Conversion to Oral Controlled-Release Oxycodone From Intravenous Opioid Analgesic in the Postoperative Setting

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ABSTRACT

Objective. This study assessed conversion factors utilized by physicians to transfer postoperative patients from intravenous opioids to oral controlled-release (CR) oxycodone and the subsequent analgesic effectiveness.

Design. This was a multicenter, open-label, usual-use study of 189 hospitalized postoperative patients receiving opioid (usually morphine) intravenous patient-controlled analgesia (IV PCA) for at least 12 to 24 hours post-procedure. Patients who were tolerant of oral medications and without signs of paralytic ileus were converted to oral CR oxycodone, given every 12 hours for up to 7 days.

Results. The mean (±SE) conversion factor used to convert IV PCA morphine to CR oxycodone was 1.2 ± 0.1 (N = 159). The initial CR oxycodone doses, based on individual conversion factors from IV PCA morphine, produced significant reductions in pain intensity (scores ≤4) within 6 hours after the initial dose. The mean ± SE initial dose of CR oxycodone, for patients converted from IV PCA morphine, was 27 ± 1 mg; that for all patients was 29 ± 2 mg. Pain at the end of the first 12 hours was controlled with these initial doses. The most common adverse events were constipation, nausea, and pruritus.

Conclusions. Administered at least 12 hours following abdominal, orthopedic, or gynecologic surgery, an initial oral CR oxycodone dose calculated by multiplying the amount of IV morphine used in the previous 24 hours (immediate postoperative period) by a conversion factor of 1.2, on average, provided adequate pain control during the subsequent 12-hour dosing interval and for a maximum of 7 days. Adverse events were consistent with opioid side effects.

Key Words. Oxycodone; Postoperative Pain; Controlled-Release Formulation; Opioid Dose Conversion

Introduction

Moderate-to-severe pain can persist for several days to weeks following major surgery and is often poorly controlled [1–8]. Poorly controlled pain can contribute directly or indirectly to postoperative complications, such as myocardial ischemia, pulmonary dysfunction, a delayed return of gastrointestinal function, and decreased mobility [1,9,10]. Parenteral administration of opioid analgesics via intravenous patient-controlled analgesia (IV PCA) is commonly used to treat moderate-to-severe pain during the immediate postoperative period. Once patients are able to tolerate oral medications, the oral route is preferred postoperatively because it is more convenient, noninvasive, and less expensive [10]. Around-the-clock oral dosing of immediate-release (IR) or short-acting opioids provides
adequate pain relief, however, missed doses or delays in administration can allow plasma opioid concentrations to fall below minimally effective concentrations, resulting in periods of inadequate pain control [1,9]. In order to avoid troughs of analgesic effect and provide more stable pain control, controlled-release (CR) formulations have been used in a variety of settings with proven efficacy [11,12].

CR oxycodone has a fairly rapid onset of effect, high oral bioavailability, and a prolonged and uniform duration of action [12–14]. This pharmacokinetic profile suggests that CR oxycodone could effectively facilitate and be useful for the conversion of postoperative patients requiring opioids for an extended period of time from the parenteral to the oral route. This open-label study was conducted in a usual-use setting with patients who had undergone a variety of elective major surgical procedures and who were expected to require opioids for an extended duration. This study examined conversion factors usually chosen by physicians to convert or transition postoperative patients from IV opioids (primarily morphine) to oral CR oxycodone and evaluated the effectiveness of the initial CR oxycodone dose utilized. In addition, the safety and effectiveness of CR oxycodone every 12 hours (q12h) given at least 12 hours after surgery was assessed for up to 7 days after the start of oral therapy.

Methods

Selection of Patients
Hospitalized patients (aged 18–70 years) recovering from elective major surgery (abdominal, orthopedic, gynecologic, or urologic) who had been treated postoperatively with IV opioid analgesics for at least the first 12 hours after surgery, either by continuous infusion (CI) or by IV PCA, were eligible for this study. Patients who were anticipated to require opioid analgesia for more than a few days were enrolled when they could tolerate oral medications. Those patients with evidence of paralytic ileus, nausea and vomiting, significant respiratory depression, or other known contraindications to opioid therapy were excluded. This study was conducted according to the ethical principles of the Declaration of Helsinki. It was approved by the institutional review board of each participating center, and all patients gave written informed consent.

Study Design
This was a multicenter, open-label, usual-use study of postoperative patients converting from IV PCA opioids to oral CR oxycodone. All patients received IV opioid therapy in the immediate postoperative period and were converted to oral CR oxycodone therapy at least 12 hours after surgery.

