Efficacy Assessment of Meloxicam, a Preferential Cyclooxygenase-2 Inhibitor, in Acute Coronary Syndromes Without ST-Segment Elevation

The Nonsteroidal Anti-Inflammatory Drugs in Unstable Angina Treatment-2 (NUT-2) Pilot Study

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Background—Despite the use of heparin, aspirin, and other antiplatelet agents, acute coronary syndrome patients without ST-segment elevation remain at risk of cardiovascular thrombotic events. Given the role of inflammation in the pathogenesis of arterial thrombosis, we tested the hypothesis that the combination of meloxicam, a preferential COX-2 inhibitor, and heparin and aspirin would be superior to heparin and aspirin alone.

Methods and Results—In an open-label, randomized, prospective, single-blind pilot study, patients with acute coronary syndromes without ST-segment elevation were randomized to aspirin and heparin treatment (n=60) or aspirin, heparin, and meloxicam (n=60) during coronary care unit stay. Patients then received aspirin or aspirin plus meloxicam for 30 days. During the coronary care unit stay, the primary outcomes variable of recurrent angina, myocardial infarction, or death was significantly lower in the patients receiving meloxicam (15.0% versus 38.3%, P=0.007). The second composite variable (coronary revascularization procedures, myocardial infarction, and death) was also significantly lower in meloxicam-treated patients (10.0% versus 26.7%, P=0.034). At 90 days, the primary end point remained significantly lower in the meloxicam group (21.7% versus 48.3%, P=0.004), as did the secondary end point (13.3% versus 33.3%, P=0.015) and the need for revascularization alone (11.7% versus 30.0%, P=0.025). No adverse complications associated with the meloxicam treatment were observed.

Conclusions—Meloxicam with heparin and aspirin was associated with significant reductions in adverse outcomes in acute coronary syndrome patients without ST-segment elevation. Additional larger trials are required to confirm the findings of this pilot study. (Circulation. 2002;106:191-195.)

Key Words: inflammation ▪ coronary disease ▪ thrombosis ▪ aspirin

Vessel wall inflammation influences the pathogenesis of unstable angina (UA), contributing to plaque instability and endothelial cell dysfunction.1–5 It is critically involved in destabilizing atheroma, with inflammatory cells secreting proteolytic enzymes that degrade fibrous plaque, potentially constituting a thrombogenic stimulus.6,7 The fibrinolytic and matrix metalloproteinase systems, which are known to degrade extravascular matrix8 and may contribute to plaque disruption, are upregulated by proinflammatory mediators.9 These observations suggest that inflammatory status is an important determinant of short-term outcome in patients with UA, a view supported by the prognostic power of the inflammatory markers interleukin-6 and C-reactive protein.11

A new generation of nonsteroidal anti-inflammatory drugs (NSAIDs) has recently been described that selectively inhibits the expression of the cyclooxygenase isoform COX-2. COX-2 plays an important role in inflammation through its involvement in prostaglandin synthesis.12 The group of COX-2 inhibitors includes meloxicam, which has potent anti-inflammatory activity and low gastric toxicity.13,14 Studies show that meloxicam inhibits prostaglandin biosynthesis more potently at the site of inflammation than in the gastric mucosa or the kidney.15

Although previous clinical studies with anti-inflammatory drugs did not demonstrate improved outcomes in patients

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191
with UA or myocardial infarction (MI).16,17 we wished to assess the efficacy of the COX-2 inhibitor meloxicam in patients with acute coronary syndromes (ACS) without ST-segment elevation. Meloxicam was given in conjunction with standard antithrombotic therapy, either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), and aspirin.

Methods
We performed an open, randomized, prospective, single-blind pilot study of the use of meloxicam in ACS patients without ST-segment elevation. Patients were recruited from the Centro de Salud and the Centro Modelo de Cardiologia, Tucuman, Argentina. The study was granted ethical approval by the participant institutions, and written informed consent was obtained from patients before enrollment.

Inclusion criteria were chest pain within the previous 24 hours associated with ST-segment depression (≥0.5 mm) and either ECG evidence of ischemia or previously documented coronary artery disease. Exclusion criteria were persistent ST-segment elevation and increased levels of the MB isoenzyme of creatine kinase (CK-MB) consistent with acute myocardial infarction, revascularization procedures within the preceding 6 months, malignancy, pregnancy, renal or hepatic diseases, use of antiplatelet antagonist, treatment with anti-inflammatory drugs, or contraindication of the study drugs.

