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# The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain

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**Editor's note:** This article deals with parecoxib, a cyclo-oxygenase, or COX, -2 inhibitor. Several of our readers have asked about the safety of COX-2 inhibitors in light of recent news about the removal of Vioxx (rofecoxib) from the market by Merck & Co., Whitehouse Station, N.J. Since all drugs of a given class are not alike, JADA strongly advises that practitioners remain current by reading the literature. Additional information on these and other drugs is available from the U.S. Food and Drug Administration and may be found at "www.FDA.gov".

Orally administered nonsteroidal anti-inflammatory drugs, or NSAIDs, commonly are used to manage acute postoperative pain.<sup>1,2</sup> However, oral administration of analgesics is not always practical or feasible. Administration of parenteral analgesics may be required for patients unable to swallow or tolerate orally administered medication, or to provide a more rapid onset of action. Similarly, postoperative patients experiencing severe nausea and vomiting often require parenteral analgesia. The parenteral nonselective NSAID ketorolac tromethamine, at a recommended initial loading dose of 30 to 60 milligrams,<sup>3</sup> effectively alleviates postoperative pain during a six-hour period.<sup>4</sup> Although several

**A 20-milligram intramuscular dose of parecoxib sodium is an effective analgesic dose.**

**Background.** The parenteral cyclo-oxygenase, or COX, -2 selective inhibitor parecoxib sodium in a 40-milligram dose for intravenous/intramuscular, or IV/IM, administration is approved for postoperative pain in Europe, but not yet in the United States. However, previous trials in dental surgical patients have indicated that lower doses may be as effective.

**Methods.** The authors enrolled 353 patients in a single-center, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and tolerability of single IM doses of parecoxib (1-20 mg) with ketorolac tromethamine 30 mg IM after dental surgery. Pain assessments occurred at baseline and through 24 hours postdose.

**Results.** A 20-mg dose of parecoxib was significantly more effective than were 1-mg to 10-mg doses and than placebo. The analgesic onset of a 20-mg dose of parecoxib was similar to that of a 30-mg dose of ketorolac. The magnitude of analgesia with a 20-mg dose of parecoxib was significantly lower than that with ketorolac, according to the mean pain intensity difference, or PID, scores from one and one-half to four hours postdose or summed PID, or SPID, -categorical scores at six hours postdose. However, there was no significant difference in mean pain relief; total pain relief, or TOTPAR; and SPID-visual analog scale, or VAS, scores six hours postdose. Mean PID scores for parecoxib 20 mg from 12 to 24 hours postdose were significantly higher than those for ketorolac for the same period. However, the TOTPAR, SPID-categorical and SPID-VAS mean scores were not statistically significantly different from eight hours onward.

**Conclusions.** Parecoxib 20 mg IM is an effective analgesic dose with an onset and magnitude of analgesic effect approaching that of ketorolac 30 mg IM after dental surgery. It also is well-tolerated.

**Clinical Implications.** These findings support the use of parecoxib 20 mg IM as an initial dosing option for postoperative pain management in countries in which it is approved.

## DISCLOSURE

The study described in this article was sponsored by Pfizer Global Pharmaceuticals, New York, and Pharmacia Corporation, Skokie, Ill. R.C. Hubbard is an employee of Pfizer Global Research and Development. D.R. Mehlisch, P.J. Desjardins and S. Daniels have served as consultants to Pfizer Global Research and Development.

parenteral nonselective NSAIDs (such as diclofenac, ketoprofen, indomethacin and acetaminophen) are available in other countries, ketorolac is the only parenteral NSAID available for use in the United States.<sup>5-8</sup> However, owing to reports of serious or fatal adverse events associated with ketorolac treatment in several countries, its use in the United States has been restricted to a maximum of five days.<sup>7,8</sup>

Cyclo-oxygenase, or COX, -2 selective inhibitors (such as celecoxib and rofecoxib) effectively alleviate acute and chronic pain.<sup>9-12</sup> In clinical trials of six to 52 weeks' duration, treatment with COX-2 selective inhibitors has been associated with significantly improved gastrointestinal tolerability in comparison with nonselective NSAIDs (such as naproxen, ibuprofen, diclofenac and nabumetone) in osteoarthritis and rheumatoid arthritis patients.<sup>9,13,14</sup> At present, COX-2 selective inhibitors are available only in oral formulations in the United States, while in Europe parecoxib sodium, a prodrug of the COX-2 selective inhibitor valdecoxib,<sup>15</sup> is approved for parenteral administration at an initial dose of 40 mg (either intravenous, or IV, or intramuscular, or IM).

Single 20-mg and 40-mg IV doses of parecoxib sodium demonstrated an analgesic effect similar to that of a 30-mg IV dose of ketorolac when administered after orthopedic or gynecological surgery.<sup>16-18</sup> Parecoxib was approved at an initial dose of 40 mg IV/IM for the short-term treatment of postoperative pain in Europe. However, when administered after dental surgery, a 20-mg IV dose of parecoxib was as effective as were IV doses of 40 mg or higher in clinical trials.<sup>19,20</sup> Furthermore, 20-mg and 40-mg IV doses of parecoxib both were as effective as the highest initial dose of ketorolac (60 mg IM) approved in the United States when administered to patients after dental surgery.<sup>19</sup> A similar trend toward increased analgesic effectiveness in patients who had undergone oral surgery relative to patients who had undergone orthopedic surgery also was observed in a published trial of valdecoxib, the active form of parecoxib.<sup>21</sup> This variation in analgesic effectiveness between surgical models may be caused by differences in the intensity of postoperative pain experienced by patients undergoing different types of surgery and in the duration of the surgical procedures. In addition, differences in sensory innervation at the sites of surgical trauma, and in the degree of inflammation before and

after surgical intervention also may have an impact on analgesic efficacy.<sup>21</sup>

Therefore, patients who have undergone dental surgery might benefit from an initial 20-mg dose of parecoxib, which is lower than the 40-mg dose currently recommended in Europe.

