Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis
The CLASS Study: A Randomized Controlled Trial

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For editorial comment see p 1297.

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GI TOXICITY WITH CELECOXIB VS NSAIDS FOR ARTHRITIS

107,000 hospitalizations and 16,500 deaths yearly in the United States.10 NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for conversion of arachidonic acid to prosta
glandins.16 COX exists in 2 isoforms.17 COX-1 is a ubiquitous constitutive iso
zyme producing prosta
glandins that me
date pain and inflammation.17 NSAIDs inhibit both COX-1 and COX-2 to varying
degrees.18,19 Thus, the therapeutic ef
ects of conventional NSAIDs are de
rived from inhibition of COX-2, while the adverse effects of these agents, particu
larly in the upper GI tract, arise from in
hibition of COX-1 activity.

Celecoxib, a COX-2–specific inhibi
tor, recently was approved by the US Food and Drug Administration (FDA) for symptomatic treatment of rheuma
toid arthritis (RA) and osteoarthritis (OA). To determine whether the COX-2 specificity of celecoxib is associated with lower COX-1–related adverse effects, we compared celecoxib administered at 2 and 4 times the maximum FDA
approved effective dosages for RA and OA, respectively, with commonly used therapeutic dosages of ibuprofen and di
clofenac. The dosage of celecoxib ex
ceeded the maximum dosage approved by the FDA for OA and RA to permit a safety assessment of the higher dosages. However, based on previous studies,20,21 exceeding the dosages approved by the FDA would not improve patients' symptom relief. The dosages of ibuprofen and diclofenac were based on prescription data; 48% and 60% of OA and RA patients, respectively, who received ibuprofen were prescribed a dosage of at least 2400 mg/d, and 36% and 57% of OA and RA patients, respectively, who received diclofenac were pre
scribed a dosage of at least 150 mg/d.22

METHODS

Study Population

Outpatients aged 18 years or older were eligible to participate in the study if, on screening, they were diagnosed as hav

ing RA or OA evident for at least 3 months and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from study participation if at screening they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; history of gastric or duodenal surgery other than an oversew; or known im
mediate-type hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might have be
come pregnant, or were lactating.

Study Protocol

This prospective, randomized double
blind trial was conducted at 386 centers in the United States and Canada from September 1998 to March 2000 in accordance with the principles of good clinical practice and the Declara
tion of Helsinki. The protocol was ap
proved by the institutional review board at each study site, and all patients pro
vided written informed consent. Prior to enrollment, patients completed a physical examination and clinical labora
tory testing. After a baseline visit, follow
up clinical visits took place at weeks 4, 13, and 26 after the initial dose of medication, and every 13 weeks thereafter. All patients were provided an opportunity to complete a minimum of 6 months of treatment.

Patients withdrawing from study par
ticipation prior to 6 months were classi
fied as follows: preexisting violation of entry criteria, protocol noncompli
ance (investigator-defined failure to comply with the requirements of the protocol, eg, failure to take at least 70% of the study medication in any 13-week interval), treatment failure (investigator-defined failure of study medi
cation to control arthritis signs and symp	oms), or adverse effect (investigator-defined signs or symptoms unrelated to arthritis; see “Clinical Assessments” herein). These patients nonetheless were followed up for end
point evaluation for 2 months or until study termination.

Treatment

Patients were randomly assigned to receive treatments (celecoxib, 400 mg twice per day; ibuprofen, 800 mg 3 times per day; or diclofenac, 75 mg twice per day) on a 2:1:1 basis by an interactive voice response system (ClinPhone, Not
tingham, England) according to a computer-generated randomization sched
ule. All treatment regimens were blinded and double dummy. Treat
ment assignment for 3 patients was unblinded by study site personnel dur
ing trial conduct (1 at the investiga
tion site, 2 via the interactive voice response system). None of these patients experienced a study outcome event. One celecoxib patient experienced diver
ticular bleeding; 2 patients (1 cele
coxib and 1 diclofenac) experienced non–GI-related adverse events; and in no instance was the treatment assign
ment made known to personnel of the drug company (Pharmacia, Skokie, Ill) or to members of the oversight com
mittees prior to final review of all end points by a GI events committee.

Concomitant Medications

NSAIDs (except for stable dosages of aspirin up to 325 mg/d); antulcer drugs (except for occasional antacid use); an
biotics used alone or in combination with omeprazole, lansoprazole, and ran
itidine for treatment of Helicobacter pylori infection; and antineoplastics (ex
cept methotrexate or azathioprine for RA) were prohibited during the study. Use of oral, intramuscular, and intra
articular glucocorticoids and disease-modifying antirheumatic drugs was per
mitted.