The analgesic effectiveness of CR oxycodone given at least 12 hours after surgery was evaluated during repeated q12h administrations for up to 7 days after surgery. All surgical procedures were conducted according to usual care at each study site. Postoperative recovery practices were governed by local surgical and hospital customs. The initial CR oxycodone dose was determined by the treating physician based on the IV opioid dose during the previous 12–24 hours and the current pain intensity of the patient. Conservative conversion factors (Table 1) and the following formulas were used as a guideline to calculate the initial CR oxycodone dose:

1) Prior IV opioid (mg/day) × Conversion factor = Oral CR oxycodone dose (mg/day);
2) Oral CR oxycodone dose (mg/day) ÷ 2 = Initial oral CR oxycodone dose (mg q12h);
3) The dose was adjusted downward to appropriately match available tablet strengths of CR oxycodone (OxyContin®; Purdue Pharma L.P.; Stamford, CT) [15].

The current pain intensity could also affect the determination of the initial CR oxycodone dose. Upward dose adjustments (by as much as 25%) were allowed if pain had been poorly controlled with the IV opioid dose; downward dose adjustments (by as much as 25–50%) were permitted if pain was expected to improve rapidly or if the patient had been experiencing dose-limiting adverse events with the IV opioid.

The recommended supplemental analgesic was IR oxycodone administered every 4–6 hours as needed at a dose of one fourth to one third of the q12h CR oxycodone dose. Alternatively, non-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Conservative conversion factors for determination of the initial daily dose of oral CR oxycodone in the postoperative setting*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Intravenous Opioid</td>
<td>Conversion Factor</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.5</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.2</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>10</td>
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</table>

* The initial CR oxycodone dose was calculated according to the formulas:
1) Prior IV opioid (mg/day) × Conversion factor = Oral CR oxycodone dose (mg/day);
2) Oral CR oxycodone dose (mg/d) ÷ 2 = Initial oral CR oxycodone dose (mg q12h);
3) Dose was adjusted down as appropriate for CR oxycodone tablet strengths available.
teroidal anti-inflammatory drugs (NSAIDs) were allowed if considered appropriate. Since this was a usual-use study, other concomitant medications (except for opioids) could also be prescribed.

Patients were treated with CR oxycodone q12h for a maximum of 7 days, throughout which the CR oxycodone dose was titrated based on clinical response. The dose could be increased by 25–50% if pain intensity was moderate to severe or if the patient required three or more doses of supplemental analgesic in a 24-hour interval, or decreased by 50% if, during the previous 24 hours, pain was rated 0 to 3 on the numerical rating scale. CR oxycodone treatment was discontinued at any time when the patient no longer required opioids to treat their pain (defined as a 50% decrease in CR oxycodone dose and pain scores below 3 in a 24-hour period). The CR oxycodone dose could also be decreased or discontinued if the patient experienced unacceptable and unresponsive adverse events.

Assessment of Pain Control
Patients were asked to rate pain intensity using an 11-point numerical rating scale ranging from 0 = No pain to 10 = Worst possible pain. Scores of 4 and below were considered indicative of adequate pain control, as this range generally corresponds with mild to no pain [16]. The remaining assessments also used 11-point numerical scales on which a higher score indicated a better response. The comfort level scale ranged from 0 = Poor to 10 = Very comfortable. The quality of sleep and patient acceptance scales ranged from 0 = Poor to 10 = Excellent.

During the study, while hospitalized, patients rated their pain intensity just before conversion to CR oxycodone (baseline) and then daily at 6 hours after the morning dose, at 1 hour before the evening dose, and at 1 hour before the next morning dose. In addition, patients rated pain intensity during activity, such as walking, bathing, changing positions, and physical therapy. After discharge from the hospital for up to 7 days after surgery, patients were contacted daily by telephone at approximately 4–6 hours after their morning dose to obtain ratings of current pain intensity. At the time of pain assessment, patients also rated their average level of comfort and quality of sleep. At the end of the study, they rated their overall acceptance of medication.

Assessment of Safety
Over the course of the study period, adverse events reported spontaneously by patients or observed by physicians were recorded. Oxygen saturation was measured by pulse oximetry in the morning and afternoon while patients were hospitalized; values ≥94% were considered normal. Vital signs, including systolic and diastolic blood pressures, respiratory rate, and pulse were measured according to the procedures routinely used at each hospital.

