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A Single Preoperative Oral Dose of Valdecoxib, a New Cyclooxygenase-2 Specific Inhibitor, Relieves Post–Oral Surgery or Bunionectomy Pain

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Background: **The trend toward day-case surgery, with discharge on oral medication, has highlighted the need for effective and safe analgesics that facilitate a rapid recovery and discharge time. This study evaluated the analgesic efficacy, dose dependency, duration of action, and safety of the cyclooxygenase-2 specific inhibitor, valdecoxib, administered before oral or orthopedic surgery.**

Methods: **Eligible healthy adult patients were scheduled to undergo either extraction of two impacted third molar teeth (n = 284) or bunionectomy surgery (n = 223) with local anesthesia in two randomized, double-blind, placebo-controlled studies conducted at three centers in the United States. Patients received a single, preoperatively administered oral dose of placebo or 10 (oral surgery only), 20, 40, or 80 mg valdecoxib. Analgesic efficacy was assessed postoperatively, over a 24-h treatment period, or until the patient required rescue medication. Efficacy measures included time to rescue medication, proportion of patients requiring such rescue, pain intensity, and the Patient's Global Evaluation of Study Medication.**

Results: **In both studies, all doses of valdecoxib produced analgesia with a duration (time to rescue analgesia) and magnitude (Pain Intensity, Patient's Global Evaluation) significantly greater than placebo. A dose-dependent effect was observed up to 40 mg valdecoxib, with an 80-mg dose providing no additional analgesic benefit. In both models, all doses of valdecoxib were well tolerated, with no clinically significant treatment-related gastrointestinal, renal, or platelet-derived adverse events, and no evidence of a dose-related increase in adverse events.**

Conclusions: **Preoperative orally administered valdecoxib provides well-tolerated and effective analgesia for mild to moderate postoperative pain.**

DESPITE the availability of multiple analgesics and improved postoperative pain care strategies, many patients experience short-term postsurgical pain and adverse events complicating their analgesia.[1–6] The standard of postoperative pain management on surgical wards is inadequate according to 50% of anesthesiologists,[7] and 60% of in-patients report pain-related problems on hospital discharge.[8] In addition, the trend toward day-case surgery, with discharge on oral medication, has increased the risk of inadequate analgesia and side effects in ambulatory patients.[9–11] The ideal analgesic agent for day-case surgery management should provide adequate analgesia in the immediate postoperative period and enable early discharge without the sedation, dizziness, nausea, or psychomotor impairment commonly found with opiates. In addition to being convenient for postoperative care at home, the agent should also provide long-lasting pain relief with minimal side effects.

Cyclooxygenase-2 (COX-2)-specific inhibitors offer a new opportunity for the management of pain in ambulatory patients as they spare COX-1 at therapeutic concentrations and therefore do not impair platelet function or have a high risk of gastrointestinal toxicity.[12,13] Hence, COX-2–specific inhibitors, unlike nonselective nonsteroidal antiinflammatory drugs (NSAIDs), are potentially safe for oral administration preoperatively and, if able to cross the blood–brain barrier, should inhibit central and peripheral COX-2 as it is induced, to reduce postoperative pain.[5] Furthermore, COX-2–specific inhibitors are not associated with a high incidence of adverse events such as somnolence, drowsiness, nausea, and psychomotor impairment commonly associated with opioids.[6] Therefore, a multimodal pain management approach combining COX-2–specific inhibitors and opioids may provide improved overall tolerability *versus* higher doses of opioids alone and thereby benefit patients with moderate to severe pain.

Valdecoxib is a new, oral COX-2 specific inhibitor with demonstrated analgesic efficacy.[14–16] In addition, valdecoxib has been demonstrated to cross the blood–brain barrier in rodents and inhibit central COX-2, as measured by a reduction of prostaglandin E_2 concentrations in the cerebrospinal fluid (Jinhua Yuan, Ph.D., Assistant Director, Global Drug Metabolism, Pharmacia, Skokie, IL, personal written communication, July 10, 2001; James B. Jones, M.D., Pharm.D., F.A.C.E.P., Medical Director–valdecoxib, Pharmacia, Skokie, IL, personal written communication, February 14, 2002).

These studies evaluated the analgesic efficacy, optimum dose, duration of action, and safety of single pre-

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operatively administered oral doses of valdecoxib. Two surgical models were investigated: oral surgery (impacted third molar extraction), a standard model sensitive to the analgesic actions of conventional NSAIDs,[17–19] and opioids, and orthopedic foot (bunionectomy) surgery, a model not previously used to test the analgesic efficacy of conventional NSAIDs.

Materials and Methods

Patients

Eligible adult patients, weighing at least 50 kg and judged to be in good health, were scheduled to undergo either oral surgery with local anesthesia to extract two ipsilateral impacted third molars, requiring bony resection, or primary unilateral first metatarsal bunionectomy surgery with regional (Mayo block) or local anesthesia. All patients remained at the clinical research centers during the 24-h postsurgical pain assessment period.

Patients were excluded from either study if they had a history of upper gastrointestinal ulceration or other significant upper gastrointestinal complaint, or if they had received analgesics, tricyclic antidepressants, narcotics, antihistamines, tranquilizers, hypnotics, sedatives, conventional NSAIDs, or corticosteroids within 6 h of receiving study medication.

Both studies were conducted in accordance with good clinical practice and the Declaration of Helsinki and were approved by an institutional review board for each clinical research center. All participating patients provided written informed consent.

Study Design

Both studies were single-dose, randomized, double-blind, placebo-controlled, parallel-group trials conducted by investigators from the SCIREX Corporation. The post–oral surgery study was conducted at a single clinical research center in Austin, Texas, while two centers in San Antonio and Austin, Texas, participated in the postbunionectomy study.

