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Safety and Efficacy of the Cyclooxygenase-2 Inhibitors Parecoxib and Valdecoxib after Noncardiac Surgery

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Background: **Valdecoxib and its intravenous prodrug parecoxib are reported to increase thromboembolic risk after coronary artery bypass grafting. The authors conducted a randomized trial to examine their safety and analgesic efficacy in patients recovering from major noncardiac surgical procedures.**

Methods: **The trial was randomized and double-blind, with 10 days of treatment and 30 days of follow-up. Patients (n = 1,062) received either parenteral parecoxib for 3 days and oral valdecoxib for the rest of the treatment period or placebo medications throughout. The frequency of predefined adjudicated postrandomization adverse events, including cardiovascular thromboembolism, renal dysfunction, gastroduodenal ulceration, and wound-healing complications, was assessed in each group. Secondary efficacy endpoints included patients' pain ratings, opioid analgesic consumption (recorded as morphine equivalents), and reports of opioid-related adverse effects.**

Results: **Predefined adjudicated adverse events had similar frequencies among patients who received parecoxib and valdecoxib (2.7%) and placebo patients (3.2%) ($P = 0.58$), including cardiovascular thromboembolic events (1.0% in each group; $P = 1.0$). Placebo patients consumed more morphine equivalents (66.2 ± 92.4 mg) than did patients receiving parecoxib and valdecoxib (43.2 ± 65.7 mg) ($P < 0.001$). Placebo patients had higher mean pain ratings on each of study days 2–10 ($P < 0.01$) and reported more opioid-related symptom distress on days 2–6 ($P < 0.01$).**

Conclusions: **Parecoxib and valdecoxib are useful adjuncts to opioids for the treatment of postoperative pain in noncardiac surgical patients. Further study will be required to determine the safety profile of parecoxib and valdecoxib administered to patients with known atherosclerotic disease after noncardiac surgery.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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PARENTERAL administration of nonsteroidal antiinflammatory drugs is an established pharmacologic tool for reducing pain after surgery. However, the potential adverse effects of cyclooxygenase-1 inhibition, such as gastric ulceration and bleeding, have limited the use of nonspecific nonsteroidal antiinflammatory drugs in many surgical patients.[1] Selective cyclooxygenase-2 inhibitors are unlikely to cause these effects. However, their safety has recently been called into question because they may increase the incidence of thromboembolic cardiovascular events in nonsurgical patients receiving rofecoxib[2–5] or celecoxib.[3,6]

Also, two randomized trials of valdecoxib and its intravenous prodrug parecoxib in patients undergoing coronary artery bypass graft (CABG) surgery showed that patients taking these drugs had a higher rate of postoperative cardiovascular thromboembolic events than did patients taking placebo.[7,8] This difference was significant in the larger study.[8] In both trials, parecoxib and valdecoxib were also associated with a higher incidence of wound-healing complications.[7,8] However, previous short-term studies of noncardiac surgical patients receiving parecoxib and valdecoxib, *e.g.*, those undergoing dental, gynecologic, orthopedic, and other surgical procedures,[9–12] have not revealed any serious adverse effects of these drugs. Nonetheless, it is possible that the sample sizes of these studies were insufficient to detect small but clinically meaningful differences in adverse event rates between patients receiving placebo and those receiving parecoxib and valdecoxib.

To define more clearly the safety of parecoxib and valdecoxib in noncardiac surgical patients and to confirm the analgesic efficacy of these drugs, a large trial was conducted in patients recovering from a variety of major noncardiac surgical procedures.

Materials and Methods

Study Design and Procedures

The trial, conducted in 113 centers in 14 countries from September 2002 to February 2003, was a sponsor-initiated, randomized, double-blind, parallel-group, multiple-dose, placebo-controlled study with 10 days of treatment and 30 days of follow-up after study drug administration was completed. All patients had access to standard opioid medications throughout the treatment period. The institutional review board or ethics committee at each center approved the protocol, and all patients gave written informed consent.