Parecoxib has not yet been approved for treating postoperative pain in the United States, and a recommended initial dosage is not yet available. Therefore, in the trial we conducted, we evaluated the analgesic efficacy and safety of low doses of parecoxib (up to 20 mg IM) as potential initial dosing options, in comparison with a 30-mg IM dose of the nonselective NSAID ketorolac in patients after they had undergone dental surgery. We chose a 30-mg IM dose of ketorolac, the lowest initial approved dose for healthy adults in the United States, as being suitable to compare against the lower parecoxib dosages used in this trial. This decision was based on published parecoxib postoperative pain findings,<sup>16-18,20</sup> and on trials in which 30-mg IM doses of ketorolac exhibited analgesic activity superior or equivalent to that of clinically relevant single doses of the opioids morphine (12 mg) or meperidine (50 mg and 100 mg IM).<sup>22,23</sup> We used these efficacy endpoints:

- pain relief, or PR;
- pain intensity difference, or PID, measured on either a categorical scale or a visual analog scale, or VAS;
- peak pain intensity difference, or PPID, on either a categorical scale or a VAS;
- summed pain intensity difference, or SPID, on either a categorical scale or a VAS;
- peak pain relief, or PPR;
- total pain relief, or TOTPAR;
- time to onset of analgesia;
- time to perceptible PR;
- time to meaningful PR;
- time to receipt of rescue medication;
- each patient's global evaluation of his or her study medication.

## PATIENTS, METHODS AND MATERIALS

**Patients.** Patients eligible for participation in this study were adults, aged 18 to 45 years, undergoing surgical extraction of two or more impacted third molars (one of which was mandibular) requiring bone removal. Patients were recruited generally from the Austin, Texas, area, through advertising and through dental practices and referrals. To be eligible for the study, patients were required to have moderate to

severe pain intensity, or PI, as registered on the categorical scale and have a VAS PI score of  $\geq 50$  mm within the first six hours following surgery. (The categorical scale ranged from 0 = none to 3 = severe. The VAS was a 100-millimeter-long horizontal line on which 0 mm indicated no pain and 100 mm indicated worst pain.)

We excluded patients from participation if they had an uncontrolled chronic disease or any laboratory abnormalities (including aspartate aminotransferase or alanine aminotransferase  $> 1.5 \times$  the upper limit of the reference range) that could contraindicate study participation. We also excluded patients who had a history of gastrointestinal ulceration within the six months preceding the study, or a history of nasal polyps and/or a history of bronchospasm or angioedema induced by NSAIDs. Finally, we excluded patients who had used analgesics or other agents (excluding presurgical medications) during the six hours preceding dental surgery, as this may have confounded the analgesic response.

**Study design.** This single-center, double-blind, placebo-controlled, randomized, dose-ranging study was conducted in accordance with good clinical practice and the Declaration of Helsinki. It took place at the facilities of SCIREX, a drug development organization in Austin, Texas. Patients meeting all entry criteria, including PI rated as moderate or severe, randomly received a single IM dose of parecoxib 1, 2, 5, 10 or 20 mg; ketorolac 30 mg; or placebo (0.9 percent saline). We assigned patients to receive study medication sequentially, in the order in which they enrolled, according to a computer-generated randomization schedule prepared at Pharmacia (Skokie, Ill.) before the start of the trial. We reconstituted parecoxib lyophilized powder, in an identical fashion to the marketed formulation, in 0.9 percent saline USP or 5 percent dextrose USP, to yield a solution of pH 7.4. The injection volume was 1 milliliter for all doses, and the injections were administered into the gluteus maximus. Patients remained at the study site for 24 hours after dosing.

We provided rescue analgesics as needed throughout the study. These included oral acetaminophen 1,000 mg, oral hydrocodone 5 mg plus acetaminophen 500 mg, oral hydrocodone 7.5

mg plus acetaminophen 500 mg or IM meperidine 50 mg plus promethazine 25 mg. However, to provide an opportunity for the study medication to exert an analgesic effect, we encouraged patients to wait at least one hour after receiving the injection of study medication before requesting rescue medication.

**Efficacy assessments.** We used a two-stopwatch technique to measure time to onset of analgesia.<sup>24</sup> Study personnel started two stopwatches for each patient at the time of study drug administration. They then instructed patients to stop the first stopwatch when they first felt perceptible PR (in other words, began to feel any pain-relieving effect of the drug) and to stop the second stopwatch when they felt that the degree of PR was meaningful for them. We defined "time to onset of analgesia" as the time to perceptible PR, provided that the patient experienced both perceptible and meaningful PR. We classified patients who experienced perceptible but not meaningful PR as not having experienced an onset of analgesia.

Each patient performed standard pain assessments<sup>25</sup> under the supervision of trained study personnel, and they recorded these assessments in a diary booklet at five, 10, 15, 20, 30 and 45 minutes, one hour and one and one-half hours postdose, then hourly through 12 hours postdose, and at 16 hours and 24 hours postdose, or until they took rescue medication. Patients measured PI using both a categorical scale and a VAS. As previously stated the categorical scale included four categories: 0 = none, 1 = mild, 2 = moderate and 3 = severe. As stated previously, the VAS was a 100-mm-long horizontal line on which 0 mm indicated no pain and 100 mm indicated worst pain. Patients rated PR using five categories: 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete.

At the end of the 24-hour treatment period, or immediately before taking rescue medication, patients completed a global evaluation of their study medication. This evaluation was based on a four-point scale, with 1 = poor, 2 = fair, 3 = good and 4 = excellent. They also indicated their time to rescue medication, defined as the time elapsed between dosing and the receipt of rescue medication.

**Safety assessments.** We evaluated safety by

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**At the end of the  
 24-hour treatment  
 period, or  
 immediately before  
 taking rescue  
 medication, patients  
 completed a global  
 evaluation of their  
 study medication.**  
 .....

examining the number and frequency of patient-reported adverse events that occurred during the 24-hour treatment period, and between the end of the study and the follow-up visit (five to nine days after treatment). We also evaluated any changes in clinical laboratory findings during treatment and any changes in vital signs or physical examination findings up to the posttreatment visit.

**Statistical analyses.** Our sample size calculation was based on preliminary studies involving one primary efficacy variable (PID-categorical score) and comparisons of each dose of parecoxib versus placebo (D.H. Mehlisch, M.D., D.D.S., and R.C. Hubbard, M.D., unpublished data, December 2002). A sample size of 50 patients per treatment group was required to detect a difference in PID-categorical score of 0.458 at 45 minutes, with an estimate of variability of 0.66. The power of the test was 80 percent with a type 1 error at 0.01 (for a two-sided test adjusted for five comparisons).

We compared demographic and baseline patient data between groups using the  $\chi^2$  test or Fisher exact test for categorical data and a one-way analysis of variance, or ANOVA, for continuous variables.

We used the intent-to-treat, or ITT, patient cohort in the efficacy analyses. We excluded from the cohort patients who withdrew before one hour after dosing, as well as patients who missed two consecutive scheduled assessments in the first two hours. Kaplan-Meier survival analyses were performed on time to onset of analgesia, time to perceptible PR, time to meaningful PR and time to receipt of rescue medication, and overall treatment-group comparisons were undertaken using log-rank tests. When the overall log-rank was significant, we made pairwise comparisons between the treatment groups using pairwise log-rank tests (the Fisher protected least significant difference, or PLSD, method).

