Parecoxib Sodium, a Parenteral Cyclooxygenase 2 Selective Inhibitor, Improves Morphine Analgesia and Is Opioid-sparing following Total Hip Arthroplasty

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Background: This study examined the opioid-sparing effectiveness, analgesic efficacy, and tolerability of postoperative administration of the parenteral cyclooxygenase 2 selective inhibitor, parecoxib sodium, in total hip arthroplasty patients.

Methods: This was a multicenter, multiple-dose, randomized, double-blind, placebo-controlled study to compare the opioid-sparing effects, analgesic efficacy, and tolerability of postoperative 20 and 40 mg intravenous parecoxib sodium with placebo in hip arthroplasty patients. The first dose of study medication was administered after surgery with an intravenous bolus dose of 4 mg morphine when patients first requested pain medication; remedication with the study medication occurred at 12 and 24 h. Subsequent morphine doses (1–2 mg) were administered by patient-controlled analgesia. Efficacy was assessed by total morphine used, pain relief and pain intensity, time to last dose of morphine, and Global Evaluation rating of the study medication.

Results: Parecoxib sodium, 20 and 40 mg, reduced the total amount of morphine required over 36 h by 22.1% (56.5 mg morphine) and 40.5% (45.1 mg morphine), respectively, compared with placebo (72.5 mg morphine; P < 0.01). Patients receiving 20 and 40 mg parecoxib sodium experienced significantly greater maximum pain relief compared with those in the placebo group (P < 0.05). Patients who received 20 and 40 mg parecoxib sodium discontinued PCA morphine earlier than patients receiving placebo and had significantly higher Global Evaluation ratings. Parecoxib sodium, 40 mg, plus morphine demonstrated a significantly lower incidence of fever and vomiting compared with placebo plus morphine.

Conclusions: Administration of parecoxib sodium with PCA morphine resulted in significantly improved postoperative analgesic management as defined by reduction in opioid requirement, lower pain scores, reduced time on PCA morphine, and higher Global Evaluation ratings.

OPIOID agents and nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used analgesics for the treatment of postoperative pain. Opioids are highly effective but are associated with a number of adverse effects, such as respiratory depression, alterations in mental status, ileus, constipation, nausea, and vomiting.1–5 Multimodal pain therapy that combines opioids with other analgesics has been recommended in postoperative surgical patients to reduce the need for opioids and improve overall analgesic management.4 NSAIDs have been used in combination with opioid analgesics to reduce postoperative opioid consumption.5–11

Nonsteroidal antiinflammatory drugs are nonselective inhibitors of both isoforms of cyclooxygenase (COX-1 and COX-2).12 COX-1 is constitutively expressed in many tissues, including platelets, the gastric mucosa, and kidney, and mediates the production of prostaglandins that are involved in homeostasis. COX-1 inhibition by nonselective NSAIDs leads to reduced platelet aggregation, an increased risk of upper gastrointestinal bleeding, and alterations in renal function.13–16 Because of the risk of increased bleeding, nonselective NSAID use is often limited in surgical patients.13,14 COX-2 is the therapeutic target of both nonselective NSAIDs and COX-2 selective inhibitors. However, COX-2 selective inhibitors do not inhibit COX-1 at therapeutic doses and are associated with a significantly reduced degree of platelet inhibition and ulcerogenic side effects compared with nonselective NSAIDs.17–24