Patients were randomized to receive aspirin plus heparin (n=60) or aspirin, heparin, and meloxicam (n=60). The active treatment group received 15 mg of meloxicam given intravenously immediately after randomization followed by 15 mg once daily given orally during hospital stay and for 30 days after discharge. Both groups received aspirin for 30 days. The dose range was 100 to 300 mg per day at the discretion of the treating physician. CK-MB levels were measured before randomization. Additional assays were performed after an episode of chest pain to confirm the diagnosis of acute MI.

All patients received subcutaneous LMWH (either nadroparin 87 IU/kg BID or enoxaparin 1 mg/kg BID) or intravenous UFH given as an initial bolus of 5000 IU followed by continuous infusion at 1000 IU per hour for 7 days or until discharge from the hospital. The activated partial-thromboplastin time (APTT) was used to assess the degree of anticoagulation in patients receiving intravenous unfracti- onated heparin. Patients were tested every 12 hours on the first day and every 24 hours subsequently. The APTT was maintained in the range 45 to 87 seconds (normal value, 30±5 seconds).

Study End Points
The primary outcome variable was the composite of recurrent angina, MI, or death during CCU stay and after 90 days of follow-up. An additional secondary composite variable was determined: MI, death, and all revascularization procedures (percutaneous transluminal coronary angioplasty [PTCA] or coronary artery graft surgery [CABG]). Each component of the primary and secondary outcome variable was also recorded separately.

According to Degner et al,18 after bolus intravenous dose of 15 mg meloxicam, Cmax was 3.0 mg/L and tmax was 0.05 hours. These figures anticipated that intravenous administration of meloxicam would produce an immediate anti-inflammatory effect, and all events after randomization were considered as end points. Cardiac catheterization was performed at the discretion of treating physicians, but only urgent PTCA and CABG, usually after recurrent angina or MI, were considered as end points. Revascularization procedures were indicated after recurrence of chest pain refractory to medical therapy. During CCU stay and after discharge, all patients were examined for clinical events by an investigator who was unaware of treatment allocation. Patients were also instructed to report any events to study personnel immediately.

The diagnostic criteria for MI were chest pain lasting 20 minutes or more with ECG changes and an at least 2-fold elevation of CK-MB. Recurrent angina was defined as recurrence of chest pain with ECG changes refractory to medical therapy (aspirin, heparin, nitroglycerin, and β-blockers).

### Table 1. Baseline Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Meloxicam (n=60)</th>
<th>Control Group (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (51.7)</td>
<td>37 (61.7)</td>
<td>0.357</td>
</tr>
<tr>
<td>Female</td>
<td>29 (48.3)</td>
<td>23 (38.3)</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Mean</td>
<td>61</td>
<td>60.7</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>38–84</td>
<td>28–81</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>21 (35.0)</td>
<td>22 (36.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Former*</td>
<td>3 (5.0)</td>
<td>8 (13.3)</td>
<td>0.206</td>
</tr>
<tr>
<td>Never</td>
<td>36 (60.0)</td>
<td>30 (50.0)</td>
<td>0.359</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>17 (28.3)</td>
<td>10 (16.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>&gt;25</td>
<td>43 (71.7)</td>
<td>46 (76.3)</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>17 (28.3)</td>
<td>17 (28.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>11 (18.3)</td>
<td>11 (18.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous unstable angina</td>
<td>2 (3.3)</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>4 (6.6)</td>
<td>8 (13.3)</td>
<td>0.361</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>3 (5.0)</td>
<td>2 (3.3)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise indicated. *Stopped smoking>12 months ago.

Statistical Analysis
The nature of the quantitative variables distribution was assessed by the Shapiro-Wilk test. Differences between the 2 treatment groups were analyzed by the Student’s t test (independent samples) or the Mann-Whitney test, according to the nature of the distribution. Differences in terms of activated partial thromboplastin time after unfractionated heparin were assessed by a 2-way ANOVA model, with repeated measures in one of the factors (Student Newman-Keuls post-hoc test). Univariate associations between qualitative variables were assessed by χ² (Yates corrected) and Spearman rank-order correlations.

Relative risks (RRs) and their 95% CI were obtained. The RR reduction (RRR) is defined as 1 minus RR and expressed as percentage. The absolute risk reduction (ARR) was calculated as the difference between the risk in control patients minus the risk in treated patients and expressed as percentage.

A multiple logistic regression model was used to determine the predictive value of the variables associated with events at day 90 in the previous univariate analysis. The software used were CSS/Statistics 3.1 (StatSoft Corp) and EPI INFO 6 v.6.04, 1996.