Patients were randomly assigned to two treatment groups. The parecoxib–valdecoxib group received an initial parenteral dose of 40 mg parecoxib on the day of surgery (day 1), and then 20 mg parecoxib every 12 h for 3 days, followed by 20 mg oral valdecoxib every 12 h through the 10th day. The placebo group received matching placebo medications throughout the 10-day period. Patients who were unable to tolerate oral medications continued to receive the intravenous study drug. Other routinely administered postoperative medications, including prophylaxis against deep vein thrombosis, were permitted, except for nonsteroidal antiinflammatory drugs, sedating antihistamines, prophylactic antiemetic agents, intrathecal or epidural opioids, and local analgesics applied to the surgical incision. Although concomitant low-dose aspirin use was not required, patients already taking aspirin (325 mg/day or less) were allowed to continue.

Study Endpoints

Safety. The primary endpoint was the combined incidence of predefined postrandomization adverse events in the following four clinically relevant categories: cardiovascular events, renal events, surgical wound complications, and gastrointestinal complications. Cardiovascular events included cardiac, cerebrovascular, and peripheral vascular events. Cardiac events included myocardial infarction, severe myocardial ischemia (defined as typical ischemic chest discomfort lasting at least 10 min and associated with transient ST-segment changes of at least 1 mm on the electrocardiogram), sudden death from cardiac causes, or unexpected death without an identifiable noncardiac cause within 60 min after the onset of symptoms.

Myocardial infarction was diagnosed at autopsy or by the presence of two or more of the following: prolonged chest pain (lasting more than 20 min) that was not relieved by antianginal agents and was accompanied by new electrocardiographic ST changes of at least 1 mm, a creatine kinase (myocardial band) level greater than 2 times the upper limit of normal, or a peak troponin I level of at least 3.7 μg/l; new wall-motion abnormalities that were consistent with the occurrence of a myocardial infarction (a two-grade change) detected during catheterization, echocardiography, or radionuclide scanning; and new Q waves on serial electrocardiography that were consistent with the occurrence of myocardial infarction.[13] Cerebrovascular events included a new ischemic or hemorrhagic cerebrovascular accident lasting 24 h or longer or a transient ischemic attack lasting less than 24 h, diagnosed according to clinical criteria and confirmed by a diagnostic study (*e.g.*, computed tomography or magnetic resonance imaging).[14] Peripheral vascular events included deep vein thrombosis, defined as increased unilateral or bilateral leg swelling, warmth, and edema, with a confirmatory diagnostic test, and pulmonary embolism, defined as chest pain, dyspnea, or hypoxemia, with a confirmatory imaging study.

Renal events included renal failure, defined as the need for hemodialysis or peritoneal dialysis after surgery, and severe renal dysfunction, defined by a postoperative serum creatinine level of at least 2.0 mg/dl, with an increase of at least 0.7 mg/dl after randomization.[15] Gastroduodenal complications were defined as gastrointestinal ulcers resulting in bleeding (proven on the basis of endoscopy), perforation, or obstruction. Wound-healing complications included infection of the superficial incisional site, the deep incisional site, the organ itself, or the surgical space, or noninfectious separation or dehiscence of the wound.

The primary investigator at each site was responsible for reporting all adverse events to the sponsor, including directly observed events and those spontaneously reported by the patients. Definitions of the predefined endpoints of interest were described in detail in the study protocol and reiterated in a newsletter regularly distributed to all investigational sites. An independent, external endpoint committee (see appendix) whose members were unaware of the patients' treatment assignments used these definitions to review the data on adverse events. Adjudicated, predefined adverse events in all four categories were combined for the primary safety analysis. Secondary safety endpoints included the incidence of all adverse events, defined as any untoward medical occurrence that did not necessarily have a causal relation with study drug treatment, and serious adverse events, defined as any event that resulted in one or more of the following: death, life-threatening complication, prolongation of current hospitalization or requirement for rehospitalization, or persistent or significant disability. In addition, electrocardiograms, clinical laboratory assessments, and vital signs were analyzed at baseline, at the time of transition from intravenous to oral medication, and at the final visit (occurring between days 11 and 14). Patients were contacted by telephone 30 days after the last dose of study medication and were assessed for the occurrence of serious or clinically relevant adverse events. A data and safety monitoring board

(see appendix) independently monitored safety outcomes throughout the study.