Some nonselective NSAIDs, such as parenteral ketorolac (Toradol®; Roche, Nutley, NJ),6,8 and the oral COX-2 selective inhibitors rofecoxib and celecoxib,25,26 provide opioid-sparing effects when administered in postoperative surgical patients. Substantial numbers of surgical patients, however, cannot tolerate postoperative oral medication, and ketorolac is associated with decreased platelet aggregation, increased bleeding time, and gastrointestinal ulceration and bleeding.27–29 Therefore, there is a need for parenteral analgesic agents that can be administered to surgical patients without an increased risk of bleeding. Parecoxib sodium, the first parenteral COX-2 selective inhibitor to be developed for the management of pain, is a prodrug that is rapidly hydrolyzed in vivo to its active form, valdecoxib, which is approximately 28,000-fold more potent against COX-2 than COX-1.30 Recent research has demonstrated that parecoxib sodium is effective in treating postoperative oral surgery, orthopedic surgery, and abdominal hysterectomy pain,31–34 while other studies have demonstrated that parecoxib sodium has no significant effects on platelet function55 or the upper gastrointestinal mucosa.36,37 As a result of these studies, parecoxib sodium has been approved for the short-term treatment of post-
operative pain in Europe at a dose of 40 mg (to be administered intravenously or intramuscularly).

This study was designed to test the hypothesis that parecoxib sodium would improve analgesia when coadministered with morphine while reducing postoperative morphine requirements when administered following major orthopedic surgery.

Materials and Methods

Patients

The study subjects were men and women aged older than 18 yr who required a primary or revised unilateral total hip arthroplasty under spinal or general anesthesia. Patients’ preoperative health had to be graded as class I–III according to the American Society of Anesthesiologists physical status classification, based on medical history and physical examination. All patients provided written informed consent prior to enrollment. Patients who had an acute fracture of the hip, had trauma to the hip, or were due to undergo emergency hip replacement were excluded. Finally, patients who had used analgesics or any other agent that could interfere with analgesic responses during the 6 h preceding surgery were not eligible. Specifically, this included NSAIDs, tricyclic antidepressants, neuroleptic or antipsychotic agents, or corticosteroids. Eligible patients were randomized to treatment according to a computer-generated schedule in the order in which they were enrolled.

Study Design

This multicenter, multiple-dose, randomized, double-blind, placebo-controlled, parallel group study was conducted in eight hospitals in the United States (Appendix), in accordance with the principles of good clinical practice and the Declaration of Helsinki. The appropriate Institutional Review Boards approved the study. All study participants were blinded to the identity of the treatments until all study data had been collated in a database. The study was conducted between July 30, 1999 and October 9, 2000.

Patients received their first dose of study medication, 20 mg parecoxib sodium, 40 mg parecoxib sodium, or placebo, administered as a 2-ml intravenous dose, along with their first-bolus intravenous dose of 4 mg morphine sulfate, after the end of surgery, when they requested medication for pain. Thereafter, patients self-medicated with morphine (1–2 mg/dose) using a patient-controlled analgesia (PCA) pump with a 6-min lockout. PCA morphine was permitted at any time. Remedication with placebo, 20 mg parecoxib sodium, or 40 mg parecoxib sodium occurred at 12 and 24 h after the first dose.

The sample size estimate for the study was based on published data indicating the average amount of morphine consumed by PCA and bolus within 24 h in a placebo group in a similar surgical setting (i.e., 34.6 mg). Using these data, it was estimated that a sample size of 60 patients would be sufficient to detect a difference of at least 25% between placebo and 20 or 40 mg parecoxib sodium in the total dose of morphine consumed within 24 h of the first study medication dose, with an estimate of variability of 14.0 and 80% power, with type 1 error of 0.025.

Efficacy Assessments

All doses of morphine were recorded, including the date and time of administration. The total amount of morphine consumed at 12, 24, and 36 h and the amount of morphine consumed during specific time periods after administration of the first dose of study medication were measured.

Pain intensity assessments were completed by the patients at 2, 4, 6, 9, 12, 18, 24, and 36 h after the first dose of study medication. Pain intensity levels were assessed on a four-point categorical scale where 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Patients recorded maximum pain intensity on the same scale at the end of the 36-h period or at the time of early withdrawal from the study. Maximum pain relief was recorded at the end of the 36-h period or at the time of early withdrawal from the study. Pain relief was assessed on a five-point scale, where 0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete.