Results
In total, 120 patients were randomized. Sixty patients received meloxicam with aspirin and heparin, and a control group of 60 patients were given heparin and aspirin only. The baseline clinical characteristics of the patients in the 2 groups did not differ significantly (Table 1). There were more male patients in the control group (37 patients, 61.7%) than in the meloxicam group (31 patients, 51.7%), and the mean CCU stay was longer in the control group (4.4±1.6 versus 4.35±1.14 days), but these differences were not significant.
Ten patients in the meloxicam group and 24 patients in the control group were treated with LMWH. The remaining patients received UFH. In the meloxicam group, 10 patients were treated with nadroparin. In the control group, 22 patients received nadroparin and 2 received enoxaparin.

The capacity of unfractionated heparin to maintain the APTT in the therapeutic range (45 to 87 seconds) is shown in Table 2. Within the first 24 hours, 56.9% of those receiving UFH in the control group and 67.7% in the meloxicam group had an APTT in the therapeutic range and 9.8% and 6.5%, respectively, had an APTT above the therapeutic range. Thirty three percent and 26%, respectively, had an APTT in the therapeutic range (45 to 87 seconds), % 9.8 6.5 17.8 16 36.1 47.7 11.1 41.7

The reasons for stopping were the occurrence of an end point in 8 patients in the control group and 3 in the meloxicam group. One patient in each group withdrew consent, and treatment was discontinued during the in-hospital period for 5 patients in the control group and 3 in the meloxicam group.

**Primary Outcome Variables**

**Efficacy Outcomes Within the CCU Period**

The incidence of recurrent angina was significantly lower in the meloxicam-treated group compared with the control group (9 of 60 patients, 15.0% versus 21 of 60 patients, 35%; P=0.02). This corresponds to a RRR of 57.1% (95% CI, 14 to 79) (Table 3). There was a trend toward a reduced need for revascularization procedures in patients who received meloxicam, although this did not reach statistical significance (P=0.055).

Fewer composite events (recurrent angina, MI, and death) occurred in the meloxicam group (9 patients; 15%) compared with the control group (23 patients; 38.3%). The difference was statistically significant (P=0.007) and corresponds to a RRR of 60.8%, (95% CI, 23 to 80).

Composite outcomes for coronary revascularization procedures (PTCA or CABG), MI, and death occurred in 6 patients in the meloxicam group (10%) and 16 patients of the control group (26.7%). This difference was also statistically significant (P=0.034), with a RRR of 62.5% (95% CI, 11 to 84).

Treatment was discontinued during the in-hospital period for 8 patients in the control group and 3 in the meloxicam group. The reasons for stopping were the occurrence of an end point in 5 patients in the control group and 2 patients in the meloxicam group. One patient in each group withdrew consent, and treatment was discontinued in 2 patients assigned to the control group because of discharge from hospital.

**Efficacy Outcomes at 90 Days**

The differences between the meloxicam-treated group and the control group observed during the period of hospitalization were maintained during the follow-up period. The cumulative frequency of recurrent angina during the 90-day follow-up period was lower in the meloxicam group (12 patients; 20%) compared with the control group (26 patients; 43.3%). The difference was statistically significant (P=0.011) and corre-
sponded to a RRR of 53.8% (95% CI, 17 to 74) (Table 4). Significantly fewer patients in the meloxicam group required coronary revascularization (7 patients, 11.7% versus 18 patients, 30%; P=0.025, RRR 61%, 95% CI, 14 to 82). The cumulative composite end point of recurrent angina, MI, and death occurred in 13 patients (21.7%) in the meloxicam group and in 29 patients (48.3%) in the control group. The difference was statistically significant (P=0.004) and was associated with a RRR of 55.1% (95% CI, 22 to 74) for the meloxicam group. The cumulative frequency of the secondary outcome variable of coronary revascularization procedures, MI, and death was significantly lower in the meloxicam group (8 patients; 13.3%) compared with the control group (20 patients; 33.3%) (P=0.015) and corresponded to a RRR of 60.1% (95% CI, 16 to 81) (Table 4).

Temporal Trends
Within 48 hours of randomization, the primary outcome variable had been reached by 1.7% of patients in the meloxicam group and 6.7% of patients in the control group (P=0.361). At 30 days, the rates were significantly lower in the meloxicam-treated patients (20.0% versus 46.7%; P=0.004). The additional secondary outcome variable was reached at 30 days in 11.7% of the meloxicam group compared with 31.7% of the control group (P=0.015).