Clinical Assessments

Investigators were instructed to iden
ify and report all potential upper GI ul
cer complications. Evaluation of such events was outlined in a prespecified al
gorithm structured to reproduce clini
cal practice norms. Evaluation was re
quired for any of the following pre
sentations: hematemesis; melena; acute

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hypovolemia/hypotension; development of postural dizziness, lightheadedness, or syncope; history of dark stool, hematochezia, or anal or rectal bleeding; development of new anemia (defined as a hematocrit level outside of the reference range) or a decrease in hematocrit of at least 5 percentage points; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of occult blood-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator’s clinical judgment.

All documentation relating to potential ulcer complications was forwarded to a GI events committee (J.L.G., G.E., N.M.A., and W.F.S.). The committee collectively reviewed each case in a treatment-blinded fashion and assigned it by unanimous consensus as either meeting or not meeting the definition of an upper GI ulcer complication (Table 1).

Symptomatic ulcers consisted of cases that did not meet the definition of an ulcer complication but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study and included in the analysis as having had a study end point.

Adverse effect data were collected at each visit (and as reported spontaneously) using the following question: “Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?” All affirmative responses were recorded regardless of severity or relationship to study drug. Laboratory data were also collected at each visit and as indicated according to the investigators’ discretion. Clinically significant changes in hematocrit and hemoglobin were predefined as decreases of at least 10 percentage points and 20 g/L, respectively. Clinically significant changes in serum urea nitrogen and creatinine were predefined as values at 6-month follow-up of at least 40 mg/dL (14.3 mmol/L) and 1.8 mg/dL (159 µmol/L), respectively. Clinically significant changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were predefined as increases to at least 3 times the upper limit of normal. Trial safety (eg, serious adverse effects) was monitored in a treatment-blinded fashion during the study by the data safety monitoring board (G.F., T.P., A.W., and R.M.).

### Statistical Analysis

Sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect this difference with a 2-sided .05 significance level with statistical power of 85% and assuming a 35% withdrawal rate, a sample size of approximately 4000 patients was required for the celecoxib group and 2000 patients were needed for each of the 2 NSAID groups.

Homogeneity of the treatment groups at baseline was analyzed using the $\chi^2$ test for categorical data and 2-way analysis of variance with treatment and center effects for continuous-valued data. Statistical analyses were conducted on the intent-to-treat population, defined a priori in the protocol as consisting of all patients who received at least 1 dose of assigned study medication. An additional prespecified analysis was performed on the population of patients not taking aspirin (since aspirin use was a predefined risk factor for GI events). Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on cumulative event rates (symptomatic ulcers and/or ulcer complications) for the 6-month study period and are expressed as annualized incidence rates (number of events per 100 patient-years of exposure or percentage). The log-rank test was used to compare time-to-event curves among treatment groups. Based on the recommendation of the GI events committee and as specified by the protocol a priori, upper GI ulcer complications were defined as a study end point (ie, an uncensored event) if they occurred within the 6-month treatment period and occurred 48 hours after the first dose day or before 14 days after the last known dose of study drug (to avoid confounding due to prestudy or poststudy NSAID use). Patients who had upper GI ulcer complications outside of the specified

### Table 1. Protocol-Specified Definitions and Adjudication Criteria for Ulcer Complications

<table>
<thead>
<tr>
<th>Event</th>
<th>Criteria for Confirmed Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric or duodenal perforation</td>
<td>Perforated lesion requiring surgery. Could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible on radiograph or peritoneal signs on physical examination.</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>Gastric outlet obstruction requiring diagnosis by investigator; diagnosis was required to be supported by endoscopy (eg, ulcer with a tight edematous pyloric channel) or by radiographic results (eg, dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, severe outlet narrowing and edema)</td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding</td>
<td>Hematemesis with a lesion (ulcer or large erosion) on endoscopy or radiograph</td>
</tr>
<tr>
<td></td>
<td>Lesion (ulcer or large erosion) on endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)</td>
</tr>
<tr>
<td></td>
<td>Melena with a lesion (ulcer or large erosion) on endoscopy or radiograph</td>
</tr>
<tr>
<td></td>
<td>Occult blood-positive stool with a lesion (ulcer or large erosion) on endoscopy or radiograph</td>
</tr>
<tr>
<td></td>
<td>Transfusion of ≥2 units of blood</td>
</tr>
<tr>
<td></td>
<td>Blood in stomach on endoscopy or nasogastric aspiration</td>
</tr>
</tbody>
</table>
Baseline Patient Characteristics

6 Months Flowchart of Patient Disposition at

Figure 1. Flowchart of Patient Disposition at 6 Months

Table 2. Baseline Patient Characteristics*

Table 3

GI Toxicity

except for liver enzyme elevations, for which results are presented separately.