Patients completed a Global Evaluation of study medication at 12, 24, and 36 h after the administration of study medication. They were asked to rate the study medication that they had received according to a four-point scale, where 1 = poor, 2 = fair, 3 = good, and 4 = excellent. The time to the last dose of morphine was recorded for each patient.

Tolerability and Safety Assessments

General clinical tolerability/safety was monitored by the incidence of patient-reported treatment-emergent adverse events and clinical laboratory tests. Adverse events reported by patients were confirmed by the investigators and recorded. Patient vital signs were monitored by the study staff.

Statistical Analysis

Efficacy data were based on the modified intent-to-treat cohort, which consisted of all randomized patients who received study medication, who did not withdraw before 24 h from the first dose of study medication for reasons other than discontinuation of PCA morphine because of lack of pain, who had 24-h total morphine consumption data, and whose surgery was no more than 4 h in duration. Efficacy analyses were performed using the Last Observation Carried Forward approach. The cumulative amount of morphine consumed at specific time points, the amount of morphine consumed for each
time period, and time-specific pain intensity difference (categorical) were analyzed using analysis of covariance with treatment and center as factors and baseline pain intensity as a covariate. Pain intensity difference was calculated as the difference between baseline pain intensity score and pain intensity at specific time points.

Maximum pain intensity, maximum pain relief, and Patient’s Global Evaluation of study medication were analyzed using the Cochran-Mantel-Haenszel test stratified by center. Time to last dose of morphine for each treatment group was calculated using the Kaplan-Meier product estimator, using the adjustment suggested by Miller, and 95% confidence intervals for the median time to last dose of morphine were calculated using the method of Simon and Lee. A log-rank test with Fisher least significant difference was used to determine the statistical significance of the overall treatment group difference in the distribution of the time to the last dose of morphine. Pairwise comparisons were conducted between treatment groups if the overall test result was significant.

Each randomized patient who received at least one dose of study medication was included in the tolerability/safety analysis. The incidence of treatment-emergent adverse events was tabulated by treatment group, body system, and degree of severity.

Results

Patients

A total of 201 patients were randomized to receive study medication and were included in the analyses of demographics, other baseline characteristics, and safety assessment. There were no significant differences across treatment groups with respect to demographics, baseline vital signs, type or duration of surgical procedure, type or duration of anesthesia, baseline pain intensity, or time from end of surgery to administration of study medication (table 1). Randomized patients who received study medication, who did not withdraw before 24 h following the first dose of study medication for reasons other than discontinuation of PCA morphine because of lack of pain, and for whom complete morphine dosing information was available were included in the modified intent-to-treat cohort. Efficacy data were based on this modified intent-to-treat cohort (n = 181), which included 65 patients who received placebo, 61 patients who received 20 mg parecoxib sodium, and 55 patients who received 40 mg parecoxib sodium. Patients who withdrew for reasons other than discontinuation of PCA morphine because of lack of pain (four in the placebo, two in the 20 mg parecoxib sodium, and six in the 40 mg parecoxib sodium groups) or who did not have 24 h of valid morphine data (one in the placebo, four in the 20 mg parecoxib sodium, and three in the 40 mg parecoxib sodium groups) were not included in the modified intent-to-treat cohort.

Morphine Use

The mean total cumulative amount of morphine administered over the 36-h period following the end of surgery was statistically significantly less in both parecoxib sodium groups compared to placebo (22.1% less in the 20 mg parecoxib sodium group and 40.5% less in the 40 mg parecoxib sodium group; P < 0.01 for both active treatment groups vs. placebo; table 2). Total mor-