The univariate Spearman rank-order correlations showed a significant association between events during the 90-day follow-up period and hypertension (rS=0.24, P=0.007), hypercholesterolemia (rS=0.20, P=0.024), diabetes mellitus (rS=0.26, P=0.004), and treatment group (rS=−0.28, P=0.002). In the multivariate analysis (Table 5), only hypertension, diabetes, and treatment group were significantly associated with events during the 90-day follow-up period.

TABLE 5. Multivariate Association Between Events and Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.31</td>
<td>1.00−5.38</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.43</td>
<td>1.01−6.36</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.33</td>
<td>0.14−0.77</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Logistic regression (maximum likelihood), χ²=22.36; df: 4, P=0.0002.

Safety
No bleeding complications, side effects, or intolerance was observed in any patients throughout the course of the study. This agrees with the fact that with dosing regimens 3- to 10-fold higher than the anti-inflammatory doses of meloxicam, no evidence of impairment of the central nervous, cardiovascular/pulmonary, renal, musculoskeletal, or autonomic systems was observed.

Discussion
Limited by the single-blind design and non–placebo-controlled nature, our study suggests benefits in adding the selective COX-2 inhibitor meloxicam to recommended treatment regimens for ACS patients without ST-segment elevation. An initial significant reduction in the number of events was observed during the CCU period, which was sustained through the 90-day follow-up period.

The significant difference between the control and meloxicam groups was driven by the differences in the rates of recurrent chest pain, with a RRR of 57.1%, an absolute risk reduction (ARR) of 20%, and a reduction in the need for myocardial revascularization procedures (RRR 60.8%; ARR 15%) during the CCU period. The ARR in recurrent angina improved during the 30-day treatment period by 3.3%. At 90 days of follow-up, the differences were sustained with only one additional death reported in each group.

Meloxicam was given in addition to the standard antithrombotic therapies of aspirin and heparin, because aspirin in the used dose has a feeble anti-inflammatory effect and because aspirin and heparin represent the standard of care in patients with ACS. COX-2 inhibitors do not inhibit platelet activation but significantly reduce systemic production of prostacyclin,19 potentially shifting the hemostatic balance toward a prothrombotic state,19–21 although this has been challenged.22 Because of this, we felt that inhibition of platelet function with aspirin was a mandatory concomitant therapy when using COX-2 inhibitors.23 Concurrent treatment with aspirin increases the plasma concentration of meloxicam (Cmax by 25% and AU0–∞ by 10%), but this is not considered clinically relevant.24 In this study, meloxicam was given intravenously to obtain an immediate anti-inflammatory effect, and oral therapy was continued for 30 days. Nevertheless, we cannot eliminate the possibility of other effects of meloxicam, which may contribute to its beneficial effects.25,26
Although the relationship may be of lesser significance when patient follow-up is <1 year, establishing the number of patients needed to treat for one therapeutic success is a useful tool to examine the potential advantages of the medication for daily practice. At 90 days of follow-up, meloxicam therapy resulted in a reduction of 1 event (recurrent chest pain, MI, or death) per 3.8 patients and the reduction of 1 hard event (coronary revascularization procedure, MI, or death) per 8.3 patients. The therapy used was well tolerated, with no side effects described in the treatment group. Potential limitations of our study include the single-blind design and the choice of heparin. Certainly, because some principal outcomes may be subjective, an important limitation of this trial is its single-blind design and the lack of a placebo control. Nevertheless, a study with similar limitations was published by Gurfinikel et al., and, subsequently, a larger trial was performed, with the new data confirming the previous results. Moreover, because in our study all patients were examined for clinical events during CCU stay and after discharge by an investigator who was unaware of treatment allocation and because the incidence of deaths or MI were similar to those obtained in other studies in patients with acute coronary syndromes without ST-segment elevation, potential bias was an independent predictor of outcome after adjusting for statistical adjustments support the conclusion that treatment assignment was an independent predictor of outcome after adjusting for hypertension and diabetes.

This study supports our hypothesis and indicates the potential benefits of meloxicam treatment, indicating that inhibition of inflammation potentially decreases short-term events, mainly the occurrence of angina pectoris and revascularization in ACS patients without ST-segment elevation. Additional trials including a larger numbers of patients in a prospective double-blind randomized study will be required to confirm these results and to assess the effects of combining meloxicam with other newer antithrombotic therapies.

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