The post–oral surgery study evaluated the comparative analgesic efficacy of a single oral dose of placebo or 10, 20, 40, or 80 mg valdecoxib. Eligible patients were randomized to receive study medication using a computer-generated randomization schedule. Study medication was administered 60–75 min before surgery. Lidocaine 2% with 1:100,000 epinephrine was administered 15 min before surgery as a local anesthetic, and nitrous oxide–oxygen sedation was also available, if required. The surgical procedure was expected to last between 20 and 30 min. In the post–oral surgery study, the oral surgeon rated the extent of surgical trauma as moderate (extraction involving mucoperiosteal flap and bone removal) or severe (extraction involving flap and bone removal, and sectioning of the tooth).

The postbunionectomy study evaluated the comparative efficacy of single oral doses of placebo or 20, 40, or 80 mg valdecoxib. Eligible patients were randomized to receive study medication (as in the post–oral surgery study) 45–75 min before bunionectomy surgery. Patients then received regional anesthesia (Mayo block) using lidocaine without epinephrine as a local anesthetic, 5–15 min before surgery. If pain persisted, additional lidocaine was administered to achieve full anesthesia. A continuous infusion of up to 200 μg/kg of the sedative, propofol, was used during the surgery, which was expected to last 30–90 min. In both studies, rescue medication could be requested by the patient at any time and was administered in accordance with the standard practices at each study site.

Efficacy Measurements

Efficacy assessments in both studies were recorded during the 24 h following completion of surgery. Patients were required to stay in the study center throughout this period.

Efficacy measures in each study included the time to rescue medication (time elapsed from administration of study drug to rescue medication) and the proportion of patients within each treatment group that received rescue medication. Patients also assessed their pain intensity (PI) on a four-point categorical scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain) every 30 min following the end of surgery for 2 h, and then at 2-hourly intervals until 24 h after surgery. Patients also completed a Global Evaluation of study medication just before receiving rescue medication or 24 h after the end of surgery, by providing a graded response (4 = excellent, 3 = good, 2 = fair, or 1 = poor) to the statement "How would you rate the study medication you received to delay pain?" Each patient then recorded the time at which the statement was completed.

Safety

Adverse events were monitored throughout the study period and up to 9 days following oral surgery, or 2 weeks after bunionectomy. Safety was assessed by routine clinical laboratory analyses (hematology; biochemistry, including markers of renal function such as creatinine, blood urea nitrogen, and alkaline phosphatase), physical examinations, and measurement of vital signs before surgery and at 30 min and 2, 4, and 24 h following surgery.

Statistical Analysis

Sample Size. A sample size of 55 patients per treatment group was required in both studies to detect a difference of 3 h in the median time to rescue medication, with a power of at least 80% and a type I error at 0.013 (two-sided test adjusted for four comparisons).

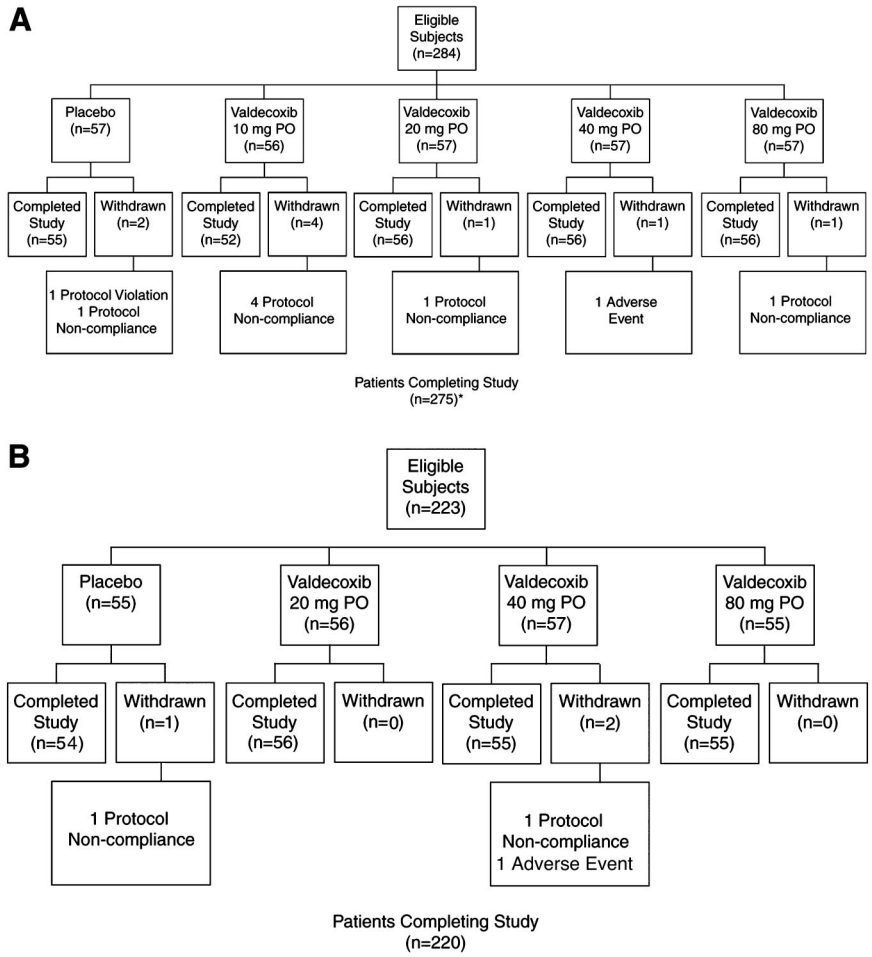

Fig. 1. (*A*) Disposition of patients in postoral surgery study. *Three patients lost to follow-up because of noncompliance after completing efficacy analyses. (*B*) Disposition of patients in postbunionectomy study.