We derived the PID-categorical or PID-VAS during the study period by subtracting the patient's PI (categorical or VAS) score at each time point from his or her baseline PI (categorical or VAS) score. A positive value indicates a reduction in pain; a negative value indicates a worsening of pain. We determined the time-interval-weighted SPID-categorical or SPID-VAS by combining the time-weighted PID-categorical or PID-

VAS scores up to the six-, eight-, 10-, 12-, 16- and 24-hour assessments. We calculated the PPID-categorical or PPID-VAS (defined as the highest PID-categorical or PID-VAS score throughout the 24-hour evaluation period) and the PPR (defined as the highest PR score throughout the 24-hour evaluation period). We derived the time-specific TOTPAR by summing the time-interval-weighted PR scores through the first six, eight, 10, 12 and 24 hours. Using ANOVA, we compared mean PR and TOTPAR, and we performed pairwise comparisons between the seven treatment groups using the Fisher PLSD method. We compared mean PID, PPID, PPR and SPID using an analysis of covariance model with baseline PI and treatment-by-baseline interaction. A further analysis tested for treatment-by-baseline interaction. For the patients' global evaluations, we compared the distribution of patients who rated their study

medication as poor/fair or good/excellent using the pairwise  $\chi^2$ . To account for missing data due to patients' taking rescue medication or withdrawing from the study, we used the last-observation-carried-forward approach in the analysis of time-specific pain assessments. Thus, we included in the analyses only pain assessments made before the administration of rescue medication. We imputed isolated missing pain data on a patient-by-patient basis by means of linear

interpolation.

All patients who received a dose of study medication were included in the safety analysis. We compared end-of-treatment evaluations of vital signs and changes from baseline among the seven treatment groups using ANOVA, with treatment as a factor.

## RESULTS

**Study patients.** Three hundred and fifty-three patients were enrolled and randomly assigned to receive one of the seven treatments. One patient in each treatment group—ketorolac 30 mg and parecoxib 10 mg—was withdrawn from the study owing to a protocol violation. The ITT cohort used in the efficacy analyses, therefore, comprised 351 patients.

**Baseline characteristics.** There were no statistically significant differences among treatment

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**The time elapsed  
 from the end of  
 surgery to the  
 development of  
 moderate-to-severe  
 pain requiring  
 analgesia was  
 similar for all  
 treatment groups.**  
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TABLE 1

BASELINE DEMOGRAPHICS.							
DEMOGRAPHIC	TREATMENT						
	Placebo	Ketorolac 30 mg*	Parecoxib 1 mg	Parecoxib 2 mg	Parecoxib 5 mg	Parecoxib 10 mg	Parecoxib 20 mg
<b>Patients (n)</b>	50	51	51	50	51	50	50
<b>Mean Age (Years)</b>	23.0	24.0	22.1	22.9	23.4	22.5	23.8
<b>Race (n [%])</b>							
White	36 (72)	34 (67)	39 (76)	30 (60)	36 (71)	37 (74)	32 (64)
African-American	3 (6)	2 (4)	4 (8)	1 (2)	3 (6)	4 (8)	8 (16)
Asian	4 (8)	3 (6)	1 (2)	1 (2)	2 (4)	2 (4)	1 (2)
Hispanic	7 (14)	12 (24)	6 (12)	18 (36)	10 (20)	7 (14)	9 (18)
Other	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Sex (n [%])</b>							
Female	28 (56)	23 (45)	29 (57)	26 (52)	31 (61)	31 (62)	28 (56)
Male	22 (44)	28 (55)	22 (43)	24 (48)	20 (39)	19 (38)	22 (44)
<b>Mean Weight (kg<sup>†</sup>)</b>	68.9	75.4	69.8	73.5	73.6	72.3	71.3
<b>Mean No. of Molars Extracted</b>	2.1	2.1	2.1	2.1	2.0	2.0	2.1
<b>Degree of Bony Impaction (n [%])</b>							
Partial	29 (58)	32 (63)	25 (49)	30 (60)	25 (49)	24 (48)	25 (50)
Complete	21 (42)	19 (37)	26 (51)	20 (40)	26 (51)	26 (52)	25 (50)
<b>Baseline Pain Intensity (Categorical) (n [%])</b>							
Moderate	33 (66)	33 (65)	40 (78)	40 (80)	32 (63)	31 (62)	32 (64)
Severe	17 (34)	18 (35)	11 (22)	10 (20)	19 (37)	19 (38)	18 (36)
<b>Mean Baseline Pain Intensity (VAS<sup>‡</sup>)</b>	63.0	64.2	61.0	60.5	64.6	63.4	63.7
* mg: Milligrams. † kg: Kilograms. ‡ VAS: Visual analog scale (a 100-millimeter-long horizontal line on which 0 mm indicated no pain and 100 mm indicated worst pain).							

groups with respect to baseline demographics (Table 1). Mean ages for all groups were between 22 and 24 years.

The distribution of patients with complete bony impaction or partial bony impaction was similar among treatment groups. Treatment groups also were well-matched with regard to baseline PI. The time elapsed from the end of surgery to the development of moderate-to-severe pain requiring analgesia was similar for all treatment groups. Mean times ranged from 153.0 minutes (2.55 hours) to 165.9 minutes (2.77 hours).

**Efficacy.** *Time to perceptible pain relief, meaningful pain relief and onset of analgesia.* According to the median time to perceptible PR, meaningful PR and onset of analgesia measures, the 1-mg dose of parecoxib was the only active treatment without a significant analgesic effect compared with placebo (Table 2). The percentage of patients experiencing an onset of analgesia was higher for all active treatments relative to placebo (Table 2).

The median time to perceptible PR (13 minutes) and the median time to onset of analgesia (14 minutes) were identical in the groups receiving ketorolac 30 mg and parecoxib 20 mg (Table 2). The median time to meaningful PR was higher in the ketorolac 30-mg group (43 minutes) than in the parecoxib 20-mg group (37 minutes); however, this difference was not statistically significant. The percentage of patients experiencing an onset of analgesia was higher for ketorolac (82 percent) relative to parecoxib 20 mg (72 percent) and the lower 1 to 10 mg (31 to 57 percent) doses. Single 20-mg doses of parecoxib and 30-mg doses of ketorolac were significantly more effective than were single 1- to 10-mg doses of parecoxib, according to the measures of median time to perceptible PR, meaningful PR and time to onset of analgesia ( $P < .05$ ) (Table 2).