RESULTS

A total of 8059 patients were randomized (FIGURE 1). Ninety-one patients did not receive study drug (32 were randomized and found to be ineligible prior to administration of study drug; 59 withdrew consent prior to taking study drug). Of these 91 patients, 44 were randomized to celecoxib and 47 were randomized to NSAIDs.

A total of 7968 patients received at least 1 dose of medication. Of these, 3987 patients were treated with celecoxib, 400 mg twice per day, and 3981 patients were treated with NSAIDs (1985 received ibuprofen, 800 mg 3 times per day, and 1996 received diclofenac, 75 mg twice per day). The celecoxib and NSAID groups had 1441 and 1384 total patient-years of exposure, respectively. Baseline characteristics did not differ significantly between groups (TABLE 2). More than 20% of the patients were taking low-dosage aspirin (≤325 mg/d). Approximately 57% of the patients (n = 4573) completed 6 months of treatment (Figure 1). More patients in the NSAID treatment group withdrew from the study for either adverse effects (n = 822 [20.6%]) or lack of therapeutic efficacy (n = 589 [14.8%]) than did celecoxib-treated patients (n = 732 [18.4%] and n = 503 [12.6%], respectively; P = .01 and P = .005; Figure 1). No patients were lost to follow-up (ie, a cause of withdrawal was determined for all patients who withdrew).

GI Toxicity

A total of 260 cases were selected by the GI events committee for adjudication. The committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic but uncomplicated gastroduodenal ulcers (TABLE 3). Four upper GI ulcer complications (2 in celecoxib-treated patients and 2 in NSAID-treated patients) were censored according to predetermined criteria (see “Methods” section). The remaining 177 cases not meeting the definition of gastroduodenal ulcer or ulcer...
complication were assigned a diagnosis from the categories listed in Table 3. The annualized incidence of upper GI ulcer complications in celecoxib-treated patients was 0.76% (11 events/1441 patient-years) vs an incidence of 1.45% (20 events/1384 patient-years) for patients taking NSAIDs (P = .09; Figure 2A). The relative risk (RR) for celecoxib compared with NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was 2.08% (30 events/1441 patient-years) vs 3.54% (49 events/1384 patient-years) for patients taking NSAIDs (P = .02; Figure 2A). The RR for celecoxib compared with NSAIDs was 0.59 (95% CI, 0.38-0.94).

Inclusion of the 2 censored events in each group did not alter the interpretation of results. For upper GI ulcer complications, the rates without censoring were 0.90% (13 events/1441 patient-years) and 1.59% (22 events/1384 patient-years) for celecoxib and NSAIDs, respectively (P = .11). For upper GI ulcer complications plus symptomatic ulcers, the rates were 2.22% (32 events/1441 patient-years) and 3.68% (51 events/1384 patient-years) for celecoxib and NSAIDs, respectively (P = .03). Corticosteroid use was not significantly associated with the incidence of upper GI ulcer complications in either treatment group (RR, 0.2 and 0.6 for patients treated with celecoxib and NSAIDs, respectively; P = .13 and P = .27).

### GI Toxicity With Aspirin Use

Based on time-to-event analyses using a Cox proportional hazard model, low-dosage aspirin use was found to have a significant effect on the incidence of upper GI ulcer complications in celecoxib-treated patients. Within the celecoxib treatment group, the RR of an upper GI ulcer complication was 4.5 with low-dosage aspirin use: 6 events in 833 patients taking low-dosage aspirin vs 5 events in 3154 non-aspirin users (P = .01). Low-dosage aspirin use did not have a significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (RR, 1.7; P = .29).