Efficacy. Efficacy measures, as secondary endpoints, included patients' use of any supplemental opioid analgesics, converted to morphine equivalents according to published potency ratios.[16] On days 1–10, using a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), patients recorded their current pain level in a preprinted diary at 2, 4, 8, 12, and 24 h after the first daily dose. Also, once per day, using four-point scales, patients rated their distress from opioid-related symptoms in terms of frequency (rarely, occasionally, frequently, almost constantly), severity (slight, moderate, severe, very severe), and degree of bother (a little bit, somewhat, quite a bit, very much). Symptoms included fatigue, drowsiness, inability to concentrate, confusion, dizziness, constipation, itching, difficulty with urination, nausea, and retching/vomiting.[17]

Patient Population

Patients were men and women who were scheduled to undergo major orthopedic, abdominal, gynecologic, or noncardiac thoracic surgery requiring general or regional anesthesia and who were expected to require opioids for postoperative pain. Patients undergoing vascular surgical procedures (*e.g.*, carotid endarterectomy, femoral–popliteal bypass, or aortic arch or aneurysm repair), partial hepatic resection, organ transplant, or intracranial surgery were excluded. Inclusion criteria were an age of 18–80 yr, a body mass index of no more than 40 kg/m^2, a weight of more than 55 kg, and an American Society of Anesthesiologists physical status classification of I–III.[18]

Exclusion criteria were emergency surgery, a thromboembolic event (cerebrovascular accident, transient ischemic attack, unstable angina, myocardial infarction, deep vein thrombosis, or pulmonary embolism) within 3 months before study entry, renal disease that was considered clinically significant by the investigator, or active gastrointestinal bleeding in the 60 days before surgery. Before randomization, other exclusion criteria included a surgical procedure longer than 4 h, inability to extubate the trachea within 4 h after operation, evidence of a new postoperative myocardial infarction, abnormal postoperative mental status or any new neurologic deficit, postsurgical bleeding considered significant by the investigator, a hemoglobin level of less than 8 g/dl, or a urine output of less than 30 ml/h.

Statistical Analyses

The sample size of 500 patients per treatment arm provided at least 80% power to detect a doubling of the 4% estimated background incidence of all predefined adverse events combined. All eligible patients were stratified according to geographic location (North America, Europe, or another location) before randomization.

Analyses were performed on the modified intent-to-treat population, which was defined as those patients who were randomized and who received at least one dose of study medication. The primary safety analysis used the Fisher exact test to examine the proportion of patients in each group with at least one predefined adverse event. Similar analyses were performed for individual confirmed events within each of the four endpoint categories. For predefined cardiovascular events, analyses of the time to a first event were performed with the log-rank test and presented by means of Kaplan-Meier curves.

Efficacy measurements were made on each study day, *i.e.*, the time period between the morning dose on a given day and the morning dose on the next day. Supplemental analgesia was examined by analysis of variance of observed data only, without imputation of data after a patient withdrew from the study. Summed pain intensity scores were calculated from the five categorical pain intensity assessments recorded each day. Each rating was weighted by the number of hours between the time it was obtained and the time the previous rating was obtained, so that the summed pain intensity score = (2-h rating × 2) + (4-h rating × 2) + (8-h rating × 4) + (12-h rating × 4) + (24-h rating × 12). The potential range of these scores was 0–72. Daily summed pain intensity scores were analyzed with general linear models. For opioid-related symptom distress, an overall composite score—the mean of the frequency, severity, and degree of bother scores for all opioid-related symptoms—was calculated for each day. These composite scores were analyzed with analyses of variance. All statistical comparisons included treatment and country as factors, were two tailed, and used an α value of 0.05. There were no prespecified stopping rules, and none of the comparisons were adjusted for interim analyses.