Statistical Analyses
Analyses were performed on the intent-to-treat population, which included all patients who took at least one dose of study medication. An average of individual conversion factors used by the physicians to calculate the initial CR oxycodone dose was calculated for each IV opioid used before study entry. Initial CR oxycodone dose and pain intensity at baseline and 6 hours after the initial CR oxycodone dose were averaged by type of surgery (categorized as abdominal, orthopedic, gynecologic, and urologic) and for all patients combined. The change in current pain intensity from baseline to 6 hours after the initial CR oxycodone dose was analyzed using a paired t-test (for those patients with baseline and Hour 6 assessments only). The percentage of patients requiring dose escalation after the initial dose was also determined. Average daily doses of CR oxycodone and average pain intensity at 6 hours after the morning dose were calculated by study day. The following variables were summarized by study day: Pain during activity, comfort level, quality of sleep, acceptance of therapy, and supplemental analgesic use. The average number of days of oral opioid use was also determined. For patients converted from IV PCA morphine (the most common prestudy opioid), the average conversion factor and initial CR oxycodone dose were calculated and categorized by type of surgery. Average pain scores, at 6 hours after the initial dose and at 1 hour prior to the second dose, were calculated by morphine conversion factor. Morphine conversion factors were grouped into the following ranges for the purposes of analysis: ≤1.0, >1.0 to ≤1.5, and >1.5.

Results
Patient Demographics
One hundred ninety-two patients were enrolled at seven study centers. Of these patients, 189 were converted to CR oxycodone and were evaluated for effectiveness and safety. The mean age of
patients receiving CR oxycodone was 44 years (range: 20–69); 78% were women. One hundred thirty-nine patients (74%) completed the study by remaining on CR oxycodone until opioid therapy was no longer required or for a maximum of 7 days. Fifty patients (26%) discontinued prematurely: 29 patients (15%) withdrew from the study due to adverse events; nine patients (5%) discontinued due to inadequate pain control; eight patients (4%) were discontinued because they were protocol violators; and four patients (2%) were lost to follow-up.

**Conversion From IV to Oral CR Oxycodone**

The most common prior opioid therapy was IV PCA morphine (85%), followed by meperidine (7%), hydromorphone (5%), and fentanyl (3%). Mean conversion factors for patients converting from IV morphine to oral CR oxycodone for the various types of surgery ranged from 1.2 to 1.3, with the overall average being 1.2 (±0.1 SE) (Table 2). Ten patients (6%) who had received PCA morphine required upward dose titration after converting to CR oxycodone; five of those patients had been converted to CR oxycodone using a conversion factor of ≤1.0.

The majority of patients (59–67% of those patients undergoing abdominal, orthopedic, and gynecologic surgery) were converted to oral CR oxycodone therapy on the first postoperative day, although the time of conversion to oral therapy ranged from 12 hours to 6 days postoperatively. The mean dose of morphine given in the 24 hours before converting to CR oxycodone was highest following orthopedic surgery and lowest after gynecologic surgery (Table 2).

For all patients, the initial (q12h) CR oxycodone dose averaged 29 (±2 SE) mg; the highest dose was observed in patients recovering from orthopedic surgery (Table 3). The average daily dose of CR oxycodone and the number of patients requiring CR oxycodone therapy declined over the 7-day study period. The mean (±SE) daily dose of CR oxycodone was 56 ± 3 mg on Day 1 and was 27 ± 3 mg on Day 7 (Figure 1). Approximately one third of the patients remained on study medication on Day 7. The mean (±SE) duration of therapy was 4.3 ± 0.2 days (range: 0.5–7). Of the categories included, patients recovering from abdominal surgery required the shortest duration of treatment (mean: 3.8 ± 0.3 SE days); while those who underwent orthopedic surgery required the longest treatment (mean: 4.9 ± 0.3 SE days).

**Pain Assessments**

Average pain scores for all patients combined were 4.1 ± 0.2 SE at baseline and 3.3 ± 0.2 SE at 6 hours after the initial dose of CR oxycodone (Table 3). The reduction in pain scores from baseline was statistically significant for the abdominal surgery

### Table 2  Conversion of patients from IV PCA morphine to oral CR oxycodone

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>N</th>
<th>IV Morphine (mg) in Prior 24 Hours (mean ± SE)</th>
<th>Conversion Factor (mean ± SE)</th>
<th>Initial CR Oxycodone Dose (mg q12h) (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>67</td>
<td>51 ± 4</td>
<td>1.2 ± 0.1</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>54</td>
<td>59 ± 6</td>
<td>1.3 ± 0.1</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>37</td>
<td>39 ± 4</td>
<td>1.3 ± 0.2</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>All*</td>
<td>159</td>
<td>51 ± 3</td>
<td>1.2 ± 0.1</td>
<td>27 ± 1</td>
</tr>
</tbody>
</table>

* One subject had urological surgery. Detail data not listed, but data included in summary values.