When the non–aspirin-using cohort was examined, 2 upper GI ulcer complications were censored (1 in each group). The annualized incidence of upper GI ulcer complications in non–aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% [5 events/1143 patient-years] vs 1.27% [14 events/1011 patient-years]; P = .04; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence

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**Table 3. Adjudicated Cases Meeting and Not Meeting Prespecialized Definitions of Gastroduodenal Ulcers and Ulcer Complications**

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib Group (n = 3987)</th>
<th>NSAID Group (n = 3981)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total No. of cases adjudicated</strong></td>
<td>111</td>
<td>1491</td>
</tr>
<tr>
<td><strong>No. of adjudicated cases not meeting the definition of a gastroduodenal ulcer or ulcer complication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal disease</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Gastroduodenitis</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Colonic or small bowel disease</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Nonulcer bleeding</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Miscellaneous GI symptoms</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>79</td>
<td>98</td>
</tr>
<tr>
<td><strong>No. of adjudicated cases meeting the definition of a gastroduodenal ulcer or ulcer complication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroduodenal ulcers</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Ulcer complications†</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Upper GI bleeding</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Perforation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>32</td>
<td>51</td>
</tr>
</tbody>
</table>

*NSAID indicates nonsteroidal anti-inflammatory drug; GI, gastrointestinal.
†P = .001 vs celecoxib group.
‡Four ulcer complications (2 in the celecoxib group and 2 in the NSAID group) were censored from the analysis because of the timing of the event based on a prior–specified definition.

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GI TOXICITY WITH CELECOXIB VS NSAIDS FOR ARTHRITIS

of upper GI ulcer complications plus symptomatic ulcers in patients not taking aspirin was also significantly lower with celecoxib than with NSAIDs (1.40% [16 events/1143 patient-years] vs 2.91% [32 events/1101 patient-years]; P = .02; Figure 2B). The RR for celecoxib compared with NSAIDs was 0.48 (95% CI, 0.28-0.89).

Inclusion of the 1 censored event in each group did not alter the interpretation of results. For upper GI ulcer complications, the rates without censoring were 0.52% (6 events/1143 patient-years) and 1.36% (15 events/1101 patient-years) for celecoxib and NSAIDs, respectively (P = .05). For upper GI ulcer complications plus symptomatic ulcers, the rates were 1.49% (17 events/1143 patient-years) and 3.00% (33 events/1101 patient-years) for celecoxib and NSAIDs, respectively (P = .02).

Table 4. Adverse Effects During the 6-Month Treatment Period

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>All Patients</th>
<th>Patients Not Taking Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib Group (n = 3987)</td>
<td>NSAID Group (n = 3981)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>575 (14.4)</td>
<td>640 (16.1)†</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>387 (9.7)</td>
<td>522 (13.1)†</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>373 (9.4)</td>
<td>392 (9.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>277 (6.9)</td>
<td>370 (9.3)†</td>
</tr>
<tr>
<td>Constipation</td>
<td>68 (1.7)</td>
<td>234 (5.9)†</td>
</tr>
<tr>
<td>Total</td>
<td>1250 (31.4)</td>
<td>1465 (36.8)†</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>345 (8.7)</td>
<td>427 (10.7)†</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated serum ALT</td>
<td>23 (0.6)</td>
<td>88 (2.2)†</td>
</tr>
<tr>
<td>Elevated serum AST</td>
<td>18 (0.5)</td>
<td>73 (1.8)†</td>
</tr>
<tr>
<td>Total</td>
<td>24 (0.6)</td>
<td>93 (2.3)†</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>2 (&lt;0.1)</td>
<td>46 (1.2)†</td>
</tr>
<tr>
<td>Bleeding-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>81 (2.0)</td>
<td>175 (4.4)†</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>28 (0.7)</td>
<td>32 (0.8)</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>17 (0.4)</td>
<td>40 (1.0)†</td>
</tr>
<tr>
<td>Total</td>
<td>123 (3.1)</td>
<td>238 (6.0)†</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>16 (0.4)</td>
<td>26 (0.7)</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>113 (2.8)</td>
<td>138 (3.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66 (1.7)</td>
<td>90 (2.3)†</td>
</tr>
<tr>
<td>Increased creatinine level</td>
<td>28 (0.7)</td>
<td>48 (1.2)†</td>
</tr>
<tr>
<td>Total</td>
<td>200 (5.0)</td>
<td>263 (6.6)†</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>44 (1.1)</td>
<td>41 (1.0)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5 (0.1)</td>
<td>10 (0.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (0.3)</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Angina</td>
<td>24 (0.6)</td>
<td>22 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>37 (0.9)</td>
<td>39 (1.0)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>12 (0.3)</td>
<td>13 (0.3)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>218 (5.5)</td>
<td>103 (2.6)†</td>
</tr>
<tr>
<td>Pruritus</td>
<td>91 (2.3)</td>
<td>59 (1.5)†</td>
</tr>
<tr>
<td>Urticaria</td>
<td>22 (0.6)</td>
<td>14 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>298 (7.5)</td>
<td>163 (4.1)†</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>109 (2.7)</td>
<td>49 (1.2)†</td>
</tr>
</tbody>
</table>