The sponsor collected the data. The authors had complete access to the data after unblinding. All final analyses were conducted by an independent statistician at the Texas Heart Institute in Houston.

Results

Patient Characteristics

A total of 1,062 patients from 14 countries (see appendix) were randomized: 533 to the group given parecoxib and valdecoxib and 529 to the placebo group. Enrollment and outcomes are outlined in figure 1. There were no significant differences between the two groups in preoperative characteristics, including cardiovascular risk factors (table 1), or in the proportion of patients undergoing orthopedic, gastrointestinal, gynecologic, thoracic, or other types of surgery (table 2). Duration of surgery and time from the end of surgery until administration of study medication were comparable between the two groups (table 2).

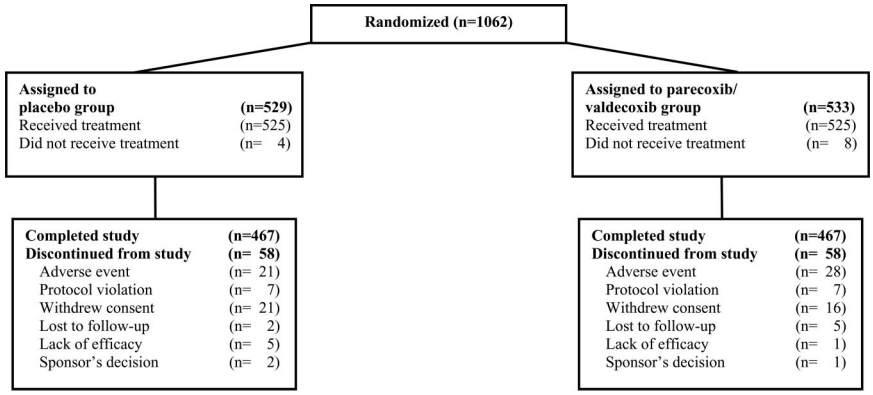

Fig. 1. Enrollment and outcome. Discontinued patients were included in all analyses. All decisions about discontinuation were made by the primary investigator, except for those noted as the sponsor's decisions (made while study group assignment was still blinded) in the case of three patients (*e.g.*, because of failure to comply with the treatment regimen after discharge from the hospital). In the parecoxib–valdecoxib group, 458 of 533 patients completed 10 days of treatment, as did 457 of 529 patients in the placebo group.

Primary Endpoint: Predefined Adjudicated Adverse Events

The patients given parecoxib and valdecoxib did not differ from the placebo patients in the incidence of predefined adjudicated adverse events in any of the four categories, or in the percentage of patients with at least one event (table 3). Cardiovascular event rates were identical in the group given parecoxib and valdecoxib and the group given placebo (1.0% *vs.* 1.0%; risk ratio, 1.0; 95% confidence interval, 0.29–3.5; $P = 1.0$; table 3). The time-to-event analysis revealed that cardiovascular events occurred throughout and after the 10-day period of drug administration in both groups (fig. 2). Likewise, surgical wound event rates were similar in the group given parecoxib and valdecoxib and the group given placebo (1.7% *vs.* 2.1%; risk ratio, 0.81; 95% confidence interval, 0.3–2.0; $P = 0.65$).