*PID on a categorical scale and PR.* Parecoxib 20 mg and ketorolac 30 mg provided significantly greater analgesia than placebo from 15 minutes

TABLE 2

TIME TO ONSET OF ANALGESIA, PERCEPTIBLE PAIN RELIEF AND MEANINGFUL PAIN RELIEF.							
AGENT AND DOSE	MEDIAN TIME TO PERCEPTIBLE PAIN RELIEF (HOURS: MINUTES)	MEDIAN TIME TO MEANINGFUL PAIN RELIEF (HOURS: MINUTES)	MEDIAN TIME TO ONSET OF ANALGESIA (HOURS: MINUTES)	PATIENTS WITH ONSET OF ANALGESIA n (%)	PEAK PAIN INTENSITY DIFFERENCE		PERCEPTIBLE PAIN RELIEF
					Categorical Mean (SD)*	Visual Analog Scale Mean (SD)	
Placebo	> 24	> 24	> 24	13 (26)	0.44 (0.84)	14.2 (21.9)	0.98 (1.38)
Ketorolac 30 mg <sup>†</sup>	00:13 <sup>§</sup>	00:43 <sup>§</sup>	00:14 <sup>§</sup>	41 (82)	1.68 (0.89) <sup>§</sup>	49.7 (21.8) <sup>§</sup>	3.08 (1.19) <sup>§</sup>
Parecoxib 1 mg	00:25	> 24	> 24	16 (31)	0.61 (0.87)	20.9 (23.7)	1.41 (1.36)
Parecoxib 2 mg	00:14 <sup>‡</sup>	04:00 <sup>‡</sup>	1:50 <sup>‡</sup>	25 (50)	0.74 (0.80) <sup>‡</sup>	26.2 (22.6) <sup>‡</sup>	1.74 (1.41) <sup>‡</sup>
Parecoxib 5 mg	00:19 <sup>‡</sup>	> 24 <sup>‡</sup>	> 24 <sup>‡</sup>	22 (43)	0.82 (0.91) <sup>‡</sup>	26.2 (24.0) <sup>‡</sup>	1.67 (1.35) <sup>‡</sup>
Parecoxib 10 mg	00:17 <sup>‡</sup>	01:27 <sup>‡</sup>	00:25 <sup>‡</sup>	28 (57)	1.02 (0.97) <sup>‡</sup>	29.1 (24.9) <sup>‡</sup>	1.94 (1.45) <sup>‡</sup>
Parecoxib 20 mg	00:13 <sup>§</sup>	00:37 <sup>§</sup>	00:14 <sup>§</sup>	36 (72)	1.36 (0.92) <sup>§¶</sup>	43.1 (23.1) <sup>§</sup>	2.56 (1.39) <sup>§</sup>

\* SD: Standard deviation.  
<sup>†</sup> mg: Milligrams.  
<sup>‡</sup> P < .05 versus placebo.  
<sup>§</sup> P < .05 versus parecoxib, 1-mg to 10-mg doses.  
<sup>¶</sup> P < .05 versus ketorolac 30 mg.

to 24 hours postdose, as demonstrated by the significantly higher mean PID and PR scores (Figure 1, page 1584). Furthermore, single parecoxib doses of 2 to 10 mg also demonstrated significant analgesic efficacy relative to placebo for varying periods, according to the mean PID and PR scores (Figure 1). However, the mean scores for parecoxib 1 mg were only significantly higher than those for placebo according to the PID measure from 45 minutes to six hours postdose, with no significant difference on the PR measure. There was a trend toward an increased duration of significant analgesic effect relative to placebo with increasing doses of parecoxib (Figure 1).

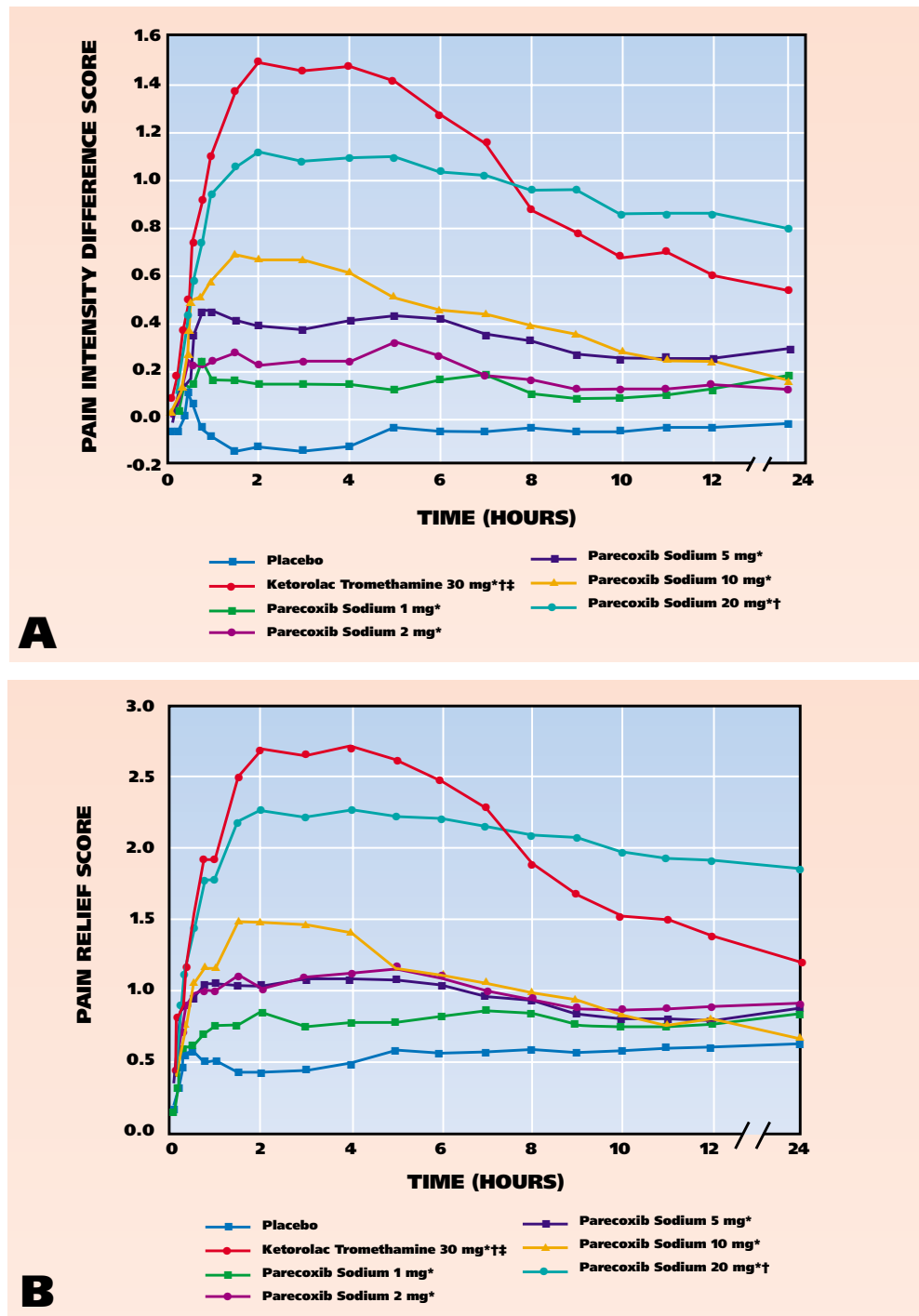
According to the mean PID scores, ketorolac 30 mg was significantly more effective than parecoxib 20 mg from one and one-half to four hours postdose. However, there were no significant differences between the two groups with respect to mean PID scores for the remainder of the study. The mean PR scores for ketorolac were numerically higher than those for parecoxib 20 mg from one and one-half to seven hours postdose. However, there was no significant difference in mean PR scores between these two treatments at all time points, up to and