This was based on an assumed median time to rescue medication of 2.62 h for the placebo group.

Efficacy Analyses. In both studies, a modified intention-to-treat cohort was used in all efficacy analyses, using a last-observation-carried-forward approach in which the last score recorded for any given efficacy assessment before withdrawal was used (carried forward) in the analysis at all subsequent time points. The modified intention-to-treat cohort comprised patients who had received study medication and completed surgery without a protocol violation that led to study withdrawal.

The median time to rescue medication was calculated for each treatment group using the Miller method,[20] 95% confidence intervals were calculated using the Simon and Lee method,[21] and time-to-event analyses were plotted as Kaplan-Meier survival curves. Pairwise comparisons were made between groups using pairwise log-rank tests (Fisher protected LSD method). The proportion of patients taking rescue medication was compared using the Fisher exact test (after oral surgery) or the Cochran-Mantel-Haenszel test (after bunionectomy).

The Patient's Global Evaluation of study medication was analyzed by analysis of variance, with treatment and center as factors, and Fisher exact test (after oral surgery) or the Cochran-Mantel-Haenszel test (after bunionectomy). PI-categorical (both studies) was analyzed using analysis of variance with treatment (both studies) and center (postbunionectomy study) as factors. Differences in least squares means were evaluated with the Fisher protected multiple comparison procedure.

Safety Analyses. All patients receiving study medication were included in the safety analyses. The incidence of adverse events was recorded in both studies.

Results

Post–Oral Surgery Study Subjects

A total of 284 healthy adults scheduled to undergo extraction of two ipsilateral third molars were randomized to receive study treatment (fig. 1A). All received one dose of study medication and were included in the demographic and safety analyses. Nine patients (3%) withdrew from the study: 2 (4%) from the placebo group, 4 (7%) from the 10-mg valdecoxib group, and 1 (2%) from each of the 20-mg, 40-mg, or 80-mg valdecoxib treatment groups (fig. 1A). Seven of these patients were withdrawn because of protocol noncompliance. Two of these patients (1 in the 10-mg valdecoxib group and 1 in the 20-mg valdecoxib group) had received study

Table 1. Post–Oral Surgery Study Baseline Patient Demographics

Post–Oral Surgery Study	Treatment Group					
	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)	*P* Value
No. of patients (n)	57	56	57	57	57	—
Mean age (yrs)	23.8	23.9	22.8	22.8	23.5	0.63
% Female	54.4	46.4	45.6	57.9	64.9	0.20
Mean weight (kg)	71.4	74.8	69.4	73.2	71.9	0.47
Moderate surgical trauma rating (%)	44	40	46	43	45	0.98
Severe surgical trauma rating (%)	56	60	54	57	55	0.98
Mean time from preoperative dose to surgery (min)	60	59.7	59.9	60	60	0.46
Mean duration of surgery (min)	11.3	10.5	10.8	10.7	10.8	0.59

medication less than 60 min before the start of surgery, one (10-mg valdecoxib group) withdrew consent before surgery, another (80-mg valdecoxib group) refused to complete surgery, and three were lost to follow-up (1 in the placebo group; 2 in the 10-mg valdecoxib group), and one because of a protocol violation (extraction of 3 instead of 2 molars). The ninth patient, from the 40-mg valdecoxib group, withdrew because of a severe adverse event (vomiting) 9 min after dose.

The modified intention-to-treat cohort comprised 278 patients and included three patients lost to follow-up because of noncompliance after completing the efficacy analyses (1 in the placebo group, 2 in the 10-mg valdecoxib group).

The treatment groups had similar demographics, with no significant differences observed in mean age, weight, sex, time from preoperative dose of study medication to surgery, or time from anesthesia to surgery. In addition, the patients in each treatment group experienced comparable baseline levels of surgical trauma (table 1).

Postbunionectomy Study Subjects

Of the 223 healthy adults scheduled for bunionectomy surgery who received a dose of study medication and were included in the baseline demographics and safety analyses, three were excluded from the modified intention-to-treat cohort used in the efficacy analyses (fig. 1B). Two patients, one from the placebo group and one from the 40-mg valdecoxib group, were withdrawn because of noncompliance (administration of protocol-prohibited medications celecoxib and diphenhydramine, respectively). One patient withdrew from the 40-mg valdecoxib group due to an adverse event (allergic reaction to propofol) before completing surgery.

The treatment groups had comparable baseline demographic characteristics, time from preoperative dose of study medication to surgery, and time from anesthesia to surgery. In addition, there was no significant difference in the duration of surgery among treatment groups (table 2).

Post–Oral Surgery Efficacy Measures

Time to Rescue Medication. Patients receiving placebo and 10- and 20-mg doses of valdecoxib had median time to rescue medication of 2 h and 59 min, 9 h and 4 min, and 13 h and 6 min, respectively, while the median time for those receiving 40- and 80-mg doses of valdecoxib exceeded 24 h. This difference in median time to rescue was significant for all valdecoxib treatment groups compared with placebo as determined by the 95% confidence intervals (table 3) and analysis of the Kaplan-Meier distributions (fig. 2). Furthermore, patients receiving the 40-mg valdecoxib dose had significantly longer median time to rescue medication values than

Table 2. Postbunionectomy Study Baseline Patient Demographics

Postbunionectomy Study	Treatment Group				
	Placebo	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)	*P* Value
No. of patients (n)	55	56	57	55	—
Mean age (yr)	40.3	42.0	42.8	43.2	0.56
% Female	86	91	90	93	0.63
Mean weight (kg)	73.6	74.2	72.4	69.1	0.29
Mean time from preoperative dose to surgery (min)	54.7	56.1	56.1	57.9	0.24
Mean time from anesthesia to surgery (min)	11.1	12.1	11.5	11.5	0.24
Mean duration of surgery (min)	39.9	38.4	40.5	39.9	0.78