Secondary Endpoints (Safety): Adverse Events, Serious Adverse Events, Clinical Laboratory Assessments, and Vital Signs

Adverse events were reported in 285 of 525 patients taking parecoxib and valdecoxib (54.3%) and in 302 of 525 placebo patients (57.5%) over the entire study period ($P = 0.29$). The frequencies of three of the four most common adverse events were nearly identical between treatment groups: Nausea was reported by 96 patients taking parecoxib and valdecoxib (18.3%) and 100 placebo patients (19.0%), vomiting was reported by 54 patients taking parecoxib and valdecoxib (10.3%) and

Table 1. Preoperative Characteristics of All Randomized Patients

Characteristic	Placebo (n = 529)	Parecoxib–Valdecoxib (n = 533)
Age, yr	52.9 ± 14.3	53.8 ± 14.4
Age ≥ 65 yr, %	122 (23.1)	140 (26.3)
Male sex, %	223 (42.2)	216 (40.5)
Race or ethnic group, %*		
White	486 (91.9)	502 (94.2)
Black	23 (4.3)	24 (4.5)
Asian	2 (0.4)	1 (0.2)
Not listed	18 (3.4)	6 (1.1)
Height, cm	168.4 ± 9.3	168.3 ± 9.3
Weight, kg	78.4 ± 15.9	77.5 ± 15.6
Body mass index	27.6 ± 4.8	27.3 ± 4.8
Body mass index ≥ 30 kg/m^2, %	144 (27.2)	141 (26.5)
β-Blocker use (preoperative and/or during the study period), %	67 (12.7)	49 (9.2)
Medical history, %		
Angina	25 (4.7)	23 (4.3)
Hypertension	181 (34.2)	175 (32.8)
Congestive heart failure	6 (1.1)	7 (1.3)
Coronary artery atherosclerosis	26 (4.9)	37 (6.9)
Myocardial infarction	13 (2.5)	13 (2.4)
Peripheral edema	9 (1.7)	9 (1.7)
Hyperlipidemia	181 (34.2)	175 (32.8)
Peripheral vascular disease	8 (1.5)	15 (2.8)
Asthma	35 (6.6)	27 (5.1)
Renal insufficiency	4 (0.8)	2 (0.4)
Diabetes mellitus	44 (8.3)	44 (8.3)
Anemia	48 (9.1)	46 (8.6)

Data are presented as mean ± SD unless otherwise noted.

* Patients must choose one of these four options.

Table 2. Surgical Procedure Details for All Randomized Patients*

Characteristic	Placebo (n = 529)	Parecoxib–Valdecoxib (n = 533)
Type of surgery, %		
Orthopedic	140 (26.5)	144 (27.0)
Knee	73 (13.8)	67 (12.6)
Hip	30 (5.7)	44 (8.3)
Neck/spine	22 (4.2)	19 (3.6)
Gastrointestinal	202 (38.2)	191 (35.8)
Gallbladder	61 (11.5)	56 (10.5)
Intestinal/rectal	57 (10.8)	57 (10.7)
Gastric	25 (4.7)	17 (3.2)
Gynecologic	103 (19.5)	103 (19.3)
Uterine	84 (15.9)	86 (16.1)
Thoracic	12 (2.3)	11 (2.1)
Other†	94 (17.8)	107 (20.1)
Duration of surgery, min	98.7 ± 45.0	100.3 ± 46.9
Number of patients with missing data‡	2	4
Time from end of surgery to study medication, min	220.2 ± 173.3	239.0 ± 192.4
Number of patients with missing data§	5	10

Data are presented as mean ± SD unless otherwise noted.

* Unless otherwise noted, the analysis includes all randomized patients. † Includes prostate, thyroid, urologic/bladder, renal, breast, and neurologic surgery. ‡ The time at which surgery ended was not recorded for these 6 patients. § The time at which surgery ended was not recorded for 6 of these 15 patients; the time at which the first dose of study medication was administered was not recorded for the remaining 9 patients.