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**The 20-milligram dose of parecoxib and the 30-mg dose of ketorolac had significantly greater peak effects than did placebo or the 1- to 10-mg doses of parecoxib.**  
 .....

including the 11-hour assessment. From 12 hours postdose through the remainder of the study, parecoxib 20 mg had significantly higher mean PR scores than did ketorolac 30 mg. The mean scores were significantly greater for parecoxib 20 mg than for all other parecoxib doses from 30 minutes (PR) or one hour (PID) to 24 hours postdose. We observed a similar significant trend for ketorolac 30 mg through all time points from 30 minutes postdose onward (Figure 1).

*PPID and PPR.* The 20-mg dose of parecoxib and the 30-mg dose of ketorolac had significantly greater peak effects than did placebo or the 1- to 10-mg doses of parecoxib, according to mean PPID-categorical or PPID-VAS scores and mean PPR scores (both P < .05) (Table 2). For each measure of peak analgesic effect, 2- to 10-mg doses of parecoxib were significantly superior to placebo. However, there was no significant difference in peak effect between a 1-mg dose of parecoxib and placebo, for each measure. According to the mean PPID-categorical score, ketorolac had a peak analgesic effect significantly greater than that of parecoxib 20 mg (Table 2). Ketorolac also had a peak analgesic effect greater than that of parecoxib 20 mg according to the PPID-VAS and

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**Figure 1. A. Pain intensity difference mean scores over 24 hours. \*P < .05 versus placebo: from 45 minutes to four hours (parecoxib sodium 1 milligram), 45 minutes to six hours (parecoxib 2 mg), 30 minutes to eight hours (parecoxib 5 mg), 30 minutes to nine hours (parecoxib 10 mg) or 15 minutes to 24 hours (parecoxib 20 mg, ketorolac tromethamine 30 mg) postdose. †P < .05 versus placebo: from 30 minutes to 24 hours (ketorolac 30 mg) or one to 24 hours (parecoxib 20 mg) postdose. ‡P < .05 versus placebo: from one and one-half to four hours postdose. B. Mean pain relief scores. \*P < .05 versus placebo: from 30 minutes to five hours (parecoxib sodium 2 mg), 30 minutes to four hours (parecoxib 5 mg), 30 minutes to six hours (parecoxib 10 mg) or 15 minutes to 24 hours (ketorolac tromethamine 30 mg, parecoxib 20 mg) postdose. †P < .05 versus placebo: from 30 minutes to 12 hours (ketorolac 30 mg) or 30 minutes to 24 hours (parecoxib 20 mg). ‡P < .05 versus ketorolac 30 mg from 12 to 24 hours postdose.**

PPR assessments, although these differences were not statistically significant (Table 2).

*TOTPAR and SPID-categorical or SPID-VAS.* Similar to the PPID-VAS and PPR findings, parecoxib 20 mg and ketorolac 30 mg provided a significantly greater magnitude of analgesia than did placebo and 1- to 10-mg doses of parecoxib at six, eight, 12 and 24 hours postdose, according to TOTPAR, SPID-categorical and SPID-VAS measures (Tables 3 and 4). Parecoxib 2- to 10-mg doses were significantly more effective than was placebo, according to the TOTPAR measure, up to eight hours (parecoxib 2 to 5 mg) or 12 hours (parecoxib 10 mg) postdose, and at most time points for the SPID-categorical and SPID-VAS assessments (Tables 3 and 4). The mean TOTPAR, SPID-categorical and SPID-VAS scores for the majority of time points confirmed the lack of analgesic effect of parecoxib 1 mg versus placebo. However, at six hours on a categorical scale or from six to 24 hours postdose on a VAS scale, parecoxib 1 mg provided a magnitude of analgesia significantly greater than that of placebo, according to the SPID measures (Table 4).

At six hours postdose, the mean SPID categorical scores for ketorolac 30 mg were significantly

TABLE 3

TOTAL PAIN RELIEF, OR TOTPAR, AT FOUR POSTDOSE MEASUREMENT POINTS.				
AGENT AND DOSE	TOTPAR SCORE MEAN (SD*), BY ELAPSED TIME SINCE ADMINISTRATION			
	6 Hours	8 Hours	12 Hours	24 Hours
Placebo	2.93 (5.42)	4.07 (7.78)	6.41 (12.6)	13.8 (28.1)
Ketorolac 30 mg <sup>†</sup>	14.6 (7.36) <sup>§§</sup>	18.8 (9.82) <sup>§§</sup>	24.9 (14.0) <sup>§§</sup>	39.4 (26.2) <sup>§§</sup>
Parecoxib 1 mg	4.67 (6.31)	6.28 (8.68)	9.30 (13.2)	19.3 (28.9)
Parecoxib 2 mg	6.37 (6.67) <sup>‡</sup>	8.29 (8.87) <sup>‡</sup>	11.8 (13.1)	22.6 (27.1)
Parecoxib 5 mg	6.11 (6.98) <sup>‡</sup>	8.01 (9.29) <sup>‡</sup>	11.2 (13.3)	21.6 (27.1)
Parecoxib 10 mg	7.61 (6.77) <sup>‡</sup>	9.65 (8.71) <sup>‡</sup>	12.9 (12.0) <sup>‡</sup>	20.5 (20.3)
Parecoxib 20 mg	12.6 (8.28) <sup>§§</sup>	16.9 (11.3) <sup>§§</sup>	24.8 (17.0) <sup>§§</sup>	47.0 (33.9) <sup>§§</sup>

\* SD: Standard deviation.  
<sup>†</sup> mg: Milligrams.  
<sup>‡</sup> P < .05 versus placebo.  
<sup>§</sup> P < .05 versus parecoxib, 1-mg to 10-mg doses.