Table 3. Median Time to Rescue Medication and Percentage of Patients Requiring Rescue Medication by 24 h Postsurgery in the Post–Oral Surgery and Postbunionectomy Studies

	Treatment Group				
	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)
Post–oral surgery (n)	56	54	56	56	56
Median time to rescue medication [h:min (95% CI)]	2:59 (2:46–3:30)	9:04* (7:18–14:35)	13:06* (9:16 to >24:00)	>24:00*† (>24:00)	>24:00*‡ (13:57 to >24:00)
Patients requiring rescue medication (%)	95	67	57	32	41
Postbunionectomy (n)	54	—	56	55	55
Median time to rescue medication [h:min (95% CI)]	3:24 (2:42–4:07)	—	7:04* (4:33–10:02)	8:03* (4:53–12:03)	8:05* (6:21–10:03)
Patients requiring rescue medication (%)	100	—	88	78	71

* Significantly different distribution compared with placebo. † Significantly different distribution compared with 10 mg and 20 mg valdecoxib. ‡ Significantly different distribution compared with 10 mg valdecoxib.

those receiving the 20-mg dose. In addition, patients receiving 80 mg valdecoxib had significantly longer median values than those receiving 10 mg valdecoxib. A plateau was reached at 40–80-mg doses of valdecoxib; patients receiving these doses had similar median times to rescue medication. Pairwise comparisons confirmed that the median time to rescue medication for all valdecoxib groups was significantly longer than placebo ($P < 0.001$). In addition, the median time to rescue was similar for the 40- and 80-mg valdecoxib groups ($P = 0.34$), but significantly longer than for the 10-mg valdecoxib group ($P \leq 0.003$).

While 95% of placebo-treated patients had received rescue analgesia by 24 h after surgery, this proportion decreased with increasing dose of valdecoxib, from 67 and 57% in the 10- and 20-mg valdecoxib groups to 32 and 41% in the 40- and 80-mg valdecoxib groups, respectively (table 3). This difference was statistically significant for all valdecoxib groups relative to the placebo group ($P < 0.001$).

Pain Intensity. The mean PI categorical score for patients receiving any valdecoxib dose was lower than placebo at all assessment points (fig. 3). This difference was significant at each assessment, up to 24 h following surgery ($P < 0.001$). Patients treated with 40 or 80 mg valdecoxib experienced a reduction of PI of more than 50%, relative to placebo-treated patients from 2 h following study drug administration onward.

Patients receiving 40- and 80-mg doses of valdecoxib experienced similar levels of analgesia, as evidenced by

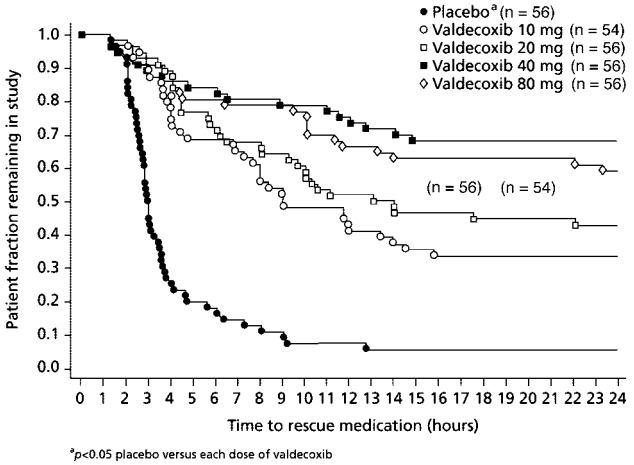

Fig. 2. Time to rescue medication after oral surgery (Kaplan-Meier product limit estimates). *$P < 0.05$ *versus* each dose of valdecoxib.

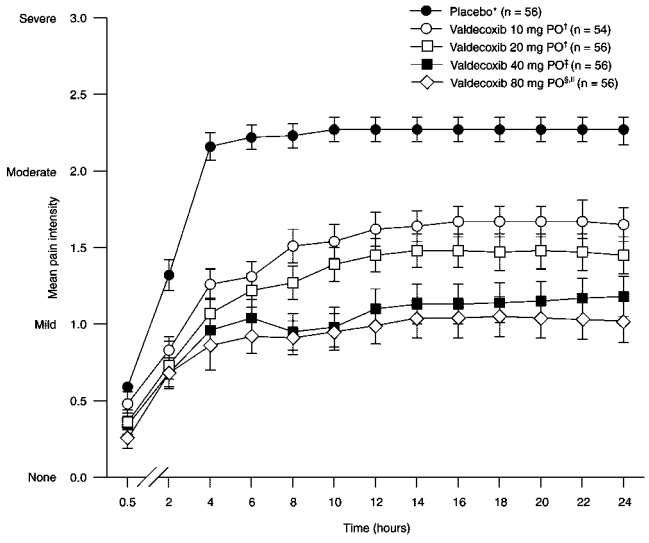

Fig. 3. Mean pain intensity (PI, categorical) scores over time for all treatment groups after oral surgery. *$P < 0.001$, placebo *versus* each dose of valdecoxib, at all time points. †$P < 0.001$, 40 and 80 mg valdecoxib *versus* 10 and 20 mg valdecoxib from 8 to 20 h. ‡$P < 0.001$, 40 mg valdecoxib *versus* 10 mg valdecoxib from 4 to 24 h. §$P < 0.001$, 80 mg valdecoxib *versus* 10 mg valdecoxib from 0.5, and 4 to 24 h. ‖$P < 0.001$, 80 mg valdecoxib *versus* 20 mg valdecoxib from 6 to 24 h.