50 placebo patients (9.5%), and constipation was reported by 64 patients taking parecoxib and valdecoxib (12.2%) and 63 placebo patients (12.0%). However, only 13 of 525 patients taking parecoxib and valdecoxib (2.5%) experienced fever, whereas 65 of 525 placebo patients (12.4%) did ($P < 0.001$). Sixty-nine serious adverse events occurred in 56 patients: 39 in 27 patients taking parecoxib and valdecoxib (5.1%) and 30 in 29 placebo patients (5.5%) ($P = 0.77$).

Seven deaths occurred during the study (table 3). Of the three deaths that occurred in patients who received parecoxib and valdecoxib, one was caused by each of the following: myocardial infarction, pulmonary embolism, and gastrointestinal hemorrhage. Four deaths occurred in patients who received only placebo; one was caused by each of the following: cardiac arrest, cardiac failure, thrombosis of a mesenteric vessel, and carcinoma. Mortality rates were not significantly different between groups ($P = 0.70$).

Abnormal laboratory findings were common in both

Table 3. Incidence of and Risk Ratios for Predefined Adjudicated Adverse Events and Death among Patients Who Received the Assigned Treatment*

Adverse Event	Placebo (n = 525)	Parecoxib– Valdecoxib (n = 525)	Risk Ratio (95% CI)	*P* Value
≥ 1 Confirmed event, %	17 (3.2)	14 (2.7)	0.8 (0.4–1.7)	0.58
Cardiovascular events, %	5 (1.0)	5 (1.0)	1.0 (0.3–3.5)	1.00
Myocardial infarction	0 (0.0)	2 (0.4)		
Cardiac arrest or sudden cardiac death	1 (0.2)	1 (0.2)		
Cardioembolic stroke	0 (0.0)	0 (0.0)		
Acute ischemic stroke	1 (0.2)	0 (0.0)		
Transient ischemic attack	0 (0.0)	0 (0.0)		
Vascular thrombosis or DVT	2 (0.4)	1 (0.2)		
Pulmonary embolism	1 (0.2)	1 (0.2)		
Renal failure or dysfunction, %†	0 (0.0)	1 (0.2)	NA‡	NA‡
Upper gastrointestinal events, %	1 (0.2)	1 (0.2)	1.0 (0.1–16.0)	1.00
Gastric or duodenal ulcer + hematemesis	1 (0.2)	0 (0.0)		
Gastric or duodenal ulcer + melena	0 (0.0)	1 (0.2)		
Gastric or duodenal ulcer§	0 (0.0)	0 (0.0)		
Perforation	0 (0.0)	0 (0.0)		
Surgical wound events, %	11 (2.1)	9 (1.7)	0.8 (0.3–2.0)	0.65
Superficial incisional SSI	7 (1.3)	5 (1.0)		
Deep incisional SSI	1 (0.2)	0 (0.0)		
Organ/space SSI	3 (0.6)	3 (0.6)		
Wound-healing complication	0 (0.0)	2 (0.4)		
Death, %	4 (0.8)	3 (0.6)	0.75 (0.2–3.4)	0.70

* Some patients had more than one event. † Renal failure/dysfunction was the only type of renal event to occur. ‡ Risk ratio could not be computed because the placebo group had no renal events. § Gastric or duodenal ulcer was documented by means of endoscopy.

CI = confidence interval; DVT = deep venous thrombosis; NA = not applicable; SSI = surgical site infection.