TABLE 4

SUMMED PAIN INTENSITY DIFFERENCE, OR SPID, ON A CATEGORICAL OR VISUAL ANALOG SCALE, OR VAS, AT FOUR POSTDOSE MEASUREMENT POINTS.				
AGENT AND DOSE	MEAN (SD*) SPID ON A CATEGORICAL SCALE, BY ELAPSED TIME SINCE ADMINISTRATION			
	6 Hours	8 Hours	12 Hours	24 Hours
Placebo	-0.51 (4.41)	-0.61 (6.13)	-0.81 (9.62)	-1.1 (20.6)
Ketorolac 30 mg <sup>†</sup>	7.80 (5.50) <sup>§§</sup>	9.84 (7.19) <sup>§§</sup>	12.6 (10.2) <sup>§§</sup>	19.1 (19.4) <sup>§§</sup>
Parecoxib 1 mg	0.84 (4.92) <sup>‡</sup>	1.10 (6.75)	1.47 (10.2)	3.51 (22.8)
Parecoxib 2 mg	1.50 (4.68) <sup>‡</sup>	1.84 (6.28) <sup>‡</sup>	2.34 (9.56) <sup>‡</sup>	3.86 (20.1) <sup>‡</sup>
Parecoxib 5 mg	2.34 (4.94) <sup>‡</sup>	3.03 (6.50) <sup>‡</sup>	4.07 (9.46) <sup>‡</sup>	7.44 (19.3) <sup>‡</sup>
Parecoxib 10 mg	3.32 (5.31) <sup>‡</sup>	4.14 (6.98) <sup>‡</sup>	5.24 (10.1) <sup>‡</sup>	7.12 (19.2)
Parecoxib 20 mg	6.00 (5.91) <sup>§§¶</sup>	7.98 (8.01) <sup>§§</sup>	11.5 (11.9) <sup>§§</sup>	21.0 (23.6) <sup>§§</sup>
AGENT AND DOSE	MEAN (SD) SPID ON A VAS, BY ELAPSED TIME SINCE ADMINISTRATION			
	6 Hours	8 Hours	12 Hours	24 Hours
Placebo	-21 (123)	-27 (171)	-38 (271)	-66 (583)
Ketorolac 30 mg	233 (143) <sup>§§</sup>	296 (187) <sup>§§</sup>	384 (263) <sup>§§</sup>	588 (497) <sup>§§</sup>
Parecoxib 1 mg	42.9 (133) <sup>‡</sup>	58.3 (184) <sup>‡</sup>	84.8 (282) <sup>‡</sup>	175 (604) <sup>‡</sup>
Parecoxib 2 mg	61.3 (144) <sup>‡</sup>	77.0 (192) <sup>‡</sup>	103 (287) <sup>‡</sup>	181 (583) <sup>‡</sup>
Parecoxib 5 mg	78.8 (131) <sup>‡</sup>	102 (174) <sup>‡</sup>	140 (251) <sup>‡</sup>	261 (515) <sup>‡</sup>
Parecoxib 10 mg	96.6 (134) <sup>‡</sup>	119 (175) <sup>‡</sup>	153 (251) <sup>‡</sup>	217 (457) <sup>‡</sup>
Parecoxib 20 mg	188 (161) <sup>§§</sup>	249 (218) <sup>§§</sup>	359 (329) <sup>§§</sup>	656 (654) <sup>§§</sup>

\* SD: Standard deviation.  
<sup>†</sup> mg: Milligrams.  
<sup>‡</sup> P < .05 versus placebo.  
<sup>§</sup> P < .05 versus parecoxib, 1-mg to 10-mg doses.  
<sup>¶</sup> P < .05 versus ketorolac 30 mg.

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greater than those for parecoxib 20 mg (Table 4). However, while the TOTPAR and SPID-VAS scores for ketorolac 30 mg were numerically greater than those for parecoxib 20 mg, there was no such significant difference between the two agents at six hours postdose for the TOTPAR and SPID-VAS measures (Tables 3 and 4). For the eight- and 12-hour TOTPAR, SPID-VAS and SPID-categorical time points there was no significant difference in the magnitude of analgesia provided by ketorolac 30 mg and parecoxib 20 mg, although the mean ketorolac scores were numerically greater (Tables 3 and 4). At 24 hours postdose, the mean scores for all three measures were numerically greater for parecoxib 20 mg relative to those for ketorolac (Tables 3 and 4).

**Patients' global evaluations.** Patients' global evaluation mean scores for parecoxib increased in a dose-dependent manner. According to the mean scores, all parecoxib doses, with the exception of the 1-mg dose, were significantly better than those of placebo (all  $P < .05$ ) (Figure 2). Furthermore, according to pairwise  $\chi^2$  tests, significantly more patients receiving parecoxib 2 to 20 mg or ketorolac 30 mg rated their medication as "good" or "excellent" than did those who received placebo (Figure 2).

There were similar levels of patient satisfaction with parecoxib 20 mg and ketorolac 30 mg. The mean score for parecoxib (2.90) was numerically but not significantly lower than the score for ketorolac (2.96) (Figure 2). Fewer patients rated parecoxib 20 mg as a good or excellent treatment (60 percent) relative to ketorolac 30 mg (68 percent), although this difference was not statistically significant (Figure 2). In contrast, the percentage of patients in the parecoxib 20-mg group (50 percent) rating their medication as "excellent" was numerically higher than that of those in the ketorolac (40 percent), placebo (8 percent) or parecoxib 1 to 10 mg (8 to 16 percent) groups rating their medication as "excellent" (Figure 2). The mean scores for parecoxib 20 mg and ketorolac 30 mg were significantly higher than those for parecoxib 1 to 10 mg doses (Figure 2).