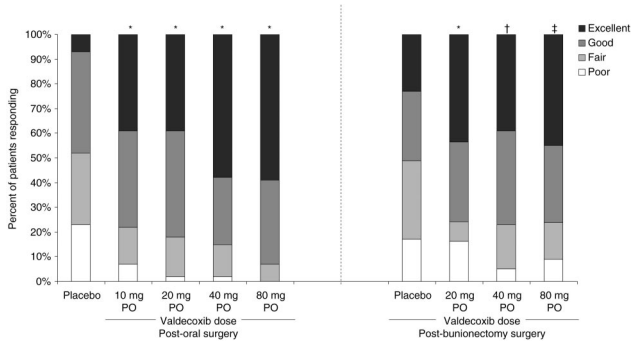

Fig. 4. Patient's global evaluation of study medication results after oral surgery (*P < 0.001 *vs.* placebo) and after bunionectomy (‡P = 0.006, †P = 0.014, or *P = 0.025 *vs.* placebo).

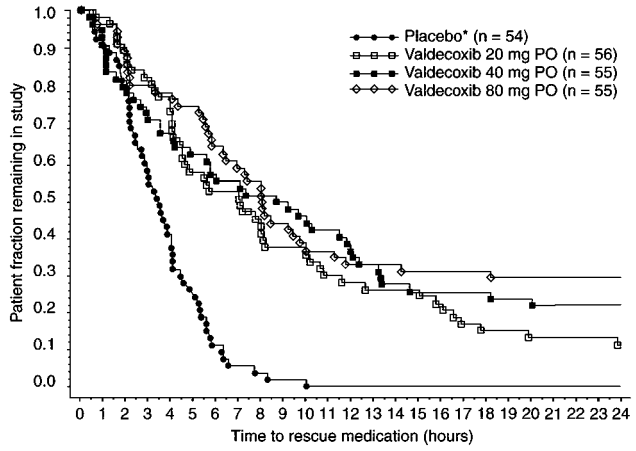

Fig. 5. Time to rescue medication after bunionectomy (Kaplan-Meier product limit estimates). *P < 0.001 *versus* placebo.

their mean PI scores at all assessments. In addition, the mean PI scores for patients receiving 40 or 80 mg valdecoxib were lower than those receiving 10 or 20 mg valdecoxib throughout the 24-h evaluation period. These differences were significant at most time points (fig. 3; $P < 0.001$).

Patient's Global Evaluation of Study Medication. The proportion of patients rating valdecoxib as "good" or "excellent" increased with increasing dose. In the 10–80-mg valdecoxib groups, 78–93% of patients rated their medication as "good" or "excellent," compared with 48% in the placebo group. This difference was significant for each valdecoxib dose ($P < 0.001$; fig. 4). Each valdecoxib treatment group also had significantly higher mean global rating scores than the placebo group ($P < 0.001$). The 40- and 80-mg valdecoxib groups had significantly higher mean scores than the 10-mg group ($P < 0.001$).

Postbunionectomy Efficacy Measures

Time to Rescue Medication. Patients receiving 20–80-mg doses of valdecoxib had median times to rescue medication ranging from 7 h and 4 min to 8 h and 5 min, which were longer than in the placebo group (3 h and 24 min; fig. 5). This difference was significant for all valdecoxib treatment groups compared with placebo (table 3). There was no significant difference in the distribution of the time to rescue medication among the valdecoxib treatment groups. In contrast, pairwise comparisons revealed that the median time to rescue for the 80-mg valdecoxib group was significantly longer than for the 20-mg valdecoxib group ($P < 0.05$; table 3).

While 100% of patients receiving placebo treatment required rescue medication by 24 h after surgery, the proportion decreased with increasing valdecoxib doses, from 88% in the 20-mg valdecoxib group to 71% in the 80-mg valdecoxib treatment group (table 3). This difference was statistically significant between the valdecoxib treatment groups and placebo ($P < 0.001$) and between the 20- and 80-mg valdecoxib groups ($P = 0.03$; table 3).

Pain Intensity. Valdecoxib-treated patients experienced a PI approximately 30% lower than those receiving placebo (fig. 6). This difference reached statistical significance by 4 h after surgery ($P < 0.001$). In addition, the mean PI scores for the 40- and 80-mg valdecoxib groups remained significantly lower than for placebo for the duration of the 24-h study period. However, the differences in mean PI scores between the 20-mg valdecoxib and placebo groups were no longer significant at 18 h after surgery and beyond.

Patient's Global Evaluation of Study Medication. Within each valdecoxib treatment group, more patients (75–77%) rated their study medication as "good" or "excellent" than did those in the placebo group (51%). This difference was significant at all valdecoxib doses (P = 0.006–0.025; fig. 4). Each dose of valdecoxib was rated as good or excellent by similar proportions of patients.

Safety. In total, adverse events were experienced by 128 patients (45%) in the post–oral surgery study and 93 patients (42%) in the postbunionectomy study (table 4).