<table>
<thead>
<tr>
<th>Table 1. Patient Baseline Characteristics</th>
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<tr>
<td></td>
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<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Female, %</td>
</tr>
<tr>
<td>Hip arthroplasty</td>
</tr>
<tr>
<td>Left, %</td>
</tr>
<tr>
<td>Type of anesthesia</td>
</tr>
<tr>
<td>General, %</td>
</tr>
<tr>
<td>Time from end of surgery to medication, h</td>
</tr>
<tr>
<td>Baseline pain intensity, categorical score</td>
</tr>
<tr>
<td>Mild, %</td>
</tr>
<tr>
<td>Moderate, %</td>
</tr>
<tr>
<td>Severe, %</td>
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</table>

Data presented as mean ± SD.
Phenylethylamine consumption over 24 h after the first dose of study medication was significantly lower in the 20 and 40 mg parecoxib sodium groups (21.7% and 38.8% less morphine, respectively) compared with placebo ($P < 0.05$; table 2).

Mean morphine use in specific time intervals in the placebo group was greater than in either parecoxib sodium treatment group. Patients taking 40 mg parecoxib sodium consumed significantly less morphine during all specific time periods between 6 and 36 h compared with those taking placebo ($P < 0.05$; fig. 1). Patients receiving 20 mg parecoxib sodium consumed statistically significantly less morphine during the 12- to 18-h interval after surgery compared with placebo ($P < 0.05$). There were no significant differences between the 20 and 40 mg parecoxib sodium treatment groups with respect to the amount of morphine consumed at specific time intervals throughout the study.

A statistically greater proportion of patients in each parecoxib sodium group no longer required morphine at 12, 24, and 36 h compared with patients in the placebo group ($P < 0.01$; table 3). At 36 h following the end of surgery, nearly a third of patients in the 40 mg parecoxib sodium group no longer required morphine compared with less than 10% in the placebo group ($P < 0.01$). Overall, patients in the 40 mg parecoxib sodium group received their last dose of morphine sooner than the other treatment groups. Time to last dose of morphine in the 40 mg parecoxib sodium group (34 h 3 min) was significantly different than those in the placebo (35 h 39 min) and 20 mg parecoxib sodium (35 h 34 min) groups ($P < 0.05$).

**Pain Relief and Pain Intensity**

Parecoxib sodium coadministered with morphine provided greater pain relief than morphine plus placebo. An overall comparison showed a statistically significant increase in maximum pain relief at the end of the 36-h study period after the first dose of study drug ($P < 0.05$). Maximum pain relief was categorized as “a lot” or “complete” by 85.2% of patients in the 20 mg parecoxib sodium group and 81.8% of patients in the 40 mg parecoxib sodium group compared with 61.9% of patients receiving placebo (fig. 2). Pairwise treatment comparisons with respect to maximum pain relief demonstrated significant differences between the placebo group and both parecoxib sodium treatment groups ($P < 0.05$).

The number needed to treat for maximum pain relief was calculated based on patients who experienced “a

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Table 3. Percentage of Patients Not Requiring PCA Morphine at 12, 24, and 36 h After the First Dose of Study Medication

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Placebo (n = 61), %</th>
<th>20 mg Parecoxib Sodium (n = 59), %</th>
<th>40 mg Parecoxib Sodium (n = 52), %</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 h</td>
<td>0</td>
<td>1.6</td>
<td>9.1</td>
<td>0.02</td>
</tr>
<tr>
<td>24 h</td>
<td>6.2</td>
<td>8.2</td>
<td>25.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>36 h</td>
<td>9.2</td>
<td>9.8</td>
<td>30.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

$^*$ Fisher Exact Test of parecoxib sodium 40 mg vs. placebo.

*PCA = patient-controlled analgesia

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Fig. 2. Maximum pain relief. Patients receiving 20 and 40 mg intravenous parecoxib sodium experienced significantly greater pain relief at 36 h ($P < 0.05$, $^{\ddagger}P < 0.01$).
lot" or "complete" pain relief on the five-point categorical scale and favored 20 or 40 mg parecoxib sodium plus morphine versus placebo plus morphine (40 mg parecoxib sodium number needed to treat = 1.22, 20 mg parecoxib sodium number needed to treat = 1.17, and placebo [morphine alone] number needed to treat = 1.62).