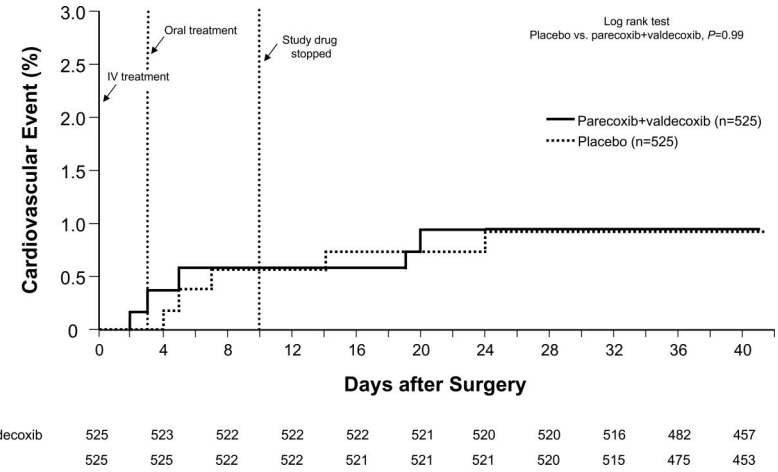

Fig. 2. Kaplan-Meier estimates of the time to a cardiovascular event. Cardiovascular events occurred throughout and after the 10-day period of drug administration in both groups. IV = intravenous.

treatment groups. Mean changes in laboratory values were generally small, and there were no significant differences between treatment groups in the incidence of extreme changes in any laboratory value. Vital signs were not adversely affected to a clinically meaningful extent by treatment with parecoxib and valdecoxib.

Secondary Endpoints (Efficacy): Supplemental Analgesia Requirements, Pain Ratings, Pain Interference with Function, and Opioid-related Symptom Distress

Mean cumulative morphine consumption over the entire study period was significantly greater in the placebo group (66.2 ± 92.4 mg) than in the group treated with parecoxib and valdecoxib (43.2 ± 65.7 mg) ($P < 0.001$). The placebo group also had significantly higher summed pain intensity scores on each of study days 2–10 ($P < 0.01$; fig. 3). In addition, the overall composite score for opioid-related symptom distress averaged across all symptoms showed significantly less distress among patients taking parecoxib and valdecoxib than among placebo patients on days 2–6 ($P < 0.01$; fig. 4).

Discussion

This study of patients recovering from noncardiac surgery is the largest single randomized controlled study to evaluate the safety of any analgesic in the general surgery setting. We did not find a higher incidence of cardiovascular thromboembolic or other adverse events among patients who received parecoxib and valdecoxib for 10 days for postoperative pain control than among patients who received placebo. In contrast, our recent study found that CABG patients who received parecoxib and valdecoxib for 10 days after surgery had a significantly higher incidence of thromboembolism than did patients who received placebo.[8] We previously speculated that the increased risk of thromboembolic events among CABG patients receiving parecoxib and valdecoxib may be due to preexisting generalized atherosclerotic disease, exposure to the additional risks of cardiopulmonary bypass, or both.[8] Data from the current study tend to confirm these speculations, because most patients were not at high risk for underlying atherosclerotic disease (fewer than 3% had a previous myocardial infarction, fewer than 7% had a history of coronary artery atherosclerosis, and fewer than 5% had a history of angina), and none of the procedures required a period of cardiopulmonary bypass. Nevertheless, one third of the

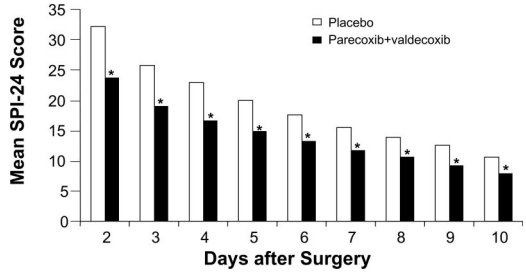

Fig. 3. Mean 24-h summed pain intensity (SPI-24) scores across all study days. The potential range is 0–72; higher scores indicate greater pain. Mean scores were significantly lower in the group that received parecoxib and valdecoxib (n = 519) than in the control group (n = 516) on study days 2–10 ($P \leq 0.05$).

