Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia

R. C. Hubbard1*, T. M. Naumann2, L. Traylor1 and S. Dhadda1

1Pharmacia, 5200 Old Orchard Road, Skokie, IL 60077, USA. 2Hessing’sche Orthopedic Clinic, Hessingstr, Augsburg, Germany

*Corresponding author. E-mail: richard.c.hubbard@pharmacia.com

Background. This multicentre, double-blind, placebo-controlled study compared the opioid-sparing effectiveness and clinical safety of parecoxib sodium over 48 h, in 195 postoperative patients after routine total knee replacement surgery.

Methods. Elective total primary knee arthroplasty was performed under spinal anaesthesia, with a single dose of spinal bupivacaine 10–20 mg, and intraoperative sedation with midazolam 0.5–1.0 mg i.v., or propofol <6 mg kg⁻¹ h⁻¹. Patients were randomized to receive either parecoxib sodium 20 mg twice daily (bd) i.v. (n=65), parecoxib sodium 40 mg bd i.v. (n=67), or placebo (n=63) at the completion of surgery, and after 12, 24, and 36 h. Morphine (1–2 mg) was taken by patient-controlled analgesia or by bolus doses after 30 min.

Results. Patients receiving parecoxib sodium 20 mg bd and 40 mg bd consumed 15.6% and 27.8% less morphine at 24 h than patients taking placebo (both P<0.05). Both doses of parecoxib sodium administered with morphine provided significantly greater pain relief than morphine alone from 6 h (P<0.05). A global evaluation of study medication demonstrated a greater level of satisfaction among patients taking parecoxib sodium than those taking placebo. Parecoxib sodium administered in combination with morphine was well tolerated. However, a reduction in opioid-type side-effects was not demonstrated in the parecoxib sodium groups.

Conclusion. Parecoxib sodium provides opioid-sparing analgesic effects in postoperative patients.

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Postsurgical pain has commonly been managed with opioid analgesics alone. Although effective, opioids (e.g. morphine) are associated with adverse effects such as respiratory depression, sedation, nausea, vomiting, constipation, and intestinal ileus.1–4 The availability of an effective, but safer analgesic, that would be co-administered and reduce the amount of opioids used, would therefore be an advantage. Conventional non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac have been shown to produce opioid-sparing effects when administered to postoperative surgical patients.5,6 However, these agents are associated with reduced platelet function, leading to prolonged bleeding time, and gastric ulceration.7–10 The clinical utility of conventional NSAIDs has, therefore, been considered to be limited in the postoperative setting.

Cyclo-oxygenase-2 (COX-2) selective inhibitors, which only inhibit COX-2 and not COX-1 at therapeutic doses, have been developed. Several studies have shown that they provide efficacy similar to conventional NSAIDs, but with improved safety and tolerability.11–14 However, until now, COX-2 selective inhibitors have only been available as oral formulations, which many patients may be unable to take, especially in the perioperative period. Parecoxib sodium is the first parenteral form of a COX-2 selective inhibitor developed for acute pain. It is an amide pro-drug that is rapidly hydrolysed in vivo to the active form, valdecoxib, a COX-2 selective inhibitor with a COX-2:COX-1 selectivity ratio of approximately 28 000:1. Clinical studies have

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demonstrated that parecoxib sodium is effective in several models of postoperative pain. In additional studies, parecoxib sodium has been shown to have no effect on platelet function or gastric mucosa at doses up to 40 mg twice daily (bd).  

The present study was designed to compare the opioid-sparing effectiveness and clinical safety of parecoxib sodium 20 mg bd i.v. and 40 mg bd i.v. over a 48-h period in postoperative patients after total knee replacement, a surgical model known to cause severe pain.

Methods
This was a multicentre, randomized, double-blind, placebo-controlled, multiple-dose study conducted at 10 sites in Belgium, France, Germany, and Sweden. Enrolment ranged from 13 to 33 patients per participating investigator, and was conducted between December 1999 and August 2000. The protocol and amendments were reviewed by the appropriate independent ethics committees, and the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Patients
Patients aged ≥18 yr, who had undergone routine total primary replacement of one knee, performed under a standardized regimen of spinal anaesthesia, were included in the study. All patients received a single dose of spinal bupivacaine 10–20 mg, and intraoperative sedation with midazolam 0.5–1.0 mg i.v., or propofol <6 mg kg⁻¹ h⁻¹. Eligible patients were in satisfactory health, as determined by medical history and physical examination. Women were eligible for the study only if they were not lactating and verified as not being pregnant.