Time-specific pain intensity, as assessed by pain intensity difference, was significantly improved in the 40 mg parecoxib sodium group at 4, 6, 9, 12, 18, and 24 h and in the 20 mg parecoxib sodium group at 4, 6, and 9 h, compared with placebo (P < 0.05).

**Patient's Global Evaluation of Study Medication**

Patients receiving 20 and 40 mg parecoxib sodium reported a significantly better Global Evaluation of their study medication at the 36-h time point compared with patients in the placebo group (fig. 3). The study medication was described as "excellent" by 43% and 60% of patients in the 20 and 40 mg parecoxib sodium treatment groups, respectively, compared with 22% of placebo patients (P < 0.001).

**Safety and Tolerability**

The incidence of adverse events reported or observed in at least 5% of patients are presented in table 4. Significantly lower incidences of fever and vomiting were observed for the 40 mg parecoxib sodium group compared with placebo (P < 0.05; table 4). A slightly higher incidence of postoperative anemia (defined by a decrease in hemoglobin of > 2.0 g/dl from baseline, a decrease in hematocrit of > 0.05 from baseline, or reduced erythrocyte count) was noted in the 40 mg parecoxib sodium group compared to the other groups. There were no investigator-reported adverse events related to excessive surgical bleeding, wound complications, renal dysfunction (no patient developed a creatinine concentration exceeding 1.6 mg/dl), cardiovascular-related events, or gastrointestinal bleeding in any of the treatment groups.

**Discussion**

Oral COX-2 selective inhibitors have demonstrated opioid-sparing effects following surgery. This study demonstrated that parecoxib sodium, the first parenteral COX-2 selective inhibitor, was opioid sparing and improved morphine analgesia in patients following total hip arthroplasty. The addition of 40 mg intravenous parecoxib sodium resulted in a significant reduction of approximately 40.5% in the amount of PCA morphine consumed by patients while reducing the amount of pain experienced and improving patients' overall analgesic management experience. Moreover, patients receiving 40 mg parecoxib sodium were able to discontinue use of PCA morphine significantly faster: 25% by 24 h and nearly a third of patients by 36 h, compared with just 9% of patients receiving morphine plus placebo by 36 h. Compared to treatment with morphine plus placebo, treatment with parecoxib sodium resulted in a significant reduction in fever and nausea.

The finding that parecoxib sodium coadministration with morphine results in an opioid-sparing effect is not unexpected. Parecoxib sodium is an antiinflammatory and analgesic agent that has been shown to have efficacy similar to that of ketorolac in treating postoperative pain.31,32,34 The importance of the current study is the demonstration that selective COX-2 inhibition results in opioid-sparing analgesia and that COX-1 inhibition, which occurs with typical nonselective NSAIDs, is not required for this effect.

The use of NSAIDs or other opioid-sparing agents to reduce opioid requirements is recommended by regula-

**Table 4. Incidence of Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 70), %</th>
<th>20 mg Parecoxib Sodium (n = 67), %</th>
<th>40 mg Parecoxib Sodium (n = 64), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>78.6</td>
<td>71.6</td>
<td>76.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>45.7</td>
<td>38.8</td>
<td>39.1</td>
</tr>
<tr>
<td>Fever</td>
<td>22.9</td>
<td>11.9</td>
<td>4.7†</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.7</td>
<td>19.4</td>
<td>4.7†</td>
</tr>
<tr>
<td>Pruritis</td>
<td>11.4</td>
<td>4.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Postoperative</td>
<td>10.0</td>
<td>7.5</td>
<td>14.1</td>
</tr>
<tr>
<td>anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.7</td>
<td>3.0</td>
<td>4.7†</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5.7</td>
<td>0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Significantly different versus placebo: *P < 0.05, †P < 0.01.
tory agencies such as the Agency for Health Care Policy and Research. Moreover, it is consistent with the common practice of multimodal analgesia, which is used to maximize pain relief while minimizing drug-related adverse events. Nonetheless, these recommendations and the practice of multimodal analgesia, concomitant administration of parenterally available NSAIDs with opioids is often limited because of the antiplatelet effects and ulcerogenic properties of nonselective NSAIDs.

