dose studies versus chronic, multiple-dose settings have also been reported for methadone [14], hydromorphone, and morphine [15]. Thus, the equianalgesic dose ratio based on well-controlled, single-dose studies provides a starting point for selecting the initial opioid dose [16]. Other factors that need to be considered are the patient's current level of pain, the presence of side effects, the patient's risk of developing side effects, and incomplete cross-tolerance between opioids. Using an equianalgesic dose ratio of 1 mg of oral oxycodone to 2 mg of oral morphine provides a conservative initial oxycodone dose. The initial dose can then be titrated as needed to achieve optimal analgesia.

The design of the present study is well established for comparing analgesic effects [5, 17]. The validity of the assay was confirmed by the significantly positive common slope, no significant deviation from parallelism in the dose–response curves with common slope, and no significant differences in analgesic effects between corresponding dose levels of CR oxycodone and CR morphine [6]. The λ value was smaller than unity for all variables, signifying a high degree of precision for an oral dosing study [6, 9]. Oral CR oxycodone was twice as potent as oral CR morphine in this single-dose, relative potency assay. When converting patients from oral morphine to

Table 4 Time to peak analgesic effects, mean ± SEM, measured in patients who had differences from baseline in pain intensity or who achieved pain relief, respectively. *CR* controlled-release; *CAT* categorical; *VAS* visual analog scale; *TPPID* time to peak pain intensity difference; *TPPAR* time to peak pain relief

Variable	Scale	CR oxycodone		CR morphine	
		20 mg	40 mg	45 mg	90 mg
TPPID (h)	CAT	1.74 ± 0.24	1.67 ± 0.21	1.63 ± 0.20	2.50 ± 0.35
	VAS	2.11 ± 0.23	2.90 ± 0.31	2.47 ± 0.28	3.08 ± 0.43
TPPAR (h)	CAT	1.60 ± 0.19	1.49 ± 0.17*	1.75 ± 0.19	2.34 ± 0.32
	VAS	2.00 ± 0.19	2.36 ± 0.25	2.25 ± 0.30	3.53 ± 0.47

*TTPAR significantly shorter in the CR oxycodone 40-mg group than in the CR morphine 90-mg group ($P<0.05$)

oral oxycodone, an initial oral oxycodone dose of one-half the oral morphine dose is recommended.

Acknowledgments This study was sponsored by Purdue Pharma L.P., Norwalk, Conn., USA. We thank Mary Clark, Ph.D., for editorial assistance. Glade B. Curtis, Gary H. Johnson, Philip Clark, and Richard Taylor were investigators in the trial and financially compensated for their efforts. Jean Brown and Roni O'Callaghan are employees of Jean Brown Associates, Inc., a contract research organization paid by Purdue to conduct the trial. Minggao Shi and Peter G. Lacouture are employees of Purdue. This trial was conducted in compliance with the current laws of the United States of America.

References

1. Houde RW (1974) The use and misuse of narcotics in the treatment of chronic pain. Adv Neurol 4: 527–536
2. Foley KM (1985) The treatment of cancer pain. N Engl J Med 313: 84–95
3. Benziger DP, Thomas G, Miotto J, Grandy R, Kaiko R, Reder R (1994) Bioavailability and pharmacokinetics of controlled release oxycodone (OxyContin) tablets vs oxycodone oral liquid (abstract). In: Proceedings of American Pain Society, 13th Annual Scientific Meeting, 10–13 November, Miami Beach, FL:A-121, no. 94732
4. Vater M, Smith G, Aherne GW, Aitkenhead AR (1984) Pharmacokinetics and analgesic effect of slow-release oral morphine sulphate in volunteers. Br J Anaesth 56: 821–827
5. Max MB, Laska EM (1991) Single-dose analgesic comparisons. In: Max M, Portenoy R, Laska E (eds) Advances in pain research and therapy, vol 18. Raven Press, New York, pp 55–95
6. Wallenstein SL, Houde RW (1975) The clinical evaluation of analgesic effectiveness. In: Ehrenpreis S, Neidle A (eds) Methods in narcotics research, Marcel Dekker, New York, pp 127–145
7. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Statistical Assoc 53: 457–481
8. Forbes JA, Beaver WT, Jones KF, Kehm CJ, Smith WK, Gongloff CM, Zeleznock JR, Smith JW (1991) Effect of caffeine on ibuprofen analgesia in postoperative oral surgery pain. Clin Pharmacol Ther 49: 674–684
9. Bloomfield SS, Cissell GB, Mitchell J, Barden TP, Kaiko RF, Fitzmartin RD, Grandy RP, Komorowski J, Goldenheim PD (1993) Analgesic efficacy and potency of two oral controlled-release morphine preparations. Clin Pharmacol Ther 53: 469–478
10. Heiskanen T, Kalso E (1997) Controlled-release oxycodone and morphine in cancer related pain. Pain 73: 37–45
11. Grossman SA, Staats PS (1994) Current management of pain in patients with cancer. Oncology (Huntingt) 8: 93–115
12. Levy MH (1996) Pharmacologic treatment of cancer pain. N Engl J Med 335: 1124–1132
13. Derby S, Chin J, Portenoy RK (1998) Systemic opioid therapy for chronic cancer pain: practical guidelines for converting drugs and routes of administration. CNS Drugs 9: 99–109
14. de Stoutz ND, Bruera E, Suarez-Almazor M (1995) Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 10: 378–384
15. Lawlor P, Turner K, Hanson J, Bruera E (1997) Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. Pain 72: 79–85
16. Acute Pain Management Guideline Panel (1992) Acute pain management: operative or medical procedures and trauma. Clinical practice guideline, AHCPR Pub. no. 92–0032, Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, Rockville, MD, pp 16–21
17. Food and Drug Administration (1992) Guideline for the clinical evaluation of analgesic drugs. DHHS Pub. no. (FDA) 93–3093, Food and Drug Administration, Public Health Service, U.S. Department of Health and Human Services, Rockville, MD, p 26