### Table 3  Initial CR oxycodone dose and current pain intensity at baseline and 6 hours after initial CR oxycodone dose *

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>N</th>
<th>Initial CR Oxycodone Dose (mg q12h) (mean ± SE)</th>
<th>Current Pain Intensity</th>
<th>6 Hours Postdose (mean ± SE)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>44</td>
<td>27 ± 2</td>
<td>4.3 ± 0.4</td>
<td>2.9 ± 0.4</td>
<td>0.0014</td>
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<tr>
<td>Orthopedic</td>
<td>42</td>
<td>34 ± 3</td>
<td>4.2 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>0.1096</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>29</td>
<td>26 ± 3</td>
<td>3.9 ± 0.5</td>
<td>3.3 ± 0.4</td>
<td>0.1444</td>
</tr>
<tr>
<td>All</td>
<td>116</td>
<td>29 ± 2</td>
<td>4.1 ± 0.2</td>
<td>3.3 ± 0.2</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

* For those patients with baseline and Hour 6 pain intensity assessments only. Patients assessed pain intensity using an 11-point numerical scale where 0 = No pain to 10 = Worst possible pain.
† Paired t-test of change from baseline to Hour 6.
Adequate and effective pain control (defined for this study as pain intensity ≤4) was maintained with CR oxycodone treatment over the duration of the study. Mean current pain intensity scores were below 4 at 6 hours after the morning dose of CR oxycodone throughout the study (Figure 1).

For patients receiving IV PCA morphine, baseline pain scores indicated that almost half of these patients (44%) were receiving inadequate pain control (pain scores >4) before converting to oral therapy. After the initial CR oxycodone dose, a smaller percentage of patients (28%) had pain scores >4. Mean current pain intensity scores at baseline and at 6 hours after the initial CR oxycodone dose, respectively, grouped by conversion factor were: ≤1.0 (4.2, 3.6); >1.0 to ≤1.5 (4.4, 3.5); and >1.5 (2.9, 2.1) (Figure 2). The mean pain intensity scores at baseline and at 6 hours for patients converted from IV PCA morphine to oral CR oxycodone were similar to the mean pain intensity scores for all subjects (4.1, 3.3, Table 3).

Average scores for pain during activity decreased from baseline over the course of the study, but were higher than current pain intensity scores. The mean ± SE score for pain during activity was 6.0 ± 0.2 at baseline before the initial dose of CR oxycodone. On Day 4, this score was 4.2 ± 0.3 and on Day 7, it was 4.0 ± 0.4.

**Other Assessments**
Patients reported an adequate level of comfort, with mean scores of >7 (0 = Poor to 10 = Very comfortable) at 6 hours after the morning dose of CR oxycodone on the first day of oral dosing and on each subsequent study day. Quality of sleep (0 = Poor to 10 = Excellent) improved from a baseline score of 5.0 ± 0.2 (mean ± SE) to 6.8 ± 0.2 on Day 2 and to 7.8 ± 0.3 on Day 7. The acceptance of medication score at the end of the study (0 = Poor to 10 = Excellent) was 8.2 ± 0.7 (mean ± SE).

**Supplemental Analgesic Use**
During the first 48 hours following conversion to CR oxycodone from IV PCA morphine, fewer rescue doses were taken when higher conversion factors were utilized to determine the initial CR oxycodone dose (Table 4). In general, across surgical procedures, patients required an average of one IR oxycodone dose as a supplemental analgesic or rescue medication per day. The percentage of patients requiring IR oxycodone as a supplemental analgesic declined from 62% on Day 1 to 38% on Day 7.

**Assessment of Safety**
One hundred forty-three patients (76%) reported adverse events; 99% of these adverse events were mild or moderate, and 59% were considered drug related by the physician. Constipation, nausea, and pruritus were the most commonly reported adverse events occurring in >10% of patients and were also the most common events leading to dose reduction or premature discontinuation. Due to adverse events, 29 (15%) patients had their daily
dose of CR oxycodone decreased and 29 (15%) patients discontinued from the study.

The most clinically significant adverse events reported during the study were constipation and paralytic ileus. Hospitalization was prolonged by 24–48 hours in two patients with constipation; a third patient was admitted to the hospital for constipation. These cases were judged by the physicians to be possibly related to CR oxycodone.