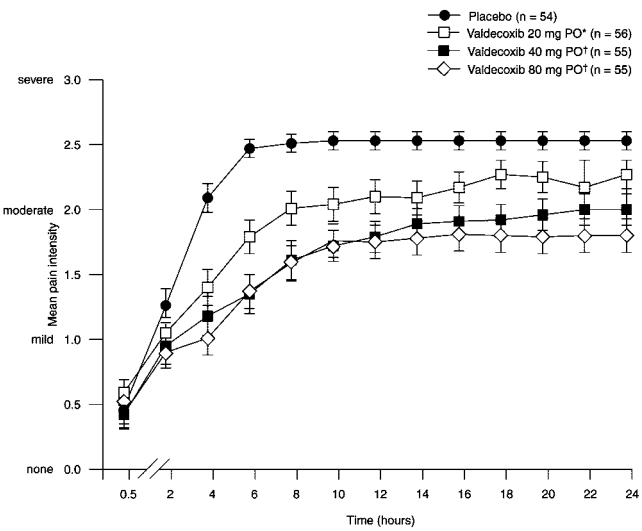

Fig. 6. Mean pain intensity (PI, categorical) scores over time for all treatment groups after bunionectomy. *P < 0.001 from 4 to 16 h for 20 mg valdecoxib *versus* placebo. †P < 0.001 from 4 to 24 h for 40–80 mg valdecoxib *versus* placebo.

Table 4. Summary of Adverse Events Experienced in the Post–Oral Surgery and Postbunionectomy Studies

	Treatment Group				
	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)
Post–oral surgery (n)	57	56	57	57	57
Total adverse events	33 (58%)	26 (46%)	18 (32%)	28 (49%)	23 (40%)
Total gastrointestinal adverse events	16 (28%)	11 (20%)	4 (7%)	8 (14%)	8 (14%)
Adverse events causing withdrawal	0 (0%)	0 (0%)	0 (0%)	1 (< 2%)	0 (0%)
Most common (≥ 2%) adverse events					
Headache	15 (26%)	9 (16%)	6 (11%)	10 (18%)	11 (19%)
Nausea	15 (26%)	9 (16%)	3 (5%)	6 (11%)	7 (12%)
Vomiting	7 (12%)	4 (7%)	1 (2%)	4 (7%)	2 (4%)
Postbunionectomy (n)	55	—	56	57	55
Total adverse events	26 (47%)	—	23 (41%)	24 (42%)	20 (36%)
Total gastrointestinal adverse events	12 (22%)	—	15 (27%)	13 (23%)	11 (20%)
Adverse events causing withdrawal	0 (0%)	—	1 (< 2%)	1 (< 2%)	0 (0%)
Most common (≥ 2%) adverse events					
Headache	4 (7%)	—	5 (9%)	1 (2%)	2 (4%)
Nausea	10 (18%)	—	13 (23%)	12 (21%)	9 (16%)
Vomiting	2 (4%)	—	5 (9%)	3 (5%)	2 (4%)

The majority were mild to moderate in intensity. Overall, three patients were withdrawn from the studies because of adverse events (one patient who received 40 mg valdecoxib in the post–oral surgery study and one patient from each of the 20- and 40-mg valdecoxib groups in the postbunionectomy study). None of these withdrawals was definitely attributable to study medication. Headache, nausea, and vomiting were the adverse events with the highest incidence (≥ 2%) in both studies (table 4).

No treatment-related platelet-derived (postoperative bleeding) or renal (edema) adverse events occurred in either study. There was no evidence of an increase in the incidence of adverse events (gastrointestinal, renal or platelet-related) or of a consistent pattern of clinically significant changes in laboratory tests (including measures of renal function such as serum creatinine, alkaline phosphatase, and blood urea nitrogen concentrations), vital signs, or physical examination results with increasing doses of valdecoxib compared with placebo in either study.

Discussion

Preoperative oral treatment with the potent COX-2–specific inhibitor valdecoxib provides effective relief from acute mild to moderate pain following oral or orthopedic surgery. All doses of valdecoxib provided a duration and magnitude of analgesia that was significantly greater than placebo. A dose-dependent analgesic effect was observed up to 40 mg valdecoxib. In both surgical models, all doses of valdecoxib were safe and well tolerated, with no clinically significant treatment-related gastrointestinal, renal, or platelet adverse events, and no evidence of a dose-dependent increase in adverse events.

Although conventional NSAIDs have been used preoperatively or perioperatively, their ability to inhibit COX-1 has raised concerns over their gastrointestinal safety and an increased risk of perioperative bleeding.[22–25] Romsing and Walther-Larsen[26] reviewed the published literature on analgesic efficacy and bleeding following the perioperative use of NSAIDs and confirmed that, although hemorrhagic events do occur in the postoperative period, there is no clear association between perioperative NSAID use and disorders in hemostasis. For maximum benefit, NSAID risk factors must be recognized, and the patient, clinical indication, individual NSAID, and timing and route of administration, must all be selected carefully.[26] Because valdecoxib is a highly selective COX-2–specific inhibitor *in vitro* (COX-2: COX-1 inhibition ratio of 28,000),[14] it should be safe in terms of platelet and gastrointestinal side effects and suitable for preoperative use. A study involving healthy adult volunteers has already confirmed that valdecoxib (40 mg twice daily for 7.5 days) has no platelet inhibitory effect.[27] The absence of clinically significant gastrointestinal side effects, clinical evidence of increased bleeding following surgical trauma and platelet abnormalities following valdecoxib treatment in the current studies support the perioperative use of valdecoxib. According to these studies, valdecoxib can be safely administered preoperatively up to a supratherapeutic dose of 80 mg without inhibiting COX-1. However, the issue of side effects and safety should be examined in other surgical models, such as tonsillectomy or hip surgery, which have different risks.