The value of opioid-sparing analgesia with parecoxib sodium is demonstrated in this investigation. The primary goal of postoperative analgesic care is to decrease levels of pain and to improve the postoperative experience and recovery for patients. In this study, parecoxib sodium-treated patients have improved maximum pain relief and Global Evaluation scores compared to placebo-treated patients. A recently published study demonstrated that 20 and 40 mg parecoxib sodium provided significant opioid-sparing effects in patients undergoing lower abdominal surgery but did not improve postoperative pain management or opioid-related side effects. However, this study involved a different surgical model and a relatively small number of patients (n = 55), which might reflect the lack of statistical significance observed in these two endpoints. The magnitude of the improvement in pain indices and patient Global Evaluation for 40 mg parecoxib sodium compared to placebo were nearly identical in the two studies, supporting the conclusion that parecoxib sodium is an effective analgesic and that the abdominal surgery study was simply underpowered for adequate comparison of the analgesic effects. Another study, in patients undergoing total knee arthroplasty, demonstrated that treatment with 20 or 40 mg parecoxib sodium plus morphine produced significant opioid-sparing effects and significantly improved postoperative pain management compared with morphine alone.

There have been some recent concerns and it has been hypothesized that COX-2 selective inhibitors might increase the risk of thromboembolic events due to inhibition of PG12 in the vascular endothelium, without the concomitant inhibition of platelet COX-1 that occurs with nonselective NSAIDs. However, the controversy that has arisen applies to data published from trials in arthritis patients, and the relevance to postoperative patients on short-term therapy is unclear. In this study, no cardiovascular adverse events, including myocardial infarction, thromboembolism, or deep vein thrombosis, were observed by the investigators, lending no support to concerns regarding the cardiovascular safety of coxibs.

Improvement in postoperative analgesic management has become a major initiative for American healthcare institutions. This study suggests that parecoxib sodium may be a useful adjunct to morphine in the treatment of postoperative pain. Since parecoxib sodium use resulted in a more rapid discontinuation of PCA morphine, the opportunity for further mobilization of patients, participation in the rehabilitation process, and faster overall recovery from surgery may be possible. Along with faster discontinuation of morphine, a reduction in some opioid-associated adverse effects such as vomiting indicates that patients may experience a more comfortable postoperative recovery with use of parecoxib sodium. These differences were seen in addition to favorable trends for nausea and other narcotic-related adverse experiences that contribute to the experience of postoperative nausea or vomiting and that are difficult to achieve in the context of a limited sample size and complexity of factors. Overall, the combination of better analgesia and reduced side effects is supported by the higher Global Evaluation ratings for patients treated with parecoxib sodium plus morphine than patients treated with morphine alone. Together, this combination of findings supports the value of parecoxib sodium in postoperative analgesic management.

References

3. Wheeler M, Oderda G, Ashburn M, Lipman A: A reevaluation of the practice of multimodal analgesia, concomitant administration of parenterally available NSAIDs with opioids and a relatively small number of patients (n = 55), which might reflect the lack of statistical significance observed in these two endpoints. The magnitude of the improvement in pain indices and patient Global Evaluation for 40 mg parecoxib sodium compared to placebo were nearly identical in the two studies, supporting the conclusion that parecoxib sodium is an effective analgesic and that the abdominal surgery study was simply underpowered for adequate comparison of the analgesic effects. Another study, in patients undergoing total knee arthroplasty, demonstrated that treatment with 20 or 40 mg parecoxib sodium plus morphine produced significant opioid-sparing effects and significantly improved postoperative pain management compared with morphine alone.

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