**Time to receipt of rescue medication.** In total, 34 percent of patients in the parecoxib 20-mg group completed the study without rescue medication, compared with eight to 16 percent in the other treatment groups (Table 5). The median time to rescue medication was significantly longer

for the groups taking parecoxib 2 to 20 mg and ketorolac 30 mg than for the placebo group. There was no significant difference in median time to rescue medication between parecoxib 20 mg and ketorolac 30 mg; however, this value was longer for ketorolac (eight hours and two minutes versus seven hours and 41 minutes (Table 5). The median time to rescue medication for the groups taking parecoxib 20 mg and ketorolac were significantly longer than for the groups taking parecoxib 1 to 10 mg (Table 5).

**Safety.** There were no serious adverse events or withdrawals due to adverse events in the study. Overall, 182 (52 percent) patients reported one or more adverse events. The incidence of adverse events in the parecoxib groups (42 to 59 percent) was similar to ketorolac 30 mg (53 percent) and placebo (52 percent), and there was no evidence of a dose-related increase in adverse events among patients receiving parecoxib. Adverse events with an incidence of 5 percent or more in any treatment group included vein pain and injection site reaction, nausea, alveolar osteitis, vomiting, pharyngitis, headache, dizziness and abdominal pain (Table 6, page 1586). There were no clinically significant changes in clinical laboratory findings, physical examination or vital signs in any of the patients during the 24-hour study period.

## DISCUSSION

Parecoxib is not yet approved by the U.S. Food and Drug Administration and currently has no initial dosing recommendation or indication for the treatment of postoperative pain in the United States. Therefore, we undertook our trial to determine the analgesic efficacy of parecoxib 1 to 20 mg IM as potential initial dosing alternatives to the 40-mg IV/IM dose approved for the short-term treatment of postsurgical pain in Europe, in patients who have undergone dental surgery.

This trial demonstrated the linear portion of the human analgesic dose-response curve for parecoxib with a high level of assay sensitivity. A single dose of parecoxib 20 mg IM was significantly more effective than lower 1- to 10-mg doses and placebo in terms of onset, magnitude and duration of analgesia in patients after dental surgery. This observation with parecoxib 20 mg IM confirms the findings of an IV dose-ranging trial in patients who had undergone dental

There were similar levels of patient satisfaction with parecoxib 20 mg and ketorolac 30 mg.

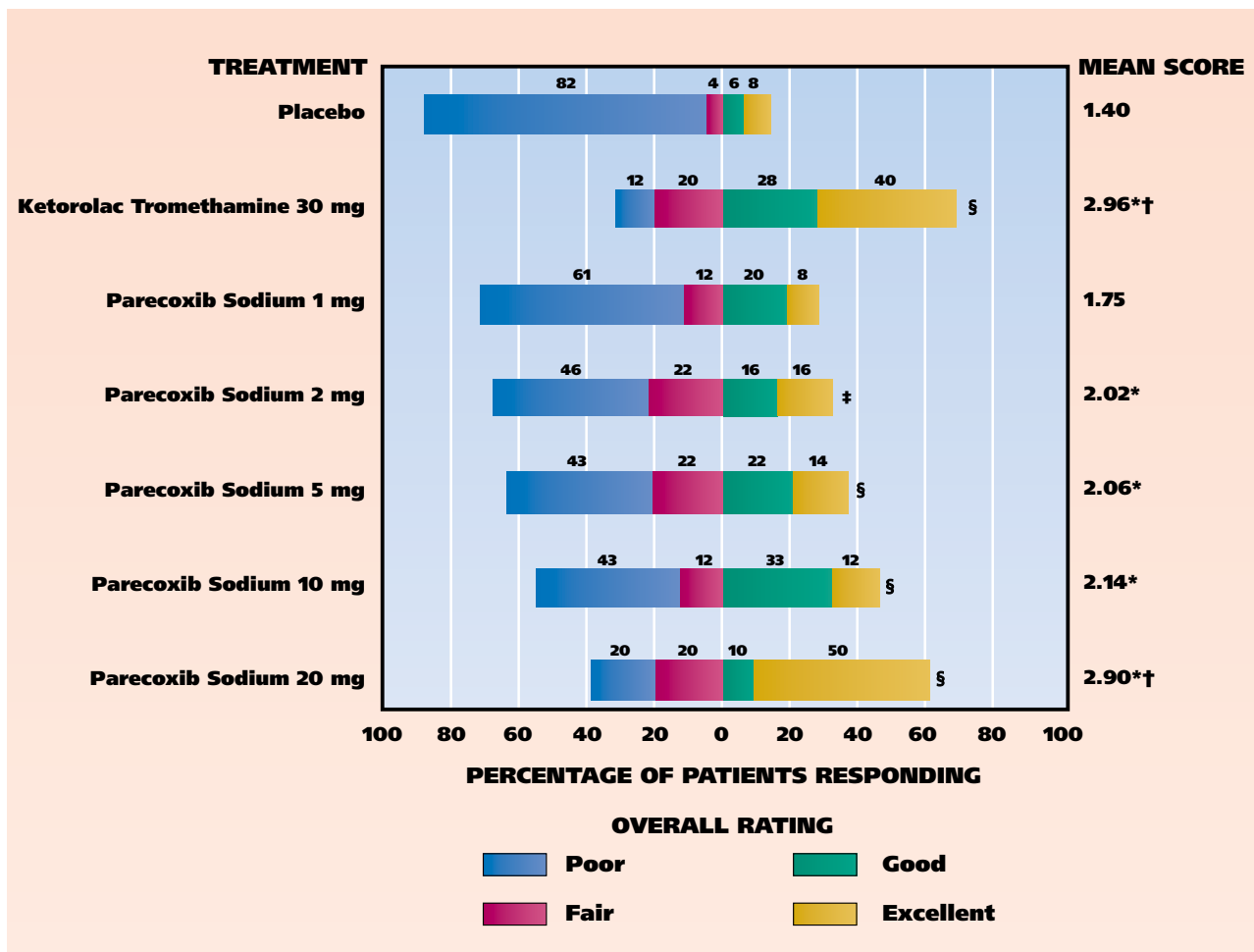


Figure 2. Patients' global evaluations of study medications. mg: Milligrams. \* $P < .05$  versus placebo and † $P < .05$  versus parecoxib sodium 1 mg, 2 mg, 5 mg and 10 mg (pairwise Fisher protected least significant difference comparisons). ‡ $P < .05$  or § $P < .01$  versus placebo (pairwise  $\chi^2$  test of distribution of patients rated "poor/fair" or "good/excellent").