Patients were excluded from the study if they had undergone a revision to a previous knee replacement, emergency knee replacement, or knee replacement as a result of a trauma. Patients with asthma or bronchospasm, requiring treatment with glucocorticoids, were excluded, as were those with inflammatory bowel disease, a chronic or acute renal or hepatic disorder, or a significant coagulation defect. Patients were not considered eligible if they had upper gastrointestinal ulceration or bleeding up to 60 days before receiving study medication. In addition, patients were excluded if they had used long-acting NSAIDs in the 4 days before the first dose of study medication, or if they had taken antidepressants, narcotic analgesics, antihistamines, antiulcer, hypnics, sedatives, NSAIDs, or corticosteroids up to 24 h before receipt of the study medication (except routine preoperative medication).

Study design
During the pretreatment period, defined as 14 days before the administration of study medication, written informed consent and medical history were obtained, and patients underwent physical examination, and testing of vital signs and clinical laboratory values. Elective total knee arthroplasty was performed under spinal anaesthesia. Duration of analgesia was defined as the time from initiation of spinal analgesia until the first toe movements after operation. Patients were eligible for enrolment at the end of surgery.

Patients were randomized, according to a computer-generated randomization schedule, to receive either parecoxib sodium 20 mg bd i.v., parecoxib sodium 40 mg bd i.v., or placebo i.v. at the completion of surgery, and at 12, 24, and 36 h after the administration of the first dose of study medication. Morphine doses (1–2 mg) could be taken by patient-controlled analgesia (PCA) or by bolus, and were permitted at any time from 30 min after the end of surgery. Patients remained at the study site until after the final assessment at 48 h. Those requiring further analgesia at any time point in addition to morphine and the study medication were withdrawn from the study after completing pain assessments and a global evaluation of the study medication.

Patients’ assessments
Patients assessed their pain intensity as ‘none’, ‘mild’, ‘moderate’ or ‘severe’ at 2, 4, 6, 9, 12, 18, 24, 36 and 48 h after administration of the first dose of study medication. If patients were asleep during the scheduled time for pain assessment, they were not awakened, except at the 12-, 24-, and 36-h assessments, which were performed immediately before the receipt of study medication. Ambulation was restricted for 15 min before each pain assessment.

Patients also provided a global evaluation of study medication at 24 h (before the administration of the third dose of study medication), and at 48 h after the administration of the first dose of study medication, using a four-point scale (1=poor, 2=fair, 3=good, 4=excellent).

Efficacy and safety endpoints
Efficacy measures included the cumulative amount of morphine consumed at 2, 4, 6, 9, 12, 18, 24, 36, and 48 h, and the amount of morphine consumed in the periods 0–2, 2–4, 4–6, 6–9, 9–12, 12–18, 18–24, 24–36 and 36–48 h after the first dose of study medication. Other efficacy measures were the proportion of patients requiring morphine between the time points; time to the first dose of morphine; time to the last dose of morphine; and patients’ global evaluation of the study medication.

Safety was assessed for the 48 h after the first dose of study medication by the incidence of treatment-emergent adverse events, results from physical examinations, and changes from baseline in vital signs and clinical laboratory values (biochemistry, haematology and urinalysis).
Statistical analyses
The sample size calculation was based on the amount of morphine expected to be consumed within 24 h, and determined that 60 patients per group would be sufficient to detect a difference of \( \geq 20\% \) decrease in the total amount of morphine used over the 24-h postoperative dose period between parecoxib sodium 20 mg bd, parecoxib sodium 40 mg bd, and placebo groups.21

All efficacy analyses were performed on the modified intent-to-treat (ITT) cohort. This included all patients who were randomized, received at least one dose of study medication, underwent a surgical procedure of no more than 4 h duration, did not require additional analgesic medication within the first 30 min, and were connected to PCA within 140 min of surgery.