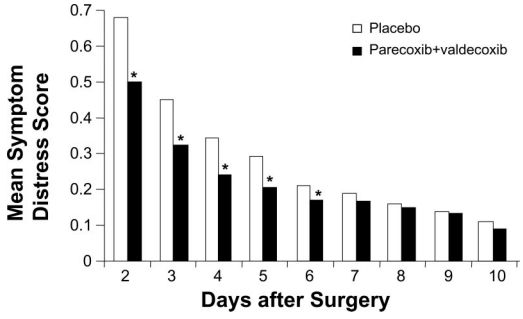

Fig. 4. Composite mean opioid-related symptom distress (frequency, severity, and degree of bother). Symptoms included fatigue, drowsiness, inability to concentrate, confusion, dizziness, constipation, itching, difficulty with urination, nausea, and retching/vomiting. Among the patients who completed the symptom distress questionnaires, composite mean scores were significantly lower in the group that received parecoxib and valdecoxib (n = 513) than in the control group (n = 509) on study days 2–6 ($P \leq 0.01$).

patients in the current study were hypertensive, and one third had hyperlipidemia.

In a previous study of CABG patients,[7] patients receiving 80 mg parecoxib or valdecoxib daily for 14 days had a significantly higher incidence of sternal wound infections and healing complications than did patients receiving placebo. Similarly, in a more recent study of CABG patients,[8] patients receiving 40 mg parecoxib or valdecoxib daily for 10 days had a numerically higher incidence of sternal wound infections and healing complications than did patients receiving placebo. We speculated that inhibition of the cyclooxygenase-2 enzyme impedes reparative inflammatory responses and increases susceptibility to wound infections or, alternatively, that the analgesic and antipyretic effects of parecoxib and valdecoxib may delay detection of incipient infection. However, in the current noncardiac surgical study, wound infections and healing complications were not more frequent in patients receiving 40 mg parecoxib and valdecoxib daily for 10 days, confirming similar findings in all previous noncardiac surgical studies of which we are aware. Possibly, in CABG surgery, the sternum is particularly susceptible to healing complications that might be affected by a selective cyclooxygenase-2 inhibitor. Other clinically relevant adverse events, including renal dysfunction and upper gastrointestinal events, were not associated with parecoxib and valdecoxib in the current study or in any previous studies.

A limitation of this study is the pooled endpoint of predefined adjudicated adverse events in four unrelated diagnostic categories (arterial or venous thromboembolic events, renal insufficiency or failure, gastroduodenal ulceration, and wound infections or healing complications). Another limitation of the study is the sample size. Although this was the largest trial of any nonsteroidal antiinflammatory drug in patients undergoing noncardiac surgery, the number of adverse events was relatively small and possibly inadequate to detect a particular safety signal. This is especially true for cardiovascular thromboembolic events, given the low level of risk in this population compared with CABG surgery patients. Nevertheless, this population was representative of the majority of patients who undergo major surgery.

The current study showed that parecoxib and valdecoxib provide effective analgesia at a dose of 40 mg/day. Other investigators have also reported reduced opioid consumption and improved pain scores with postoperative administration of 40 mg parecoxib per day.[8–12] Reduction in opioid use was accompanied by significant improvement in patients' ability to perform daily activities and a reduction in both the frequency and the severity of symptoms of opioid intolerance. In fact, efficacy may be optimal if initial administration occurs earlier, in the preoperative or intraoperative period.[19] Use of two analgesic agents that act by different mechanisms (*i.e.*, multimodal analgesia) is recommended for acute pain management because it provides superior efficacy while minimizing the adverse effects of opioids.[20] Although highly effective, opioids are associated with respiratory depression, alterations in mental status, nausea and vomiting, constipation, prolongation of paralytic ileus, pruritus, and urinary retention.[21]

Improving postoperative analgesic management has become a major initiative in American health care.[22] This trial showed that parecoxib and valdecoxib are useful adjuncts to opioids in noncardiac surgical patients if administered at recommended doses (a 40-mg loading dose followed by 20 mg every 12 h) over a short term (no more than 10 days). However, until parecoxib and valdecoxib are studied further in noncardiac surgical patients with known atherosclerotic disease, these drugs should be reserved for patients at low risk for thromboembolic events.

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