There were distinct differences between the two surgical models studied in terms of the pain experienced, the analgesic cover required, and the relative efficacy of valdecoxib. Removal of impacted third molar teeth is a standard model for assessing the efficacy of analgesics in an acute pain setting.[28] Although this model is sensitive to NSAIDs and opioids,[29,30] oral pain mediated by the

trigeminal system may differ in some respects from that in the rest of the body, and its predictability for control of other forms of postoperative pain, particularly those with a less vigorous inflammatory reaction, has not been rigorously examined. For that reason, we felt it useful to compare the oral model with another surgical model. The bunionectomy model was selected because of the relative homogeneity of the surgical and anesthetic procedures and because patients predictably require postoperative analgesic intervention. The observed differences in analgesic efficacy, and in the dose–response between the two surgical models, probably reflect differences in the intensity of postoperative pain experienced and differences in the duration of surgery, affected tissue sites, their sensory innervation, and in the extent of inflammation before and following surgical trauma.

In these protocols, the pain levels are low in the immediate postoperative period even in the placebo group, because of the residual local anesthetic effects, and only reach a peak as the anesthetic wears off and the full inflammatory response to surgery evolves. Although most noninflamed tissues have little or no COX-2 protein, local expression is induced at the site of surgical trauma by the production of proinflammatory mediators such as interleukin-1β.[31,32] In animal models, there is a delay of 2–4 h from the initial surgical incision until high concentrations of cellular COX-2 protein accumulate.[33] In addition, interleukin-1β, produced in the cerebrospinal fluid in response to a humoral signal, binds to interleukin-1β receptors on dorsal horn neurons to elicit COX-2 up-regulation within the central nervous system, a change that is not prevented by regional anesthesia.[32] The action of peripherally and centrally induced COX-2 can lead to a peripheral sensitization of nociceptor terminals and to central sensitization.[34,35] It is therefore probable that the extent to which different COX-2–specific inhibitors penetrate the blood–brain barrier (and the associated kinetics) will influence their relative analgesic efficacy. Studies in rodents have demonstrated that valdecoxib can cross the blood–brain barrier and inhibit central COX-2, as measured by a reduction in prostaglandin E_2 within the cerebrospinal fluid (Jinhua Yuan, Ph.D., Assistant Director, Global Drug Metabolism, Pharmacia, Skokie, IL, personal written communication, July 10, 2001; James B. Jones, M.D., Pharm.D., F.A.C.E.P., Medical Director–valdecoxib, Pharmacia, Skokie, IL, personal written communication, February 14, 2002). Central COX-2 inhibition may therefore contribute to the analgesic action of valdecoxib. Although it can cross the blood–brain barrier, valdecoxib was not associated with significant central nervous system–type side effects, such as somnolence and dizziness, in the current studies.

Peak pain occurred at 4 h after oral surgery (fig. 3). Between 2 and 6 h after oral surgery, almost all (92%) placebo-treated patients required rescue medication (fig. 2). Following oral surgery, the PI experienced by valdecoxib-treated patients was significantly reduced in amplitude (55%) for the entire 24 h of observation (fig. 3), paralleling the substantially diminished requirement for rescue medication (40%; fig. 2).

The bunionectomy patients also had adequate analgesic cover in the immediate postoperative period. However, once the regional anesthesia wore off, the placebo-treated patients in this study experienced more pain than those in the oral surgery study (fig. 6). Valdecoxib provided a significant reduction in PI (30%) after bunionectomy. The duration of analgesia was considerably shorter than in the oral surgery group, however, with a drift of the treated groups pain scores toward the placebo level beyond 12 h after surgery. Beyond 12 h, most patients in the valdecoxib groups required additional analgesia; hence, rescue medication was required in 71–78% of these patients, yet the time to rescue was significantly delayed relative to the placebo group (fig. 5). It is possible that bunionectomy patients would have benefited from a second oral dose of 20 or 40 mg valdecoxib later in the first postoperative day.

It is now readily accepted that waiting for a patient to report severe pain before prescribing an analgesic produces unnecessary suffering and might reduce the efficacy of any subsequent treatment. There has been considerable interest in the concept that preemptive analgesia might reduce postoperative pain by preventing central sensitization induced by nociceptive signals at the time of surgery. However, in the case of COX-2, classic preemptive therapy is not appropriate, since COX-2 specific inhibitors cannot act on this enzyme until it accumulates in cells several hours after surgery.[31,33] Although there is theoretically no difference then between preoperative, intraoperative, or immediate postoperative administration for short surgical procedures and drugs with a short T_{max}, it is more convenient to administer an oral analgesic, such as valdecoxib, preoperatively. There might potentially be some difference in efficacy between COX-2–specific inhibitors administered perioperatively and those given several hours postoperatively, once intracellular COX-2 has accumulated. This will need to be formally tested.

In conclusion, the novel potent COX-2 specific inhibitor valdecoxib is effective and well tolerated when administered orally and preoperatively for the treatment of acute postoperative pain. While oral surgery has often served as a model for demonstrating the efficacy of analgesics, this study has shown that bunionectomy is also a useful surgical model for the evaluation of the efficacy of analgesics in acute postoperative pain. Based on the data presented here, it appears that valdecoxib may be useful in the treatment of postoperative pain when administered preoperatively.

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References

1. Moore RA, McQuay HJ: Single-patient data meta-analysis of 3453 postoperative patients: Oral tramadol versus placebo, codeine and combination analgesics. Pain 1997; 69:287–94

2. Po AL, Zhang WY: Analgesic efficacy of ibuprofen alone and in combination with codeine or caffeine in post-surgical pain: A meta-analysis. Eur J Clin Pharmacol 1998; 53:303–11

3. Moore A, Collins S, Carroll D, McQuay H, Carroll D, Edwards J: Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. Cochrane Database Syst Rev 2000; 2:CD001547

4. Beauregard L, Pomp A, Choiniere M: Severity and impact of pain after day-surgery. Can J Anaesth 1998; 45:304–11

5. Tong D, Chung F: Postoperative pain control in ambulatory surgery. Surg Clin North Am 1999; 79:401–30

6. Dahl V, Raeder JC: Non-opioid postoperative analgesia. Acta Anaesthesiol Scand 2000; 44:1191–203

7. Rawal N, Allvin R, Amilon A, Ohlsson T, Hallen J: Postoperative analgesia at home after ambulatory hand surgery: A controlled comparison of tramadol, metamizol, and paracetamol. Anesth analg 2001; 92:347–51