The cumulative amount of morphine administered at each time point, and the amount of morphine consumed during each fixed time interval, was analysed using analysis of variance (ANOVA), with treatment and centre as factors. The median time to the first and last dose of morphine was calculated using the Kaplan–Meier product limit estimator with Miller’s adjustment. For patients who withdrew from the study before 48 h, the time to the last dose of morphine was considered censored at the time of withdrawal.22 Ninety-five per cent confidence intervals for the median time to the last dose of morphine were calculated using the Simon and Lee method.23 Overall and pair-wise log-rank tests were used to determine the statistical significance of the treatment group differences in the distribution of time to the first dose of morphine and to the last dose of morphine. The proportion of patients requiring morphine during each time period, and patients’ global evaluation were analysed using the Cochran–Mantel–Haenszel test, adjusted by centre. Effect of sex on morphine consumption was analysed using Fisher’s exact test.

Time-specific pain intensity (categorical) was analysed using ANOVA. Linear interpolation was used to estimate one to two missing values, and the last-observation-carried-forward method was used if there were three or more consecutive missing values, or if there were no evaluations after a certain time point.

Results
Patients
A total of 195 patients were randomized to placebo \((n=63)\), parecoxib sodium 20 mg bd \((n=65)\), or parecoxib sodium 40 mg bd \((n=67)\). The physical characteristics of the treatment groups were comparable; most patients were female (68–78%) and Caucasian (97–100%). In addition, there were no differences between treatment groups in the type of surgical procedure (surgery on right or left knee), duration of surgery, or duration of anaesthesia (Table 1).

A total of 19 (10%) patients were withdrawn from the study (Table 2), thus 176 (90%) patients completed it. The analyses of efficacy measures were performed on the ITT cohort, which included all patients who were randomized, received at least the first dose of study medication, whose operative time was <4 h, did not require analgesia within 30 min of the end of surgery, and whose PCA was instituted within 140 min of wound closure. The ITT cohort included 189 patients: 63 patients in the placebo group; 61 patients in the parecoxib sodium 20 mg bd group; and 65 patients in the parecoxib sodium 40 mg bd group.

Morphine use
Analysis of the modified ITT cohort demonstrated that patients receiving parecoxib sodium 20 mg bd or 40 mg bd consumed significantly less morphine at 24 h than patients taking placebo (both \( P<0.05 \); Fig. 1). Mean cumulative amounts of morphine consumed over 24 h were 43.5 mg in the placebo group, and 36.7 mg and 31.4 mg in the

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Table 1 Patient characteristics. Data are actual values, or mean (range or %)

<table>
<thead>
<tr>
<th></th>
<th>Placebo ((n=63))</th>
<th>Parecoxib sodium 20 mg bd i.v. ((n=65))</th>
<th>Parecoxib sodium 40 mg bd i.v. ((n=67))</th>
<th>( P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68.2 (34–89)</td>
<td>70.0 (42–86)</td>
<td>68.6 (43–83)</td>
<td>0.420</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.103</td>
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<tr>
<td>Caucasian</td>
<td>61 (97)</td>
<td>65 (100)</td>
<td>66 (99)</td>
<td></td>
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<tr>
<td>Black</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian/oriental</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0.416</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49 (78)</td>
<td>44 (68)</td>
<td>49 (73)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (22)</td>
<td>21 (32)</td>
<td>18 (27)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.08 (144.0–186.0)</td>
<td>166.42 (148.0–192.0)</td>
<td>163.58 (142.0–184.0)</td>
<td>0.224</td>
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<tr>
<td>Weight (kg)</td>
<td>80.85 (46.0–112.0)</td>
<td>79.19 (44.0–109.0)</td>
<td>80.77 (48.0–115.0)</td>
<td>0.601</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
<td>0.189</td>
</tr>
<tr>
<td>Right knee</td>
<td>37 (59)</td>
<td>28 (43)</td>
<td>36 (54)</td>
<td></td>
</tr>
<tr>
<td>Left knee</td>
<td>26 (41)</td>
<td>37 (57)</td>
<td>31 (46)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (h)</td>
<td>1.5 (0.7–2.6)</td>
<td>1.39 (0.7–2.4)</td>
<td>1.46 (0.6–2.6)</td>
<td>0.136</td>
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<tr>
<td>Duration of anaesthesia (h)</td>
<td>3.88 (2.0–8.6)</td>
<td>3.82 (1.7–8.1)</td>
<td>3.89 (1.8–8.7)</td>
<td>0.814</td>
</tr>
</tbody>
</table>
Parecoxib sodium 20 mg bd and 40 mg bd groups, respectively.