Paralytic ileus was reported in four (2.1%) patients. Of these four patients, one (on the day following discontinuation of study medication) had undergone a total abdominal hysterectomy and was readmitted to the hospital because of dehydration, vaginal cuff abscess and cellulitis, and paralytic ileus. All of these events were considered by the physician to be unrelated to CR oxycodone treatment. Of the remaining three patients with paralytic ileus, one had undergone a total abdominal hysterectomy; the other two had had orthopedic procedures. CR oxycodone was immediately discontinued, and none of the three patients required prolonged hospitalization. The ileus in these patients was considered possibly related to CR oxycodone treatment, and all patients recovered with supportive therapy.

Mean values for vital signs and oxygen saturation remained within normal limits throughout the period of hospitalization, with the exception of four patients with low oxygen saturation levels ranging from 85–93% (normal: ≥94%). At baseline, three out of four of these patients had low oxygen saturation levels. Hypoxemia was reported in one of the four patients; a ventilation-perfusion scan indicated a high probability of pulmonary embolism. This event was judged as unrelated to study medication, and the patient recovered after treatment with anticoagulant therapy.

Discussion

This open-label, usual-use study in postoperative patients undergoing a variety of surgical proce-

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Conversion Factor Used (%)</th>
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<tbody>
<tr>
<td></td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Abdominal</td>
<td>22/33 (67)</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>16/18 (89)</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>19/21 (90)</td>
</tr>
</tbody>
</table>

*Results are presented as number of patients out of total patients in surgery type, percent of total.

The mean conversion factor from IV PCA morphine to oral CR oxycodone of 1.2 ± 0.1 SE that provided effective analgesia in this study is less than the factor of 3 that has been previously reported as equianalgesic for converting parenteral morphine to oral oxycodone [17–19]. This range is, however, consistent with a previous thoracic/abdominal postoperative pain study, in which a factor of 1 provided effective analgesia for the majority of patients converted from PCA morphine to oral oxycodone [20]. Patients may require larger doses of oxycodone after more extensive thoracic or upper abdominal procedures because they may experience longer periods of rest and effort-dependent pain [20]. It should also be noted that the conversion ratio of 3 to 1, which is generally acceptable for chronic pain patients, is probably too high for an acute postsurgical model where pain intensity is expected to decrease on a daily basis.

Average pain intensity scores 6 hours after the first dose of CR oxycodone, for all patients combined and for those converted from morphine alone, were 4 or less on the 11-point numerical scale. Provided that an adequate initial CR oxycodone dose was administered (based upon the conversion factors used), postoperative pain following abdominal, orthopedic, and gynecologic surgery was controlled over the 12-hour dosing interval. Furthermore, pain control was maintained over the 7-day study period with CR oxycodone administered q12h. The average daily dose required and the number of patients requiring an opioid analgesic decreased during this period, again consistent with the expectation of decreasing pain intensity in the postoperative setting. The average duration of oral opioid therapy was approximately 4 days for abdominal and gynecologic surgery patients and about 5 days for orthopedic surgery patients. Approximately one third of the patients still required an opioid analgesic at the end of the 7-day study period (postoperative Day 7 for most patients). These durations of treatment correspond to the typical duration for moderately
severe pain previously reported for similar types of surgery, that is, 1–4 days following hysterectomy and 2–6 days following major joint surgery [1].

There were no unexpected safety concerns during the 7-day study period. The safety profile of CR oxycodone was typical of an opioid analgesic, with nausea, constipation, and pruritus being the most common adverse events. The most significant adverse event during this study was paralytic ileus, which occurred in four patients. Ileus is a potential complication of postoperative pain and can occur as a side effect with any opioid agonist regardless of the route of administration [1]. The type of surgery and surgical technique can also contribute to the occurrence of ileus. In this study, two of the four patients with paralytic ileus had undergone abdominal surgery. All four patients recovered with supportive therapy. Accordingly, it is recommended that bowel motility be monitored in postoperative patients who are receiving opioids, and stimulant laxatives be prescribed, if needed.

Oxygen saturation levels were measured throughout hospitalization since respiratory depression is the most serious potential side effect of opioid agonists such as oxycodone. No cases of respiratory depression were observed. Three of the four patients with low oxygen saturation levels (85–93%) had low baseline readings.

Conclusions

The results of this study demonstrated that, given at least 12 hours following abdominal, orthopedic, and gynecologic surgery, an initial daily oral CR oxycodone dose, calculated by multiplying the amount of IV morphine used in the previous 24 hours by a conversion factor of 1.2, on average, provided adequate pain control (pain intensity scores ≤4) during the subsequent 12-hour dosing interval and for a maximum of 7 days. In patients who were tolerant of oral medications and showed no signs of paralytic ileus, CR oxycodone given 12–24 hours after surgery was an effective analgesic for managing moderate-to-severe postoperative pain of an extended duration.

Acknowledgment

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References