*Data are given as No. (%) of patients. Categories are nonadditive; patients may have experienced more than 1 adverse event in each category. NSAID indicates nonsteroidal anti-inflammatory drug; ALT, alanine aminotransferase; and AST, aspartate aminotransferase.

†P < .05 vs celecoxib group.

For patients taking aspirin (Figure 2C), the annualized incidences of symptomatic ulcers and/or upper GI complications were not significantly different in patients taking celecoxib vs NSAIDs. For upper GI complications, the observed rates were 2.01% for patients taking celecoxib vs 2.12% for patients taking NSAIDs (6 events/298 patient-years vs 6 events/283 patient-years, respectively; P = .92). For upper GI ulcer complications plus symptomatic ulcers, the observed rates were 4.70% for patients taking celecoxib vs 6.00% for patients taking NSAIDs (14 events/298 patient-years vs 17 events/283 patient-years, respectively; P = .49). Including the 2 censored events (1 in each group), the rates were 2.35% and 2.47%, respectively, for upper GI ulcer complications and 5.03% and 6.36%, respectively, for upper GI ulcer complications plus symptomatic ulcers.

Other Adverse Effects

Adverse effects with an incidence of at least 5% in either treatment group during the 6-month treatment period were GI symptoms, upper respiratory tract infection or related symptoms, headache, and rash. Adverse effects causing withdrawal with an incidence of at least 1% in either treatment group were GI symptoms, rash, and elevated transaminase levels. For these categories, celecoxib was associated with equivalent or lower incidences of adverse effects and withdrawals compared with NSAID therapy, with the exceptions of rash and pruritus (Table 4).

Serious adverse effects (representing hospitalizations or malignancies detected during the 6-month treatment period) were reported for 4.3% of celecoxib patients (172 events/3987 patients) and 4.2% of NSAID patients (168 events/3981 patients). The most common serious adverse effects in patients taking celecoxib and NSAIDs were accidental fractures (7 and 8 events, respectively), back pain (8 and 8 events, respectively), pneumonia (9 and 9 events, respectively), cardiac failure (9 and 10 events, respectively), myocardial infarction (10 and 10 events, respectively), and infection or related symptoms, headache, and rash.
respectively), and coronary artery disease (9 and 7 events, respectively). No serious rashes or unexpected serious adverse events were observed in patients taking celecoxib.

The overall incidence of GI symptoms experienced by patients taking celecoxib was significantly lower than by those taking NSAIDs, as was the rate of withdrawal due to GI intolerability (Table 4). Of the most commonly reported GI adverse effects, dyspepsia, abdominal pain, nausea, and constipation were significantly less common with celecoxib than with NSAIDs, although there was no difference in the incidence of diarrhea (Table 4).

The overall incidence of bleeding-related adverse events, and specifically, anemia and hematocrit, experienced by patients taking celecoxib was significantly lower than that among patients taking NSAIDs for all patients and for those not taking aspirin (Table 4). Similar results were noted for patients taking aspirin; the incidences of all bleeding-related adverse events were 4.0% and 8.3% for patients taking celecoxib and NSAIDs, respectively, and for anemia were 2.6% and 6.4%, respectively (P < .001 for both comparisons). Celecoxib was also associated with a lower incidence (P < .001) of clinically meaningful reductions in hematocrit and/or hemoglobin for the entire patient cohort than NSAIDs (Figure 3). A lower incidence was noted both in patients not taking aspirin (1.3% vs 3.4% in patients taking celecoxib and NSAIDs, respectively; P < .001) and patients taking aspirin (2.6% vs 4.9% in the 2 groups, respectively; P = .02). This difference persisted when all cases selected by the GI events committee for adjudication were excluded from the analysis, thus removing all patients with ulcer complications, symptomatic ulcers, or other diagnosed GI disease (Figure 3). Mean serum iron–iron binding capacity ratios increased in patients taking celecoxib and decreased in patients taking NSAIDs (1.4% vs −2.3%; P = .007).