Patients in the parecoxib sodium groups consumed less morphine than patients in the placebo group throughout the study. The reductions in morphine consumption with parecoxib sodium compared with placebo were significant during the 6–9 and 18–24 h time intervals for the 20 mg bd dose, and during the 4–6, 6–9 and 18–24 h time intervals for the 40 mg bd dose (Fig. 2). At each time point after surgery, both doses of parecoxib sodium reduced the cumulative morphine consumption compared with placebo (Fig. 3). These reductions were significant for patients taking parecoxib sodium 40 mg bd at every time point from 6 h ($P<0.004$). In patients taking parecoxib sodium 20 mg bd, significant reductions in morphine consumption compared with placebo were obtained at 9 and 24 h.

In each time period, the proportion of patients requiring morphine was lower in the parecoxib sodium groups than in the placebo group (except the parecoxib sodium 40 mg bd group at 2–4 h). At 9–12 h, the parecoxib sodium 40 mg bd group had a significantly ($P<0.011$) lower percentage of patients requiring morphine than the placebo group. The three treatment groups were comparable with respect to both median time to the first dose of morphine (range 1.53–2.02 h) and median time to the last dose of morphine (range 44.02–46.30). The use of morphine was not affected by the patient’s sex ($P=0.19$).

### Pain intensity

Parecoxib sodium administered with morphine provided greater pain relief than morphine alone at every time point after surgery compared with placebo. The reductions in pain intensity with both doses of parecoxib sodium were statistically significantly different compared with placebo at 6 h, 24 h, and 36 h ($P<0.005$; Fig. 4). There were no significant differences in pain intensity between the two parecoxib sodium treatment groups at any time point.

### Patients’ global evaluation of study medication

The patients’ global evaluation of study medication showed that patients treated with parecoxib sodium had greater

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**Table 2** Patient numbers during the study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Parecoxib sodium 20 mg bd i.v.</th>
<th>Parecoxib sodium 40 mg bd i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>63</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>Completed study</td>
<td>55</td>
<td>57</td>
<td>64</td>
</tr>
<tr>
<td>Reason for withdrawal</td>
<td></td>
<td>Adverse events</td>
<td>Treatment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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patient satisfaction scores than those taking placebo treatment. At 24 h after the first dose of study medication, both doses of parecoxib sodium were associated with significantly better scores than placebo ($P<0.018$). The percentage of patients who rated their study medication as ‘good’ or ‘excellent’ was 71% and 79% in the parecoxib sodium 20 mg bd and 40 mg bd groups, compared with 53% in the placebo group (Fig. 5). At 48 h, parecoxib sodium 40 mg bd was associated with statistically significantly better scores than placebo ($P=0.004$). A total of 92% of patients rated their study medication as ‘good’ or ‘excellent’, compared with 70% in the placebo group. After 48 h of treatment, parecoxib sodium 20 mg bd i.v. had numerically, but not statistically significantly, better scores than placebo ($P=0.083$). A total of 84% of parecoxib sodium 20 mg bd-treated patients rated their study medication as ‘good’ or ‘excellent’.

**Safety**

All 195 patients were included in the analysis of safety. The overall incidence of adverse events among the three treatment groups was similar. Adverse events were reported for 68.3% (43/63) of patients in the placebo group, 66.2% (43/65) of patients in the parecoxib sodium 20 mg bd group, and 70.1% (47/67) of patients in the parecoxib sodium 40 mg bd group. Patients receiving parecoxib sodium 40 mg bd experienced significantly less fever than placebo patients (1.5% vs 19.0%; $P<0.001$; Table 3). The incidence of opioid-type side-effects (nausea, vomiting, constipation, intestinal ileus, central nervous system effects) was similar. The use of antiemetic medication was not different between groups. Most (>85%) of the adverse events in each group were mild to moderate in severity. Adverse events experienced by >5% of patients in any treatment group are summarized in Table 3.

Only one patient in each parecoxib sodium group discontinued treatment as a result of adverse events: pruritus and rash in one patient taking parecoxib sodium 20 mg bd; and vomiting in one patient taking parecoxib sodium 40 mg bd. In the placebo group, three patients discontinued treatment because of adverse events: they were nausea and vomiting; nausea and hypertension; and nausea. One placebo-treated patient died during the study from an acute pulmonary embolism.