8. McDonald DD: Postoperative pain after hospital discharge. Clin Nurs Res 1999; 8:355–67

9. Campbell WI: Analgesic side effects and minor surgery: Which analgesic for minor and day-case surgery? Br J Anaesth 1990; 64:617–20

10. McQuay HJ, Moore RA: Postoperative analgesia and vomiting, with special reference to day-case surgery: A systematic review. Health Technol Assess 1998; 2:1–236

11. Rawal N, Hylander J, Nydahl PA, Olofsson I, Gupta A: Survey of postoperative analgesia following ambulatory surgery. Acta Anaesthesiol Scand 1997; 41:1017–22

12. Everts B, Wahrborg P, Hedner T: COX-2-Specific inhibitors—The emergence of a new class of analgesic and anti-inflammatory drugs. Clin Rheumatol 2000; 19:331–43

13. Clemett D, Goa KL: Celecoxib: A review of its use in osteoarthritis, rheumatoid arthritis and acute pain. Drugs 2000; 59:957–80

14. Talley J, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, Perkins WE, Rogers RS, Shaffer AF, Zhang YY, Zweifel BS, Seibert K: 4-[5-methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: A potent and selective inhibitor of COX-2. J Med Chem 2000; 43:775–7

15. Desjardins PJ, Talwalker S, Hubbard RC, Recker DP, Verburg KM: Preoperative administration of valdecoxib, a potent COX-2 specific inhibitor, provides effective relief from post-operative analgesia (abstract). ANESTHESIOLOGY 2001; 95:A811

16. Daniels SE, Talwalker S, Hubbard RC, Recker DP, Verburg KM: Preoperative valdecoxib, a COX-2 specific inhibitor, provides effective and long lasting pain relief following oral surgery (abstract). ANESTHESIOLOGY 2001; 95:A810

17. Malmstrom K, Daniels S, Kotey P, Seidenberg BC, Desjardins PJ: Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: A randomized, placebo-and active-comparator-controlled clinical trial. Clin Ther 1999; 21:1653–63

18. Seymour RA, Kelly PJ, Hawkesford JE: The efficacy of ketoprofen and paracetamol (acetaminophen) in postoperative pain after third molar surgery. Br J Clin Pharmacol 1996; 41:581–5

19. Bridgman JB, Gillgrass TG, Zacharias M: The absence of any pre-emptive analgesic effect for non-steroidal anti-inflamamtory drugs. Br J Oral Maxillofac Surg 1996; 34:428–31

20. Miller RG: Survival Analysis. New York, John Wiley, 1981, pp 74–5

21. Simon R, Lee YJ: Nonparametric confidence limits for survival probability and median survival time. Cancer Treat Rep 1982; 66:37–42

22. Schmidt A, Bjorkman S, Akeson J: Preoperative rectal diclofenac versus paracetamol for tonsillectomy: Effects on pain and blood loss. Acta Anaesthesiol Scand 2001; 45:48–52

23. Splinter WM, Rhine EJ, Roberts DW, Reid CW, MacNeill HB: Preoperative ketorolac increases bleeding after tonsillectomy in children. Can J Anaesthesiol 1996; 43:560–3

24. Gallagher JE, Blauth J, Fornadley JA: Perioperative ketorolac tromethamine and postoperative hemorrhage in cases of tonsillectomy and adenoidectomy. Laryngoscope 1995; 105:606–9

25. Moote C: Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain. Drugs 1992; 44:14–29

26. Romsing J, Walther-Larsen S: Peri-operative use of nonsteroidal anti-inflammatory drugs in children: Analgesic efficacy and bleeding. Anaesthesia 1997; 52:673–83

27. Leese PT, Talwalker S, Recker DP, Kent JD: Valdecoxib, a novel COX-2 specific inhibitor, does not impair platelet function in healthy adults: Results of a randomized controlled trial. Am J Emerg Med 2002; 20:275–81

28. Desjardins PJ: Analgesic efficacy of piroxicam in postoperative dental pain. Am J Med 1988; 84:35–41

29. Likar R, Sittl R, Gragger K, Pipam W, Blatnig H, Breschan C, Schalk HV, Stein C, Schafer M: Peripheral morphine analgesia in dental surgery. Pain 1998; 76:145–50

30. Habib S, Matthews RW, Scully C, Levers BG, Shepherd JP: A study of the comparative efficacy of four common analgesics in the control of postsurgical dental pain. Oral Surg Oral Med Oral Pathol 1990; 70:559–63

31. Vane JR, Bakhle YS, Botting RM: Cyclooxygenases 1 and 2. Ann Rev Pharmacol Toxicol 1998; 38:97–120

32. Samad TA, Moore KA, Sapirstein A, Billett S, Allchorne A, Poole S, Bonventre JV, Woolf CJ: Interleukin-1-β mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001; 410:471–5

33. O'Banion MK: Cyclooxgenase-2: Molecular biology, pharmacology, and neurobiology. Crit Rev Neurobiol 1999; 13:45–82

34. Gold MS, Levine JD, Correa AM: Modulation of TTX-R INa by PKC and PKA and their role in PGE2-induced sensitization of rat sensory neurons in vitro. J Neurosci 1998; 18:10345–55

35. Southall MD, Michael RL, Vasko MR: Intrathecal NSAIDs attenuate inflammation-induced neuropeptide release from rat spinal cord slices. Pain 1998; 78:39–48