As shown in Figure 4, the incidence of serum ALT or AST elevations that exceeded 3 times the upper limit of normal was several-fold and statistically significantly higher in patients receiving NSAIDs than those receiving celecoxib. The incidence of ALT elevation for diclofenac was 3.2% vs 0.3% for ibuprofen; for AST, it was 1.8% vs 0.1%, respectively. Similarly, investigators reported a significantly higher incidence of adverse effects related to elevated ALT and AST with NSAID treatment (Table 4). Study withdrawals due to such elevations were also higher in patients receiving NSAIDs (Table 4). Overall, 97% of ALT and AST abnormalities occurred in patients receiving diclofenac.

The overall incidence of renal adverse effects, and the incidence of increased creatinine and hypertension in particular, were significantly lower in patients receiving celecoxib than in those receiving NSAIDs (Table 4). Also, significantly more patients receiving NSAIDs exhibited clinically significant elevations in serum creatinine and/or serum urea nitrogen levels than with celecoxib (Figure 4).

The overall incidence of cardiovascular events, and the incidences of cerebrovascular events and myocardial infarction in particular, were similar in the 2 treatment groups (Table 4). No treatment-related differences in such events were apparent in the cohort of patients not taking aspirin for cardiovascular prophylaxis (Table 4). Incidence of myocardial infarction in patients taking either celecoxib or NSAIDs was 0.3%, with 95% CIs of 0.12% to 0.46% and 0.14% to 0.49%, respectively. For patients not taking aspirin, incidence of myocardial infarction in patients taking celecoxib was less than 0.10% (95% CI, 0.02%–0.28%) and was also 0.10% (95% CI, 0.03%–0.32%) in patients taking NSAIDs.

COMMENT

This study determined that celecoxib, a COX-2–specific inhibitor, when used for 6 months in a dosage 2 to 4 times the maximum therapeutic dosage, is associated with a lower incidence of combined clinical upper GI events than comparator NSAIDs (ibuprofen and diclofenac).

![Figure 3. Patients With Decreases in Hematocrit and/or Hemoglobin at 6 Months](https://example.com/figure3)

Data are shown for patients with decreases from pretreatment levels in hematocrit of 10 percentage points or more, in hemoglobin of 20 g/L or more, or both. Results for the entire study population are shown on the left. On the right, results for all patients excluding those with an upper gastrointestinal (GI) ulcer complication, symptomatic ulcer, or other diagnosed GI disease are shown. NSAIDs indicates nonsteroidal anti-inflammatory drugs. Numbers above bars indicate the number of patients with the event per total number of patients in the treatment group.

![Figure 4. Patients With Increases in Serum Creatinine and/or Serum Urea Nitrogen and With Elevations in ALT and AST at 6 Months](https://example.com/figure4)

Data are shown for patients with increases from pretreatment levels in serum creatinine to 1.8 mg/dL (159 µmol/L) or more, in serum urea nitrogen to 40 mg/dL (14.3 mmol/L) or more, and for patients with elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to a level of at least 3 times the upper limit of normal (ULN). In the nonsteroidal anti-inflammatory drug (NSAID) group, 97% of ALT and AST abnormalities occurred in patients taking diclofenac. Numbers above bars indicate the number of patients with the event per total number of patients in the treatment group.
In addition to the assessment of GI effects, the present study determined that the increased dosage of celecoxib used in this study did not change the adverse effect profile observed at lower dosages. Of note, celecoxib-treated patients had a significantly lower incidence of clinically significant decreases in hemoglobin and/or hematocrit compared with NSAID-treated patients, even when patients with upper GI ulcer complications, symptomatic ulcers, and other GI diseases were excluded. Celecoxib was also better tolerated than NSAIDs, as evidenced by the decreased incidence of GI symptoms and withdrawals for such symptoms. Despite these caveats, however, our results demonstrate that celecoxib, at a dosage 2- to 4-fold greater than the maximum therapeutic dosages and those approved for labeling for RA and OA, is associated with a lower rate of upper GI toxic effects compared with standard therapeutic dosages of NSAIDs. This finding supports the COX-2 hypothesis that COX-2–specific agents exhibit decreased GI toxic effects.37,38 Despite the high dosage used, other adverse effects did not emerge. Our findings thus have significant implications with respect to drug therapy for the symptomatic treatment of RA and OA.

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REFERENCES
GI TOXICITY WITH CELECOXIB VS NSAIDS FOR ARTHRITIS


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