**Discussion**

This study shows that parecoxib sodium 20 mg and 40 mg bd i.v. produces significant opioid-sparing effects compared with placebo in postoperative patients after knee replacement surgery. Mean morphine consumption over 24 h was reduced by 15.6% and 27.8% in the parecoxib sodium 20 mg bd and 40 mg bd groups, respectively. At each time point over the 48-h postoperative period, both doses of parecoxib sodium reduced morphine consumption in a dose-dependent manner compared with placebo. The combination of better pain control and tolerability in the presence of parecoxib sodium affected the patients’ global evaluation of the study.
medication as, at 24 and 48 h, there was a greater level of satisfaction among patients taking parecoxib sodium than those taking placebo.

The use of analgesic combination therapy to achieve reductions in opioid use and improved pain control, as recommended by The Royal College of Anaesthetists and others, is supported in this study. Patients in the parecoxib sodium treatment groups not only required less morphine, but experienced greater pain relief than patients receiving morphine alone at every time point after surgery compared with placebo. These results demonstrate one advantage of multi-model therapy, that patients experience less pain even though they require less narcotic.

Parecoxib sodium is a COX-2 selective inhibitor, which reduces the number of adverse events associated with non-selective COX-1 inhibition. These include upper gastrointestinal ulceration and bleeding, renal dysfunction, and bleeding related to platelet inhibition. In this study, parecoxib sodium 20 mg bd i.v. and 40 mg bd i.v. were safe and well tolerated, as most of the adverse events in each group were mild to moderate in intensity. There were no clinically important adverse gastrointestinal, platelet-related, or renal side-effects observed in this trial, although the numbers studied were relatively small.

A reduction in opioid-type side-effects was not demonstrated in this study, however. Some postoperative side-effects, such as nausea and vomiting, which had a higher incidence in patients taking parecoxib sodium 40 mg bd than in patients taking parecoxib sodium 20 mg bd or placebo, are affected by multiple factors in the surgical environment. For example, the type of surgery, the anaesthetic and associated medication, and the pain itself. It may not be a reasonable expectation that the occurrence of such multifactorial events in the immediate postoperative period would be modified by postoperative administration of parecoxib sodium. There are several other potential explanations for the absence of any reduction in opioid-type side-effects. First, opioid symptoms and physiological effects were not prospectively identified for specific measurement in this trial. The use of specific data collection instruments (such as the Opiate Symptom Distress Questionnaire; On file, Pharmacia), physical examination (such as listening for bowel sounds), or physiological monitoring (oxygen saturation) are methods that may be able to evaluate more clearly the effects of opioid reduction. Second, the degree of reduction in opioid use may not have been sufficient to result in clinically meaningful reductions in their side-effects, or the trial may have been too small to identify differences between treatment groups. A trial of this size may also be underpowered to identify reductions in uncommon symptoms, such as respiratory depression. A review of published opioid-sparing trials with ketorolac demonstrates that opioid-sparing effects are variable and not always significantly demonstrated. The use of a patient population more susceptible to opioid side-effects than the carefully selected population in this clinical trial may be required. Consequently, additional clinical studies, using different clinical designs or different patient populations, will be helpful to define more fully any clinical benefit of the opioid-sparing effects of parecoxib sodium.

COX-2 selective inhibitors that provide opioid-sparing effects, without disrupting platelet function, are ideal in the management of postoperative patients. Although oral COX-2 selective inhibitors have demonstrated opioid-sparing effects when administered preoperatively to patients undergoing spinal fusion surgery, parecoxib sodium is the only injectable form of a COX-2 selective inhibitor in development. This is particularly important in the acutely painful postoperative setting because many surgical patients cannot tolerate oral medication or may have variable perioperative gastrointestinal absorptive function.

Parecoxib sodium has demonstrated analgesic efficacy in several postoperative pain models, and has shown a rapid onset of action and long duration. The results of the present study indicate that parecoxib sodium also provides a significant opioid-sparing effect when administered over a 48-h period in postoperative patients after total knee replacement, a surgical model known to cause severe pain.

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References

7 Borda IT, Koff R, eds. NSAIDs: a Profile of Adverse Effects. Philadelphia: Hanley and Belfus Inc.; 1995
12 Geis GS. Update on clinical developments with celecoxib, a new specific COX-2 inhibitor: what can we expect? J Rheumatol 1999; 26: 31–6
25 Guidelines for the Use of Non-steroidal Anti-inflammatory Drugs in the Perioperative Period. The Royal College of Anaesthetists, March 1998