TABLE 5

PROPORTION OF PATIENTS TAKING RESCUE MEDICATION AND MEDIAN TIME TO RECEIPT OF RESCUE MEDICATION.		
AGENT AND DOSE	PROPORTION OF PATIENTS TAKING RESCUE MEDICATION n (%)	MEDIAN TIME TO RECEIPT OF RESCUE MEDICATION (HOURS:MINUTES)
Placebo	43 (86)	01:03
Ketorolac 30 mg <sup>†</sup>	43 (86)	08:02 <sup>‡‡</sup>
Parecoxib 1 mg	43 (84)	01:32
Parecoxib 2 mg	42 (84)	01:34 <sup>†</sup>
Parecoxib 5 mg	43 (84)	01:32 <sup>†</sup>
Parecoxib 10 mg	45 (92)	04:04 <sup>†</sup>
Parecoxib 20 mg	33 (66)	07:41 <sup>‡‡</sup>

\* mg: Milligrams.  
<sup>†</sup>  $P < .05$  versus placebo.  
<sup>‡</sup>  $P < .05$  versus parecoxib, 1-mg to 10-mg doses.

TABLE 6

ADVERSE EVENTS WITH AN INCIDENCE OF  $\geq 5\%$  IN ANY TREATMENT GROUP.

VARIABLE	INCIDENCE, BY TREATMENT GROUP						
	Placebo	Ketorolac 30 mg*	Parecoxib 1 mg	Parecoxib 2 mg	Parecoxib 5 mg	Parecoxib 10 mg	Parecoxib 20 mg
Patients (n)	50	51	51	50	51	50	50
Overall Incidence of Any Adverse Event (%)	52	53	49	42	59	56	50
Injection Site Reaction (%)	0	4	4	4	6	6	0
Vein Pain (%)	0	0	2	0	0	0	6
Dizziness (%)	10	10	16	10	10	12	4
Headache (%)	10	10	4	10	12	18	10
Nausea (%)	32	24	22	22	18	14	12
Alveolar Osteitis (%)	14	12	20	8	16	10	18
Vomiting (%)	16	6	10	4	12	8	4
Abdominal Pain (%)	6	4	0	0	2	0	6
Pharyngitis (%)	0	0	0	2	6	2	2

\* mg: Milligrams.

surgery.<sup>20</sup> The significantly higher level of patient satisfaction with parecoxib 20 mg IM relative to the 1-to 10-mg doses in our trial also are consistent with the findings of the IV administration trial.<sup>20</sup>

Parecoxib 20 mg IM acted as rapidly as ketorolac 30 mg IM in our trial; both treatments had a median time to onset of 14 minutes. Similar findings have been demonstrated in other clinical trials in patients undergoing dental surgery or gynecologic laparotomy.<sup>17,20,26</sup> However, the proportion of patients experiencing an onset of analgesia in our trial was numerically greater for ketorolac (82 percent) than for parecoxib 20 mg (72 percent).

A single parenteral dose of ketorolac 30 to 60 mg provides effective analgesia for six hours postdose.<sup>4</sup> In this trial, parecoxib 20 mg IM was not significantly different from ketorolac 30 mg IM for most measures of the magnitude of analgesia (PR, TOTPAR, SPID-VAS) more than six hours postdose or for most measures of peak analgesic effect (PPID-VAS and PPR, but not PPID-categorical). However, the mean scores for ketorolac were consistently numerically higher than those for parecoxib 20 mg for these measures, and the mean PID (one and one-half to four hours) or SPID-categorical (at six hours postdose)

scores for ketorolac were significantly higher. Overall, our findings support those of other published postoperative pain trials, which have demonstrated that parecoxib 20 mg has a magnitude of analgesic effect similar to that of ketorolac 30 mg.<sup>17,20,27</sup>

In our trial, there was no significant difference in the levels of patient satisfaction with parecoxib 20 mg IM and ketorolac 30 mg IM (60 percent versus 68 percent "good" or "excellent" ratings). Indeed, investigators conducting other postoperative pain trials also have reported similar levels of patient satisfaction between parecoxib 20 mg and ketorolac 30 mg.<sup>17,20</sup>

The significantly higher mean PID scores in our trial for parecoxib 20 mg than for ketorolac 30 mg from 12 to 24 hours postdose suggest that this parecoxib dose may have a longer duration of analgesic effect than does ketorolac. This observation is consistent with the findings of two postoperative administration trials of parecoxib involving patients who had had dental surgery, in which a single 20-mg dose of parecoxib had significantly improved mean PID/PR scores from nine to 24 hours postdose compared with those for ketorolac 30 mg.<sup>19,20</sup> However, the TOTPAR, SPID-categorical and SPID-VAS mean score differences at eight, 12 and 24 hours postdose in our

trial were not statistically significant. Furthermore, although not significantly different, the median time to rescue medication—which reflects the duration of analgesic efficacy in single-dose studies—was longer for ketorolac 30 mg (eight hours and two minutes) than parecoxib 20 mg (seven hours and 41 minutes) in our trial.

Although it is not possible to conclude that parecoxib 20 mg is longer-acting than ketorolac, the comparisons with placebo and with the lower parecoxib 1- to 10-mg doses in our trial (PID, PR) clearly show that parecoxib 20 mg maintained a significant analgesic effect throughout the 24-hour postdose evaluation period. Further trials, therefore, will be required to confirm this long dosing interval for parecoxib 20 mg in dental impaction and other postoperative pain models.

Parecoxib 1 to 20 mg and ketorolac 30 mg were well-tolerated in this study. There were no apparent differences between active treatments in reported adverse events, or in clinically significant changes in clinical laboratory findings, physical examination or vital signs. Each active treatment group had an incidence of adverse events similar to that of placebo. Adverse events that occurred in more than 5 percent of patients in any group generally were related to the discomfort of the IM injection or the surgical procedure.

A limitation of this dose-ranging trial is the absence of parecoxib 40 mg IM and ketorolac 60 mg IM (the highest initial dose approved in the United States for each) treatment arms for comparison with the lower-dose parecoxib treatment arms.

## CONCLUSION

These results demonstrate that parecoxib 20 mg IM, the first injectable form of a COX-2 selective inhibitor, is an effective and rapidly acting analgesic dose in patients who have undergone dental surgery. Parecoxib 20 mg IM had an onset and magnitude of analgesic effect approaching that of ketorolac 30 mg IM in this trial. In addition, parecoxib 20 mg IM was well-tolerated. Therefore, in countries in which it is approved, a parenteral 20-mg dose of parecoxib may provide a useful alternative to the higher 40-mg IV/IM dose or a 30-mg IV/IM dose of ketorolac in patients undergoing dental surgery. ■

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