Efficacy and Safety of a Topical Diclofenac Solution (Pennsaid) in the Treatment of Primary Osteoarthritis of the Knee

A Randomized, Double-Blind, Vehicle-Controlled Clinical Trial

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Background: Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve the symptoms of osteoarthritis (OA) but can produce harmful systemic effects and end-organ damage. A topical NSAID formulation may provide symptom relief with fewer adverse effects. A new topical diclofenac sodium solution—containing the absorption enhancer dimethyl sulfoxide—was evaluated for the relief of the symptoms of primary OA of the knee.

Methods: A total of 326 patients met entry criteria (including abnormal radiographic findings and flare of pain) and were randomized to receive 40 drops of topical diclofenac solution or a vehicle-control solution, 4 times daily, for 12 weeks. We evaluated 3 primary outcome measures, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and a patient global assessment, and 2 other measures, stiffness and pain on walking, at baseline and after final application. We assessed safety by evaluation of adverse events, vital signs, and irritation at the application site.

Results: Topical diclofenac solution was significantly more effective than the vehicle-control solution for all outcome measures; pain, \( P = .001 \); physical function, \( P = .002 \); patient global assessment, \( P = .003 \); stiffness, \( P = .005 \); and pain on walking, \( P = .004 \). Among patients receiving topical diclofenac, self-limiting minor skin irritation occurred in 68 (41.5%) of 164 patients, including dryness in 60 (36.6%), rash in 18 (11.0%), and paresthesia, pruritus, and vesiculobullous rash in 1 (0.6%) each. There was no significant difference between groups in NSAID-related gastrointestinal tract complaints or in dropouts due to study-related adverse effects.

Conclusion: Topical diclofenac is effective in the treatment of the symptoms of primary OA of the knee, with only minor local irritation and no significant systemic adverse events.

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Rheumatology. On the other hand, the American College of Rheumatology has recommended the use of topical analgesics in patients who do not respond to acetaminophen and wish to avoid systemic therapy. At present, no topical NSAID for the treatment of OA has been approved in the United States. Recently, a topical 1.5% (wt/wt) diclofenac sodium solution in a carrier containing dimethyl sulfoxide (Pennsaid; Dimethaid Health Care Ltd, Markham, Ontario) was approved in Canada and several European countries for the treatment of symptomatic OA. In this study, we report on the results of a 12-week trial of this topical diclofenac solution, compared with a vehicle control solution, in the treatment of the symptoms of primary OA of the knee.

**METHODS**

**PATIENTS**

This study was conducted from December 19, 2000, to May 18, 2001, at 39 medical centers across the United States after approval by the appropriate institutional review boards. Patients were recruited from the physician’s private practice or the surrounding community. After providing written, informed consent, each patient underwent an inclusion/exclusion interview and was eligible to proceed to washout if all inclusion criteria and no exclusion criteria were met.

We included men and nonpregnant women aged 40 to 85 years with primary OA in at least 1 knee defined by (1) radiological findings of deterioration and abrasion of the articular cartilage (joint space narrowing) and/or formation of new bone (osteophytes) at the joint surface of the knee (medial, lateral, or patellofemoral) at an examination performed within the previous 3 months, (2) and (2) a flare of pain after washout of stable therapy (at least 3 days per week for 1 month) consisting of an oral NSAID or acetaminophen. Pain was measured by the Western Ontario and McMaster Universities LK3.1 OA Index (WOMAC) pain subscale, scored on a 5-point Likert scale where 0 indicates none; 1, mild; 2, moderate; 3, severe; and 4, extreme. A flare was defined as an increase on the pain subscale of at least 2 points and 25%, a score of at least 2 (moderate) on at least 1 of the 5 items/questions of the WOMAC pain subscale, and a baseline total pain score of at least 6.

We excluded subjects with secondary arthritis related to systemic inflammatory arthritis, including rheumatoid arthritis, psoriatic arthritis, postinfectious arthritis, metabolic arthritis, and traumatic arthritis or surgical joint replacements; sensitivity to diclofenac, aspirin or any other NSAID, dimethyl sulfoxide, propylene glycol, glycerin, or ethanol; clinically active renal, hepatic, or peptic ulcer disease; a history of alcohol or other drug abuse; lactation; concomitant skin disease at the application site: corticosteroid use, including oral corticosteroid within 14 days, intramuscular corticosteroid within 30 days, intra-articular corticosteroid into the study knee within 90 days, intra-articular corticosteroid into any other joint within 30 days of study entry, or ongoing use of topical corticosteroid at the site of application; use of a topical product, treatment, or device at the application site for the relief of OA; ongoing use of prohibited medication, including NSAIDs, oral analgesic, muscle relaxant, or low-dose antidepressant; ongoing use of glucosamine or chondroitin sulfate sodium (unless used continuously for 90 days before study entry); intra-articular viscosupplementation (eg, hyaluronate sodium derivative) into the study knee in the preceding 90 days; current application for disability benefits on the basis of OA of the knee; fibromyalgia; and other painful or disabling condition affecting the knee.

**OUTCOME MEASURES**

**OF EFFICACY**

The primary efficacy variables were the change from baseline to final assessment in pain and physical function, as measured by the WOMAC subscales, and in the patient global assessment ("How has the osteoarthritis in your study joint been over the last 68 hours?") as measured on a 5-point Likert scale, where 0 indicates very good; 1, good; 2, fair; 3, poor; and 4, very poor. There were no intermediate assessments. Where the patient failed to complete the final assessment, the baseline score was carried forward. The secondary variable was the change in stiffness. This core set of outcome measures follows the recommendations of Outcome Measures in Arthritis Clinical Trials (OMERACT) III,22 the Osteoarthritis Research Society (OARS),23 and the Group for the Respect of Ethics and Excellence in Science (GREES).23 The WOMAC is a validated questionnaire consisting of 24 items/questions, each scored on a 5-point Likert scale. The response to the first of the 5 WOMAC pain dimension questions ("How much pain do you have walking on a flat surface?") is the only measure of pain in many NSAID trials, was assessed also as a separate efficacy variable. Pain on walking is referred to by GREES as “use-related pain,” distinct from the WOMAC pain subscale, which is an aggregate instrument probing 5 aspects of pain.

**SAFETY ASSESSMENTS**

Safety was assessed at each clinic visit (weeks 1, 6, and 12 and dropout) and with telephone visits (weeks 3 and 9). Adverse events were recorded at baseline and at final assessment.

**SAMPLE SIZE**

Based on a power of 80% and a type 1 error rate of $\alpha = .05$ (2-tailed), a sample size of at least 80 patients per group was
required to detect a clinically significant difference of 2 in the change in WOMAC pain dimension scores (with an SD of 4.5) between the 2 treatment arms. The protocol specified a total sample size of 200 patients (100 per treatment group) to allow for a non-evaluable rate of up to 20%. No interim analysis or monitoring of the results of the study was planned.

RANDOMIZATION AND BLINDING

Study kits were prepared and numbered according to a computer-generated randomization schedule created by an outside consultant using a block size of 4. The randomization schedule was concealed from the investigators and their support staff, study patients, and the sponsor's clinical research personnel until final data lock and transfer to the statistician. Study kits were shipped to the sites in multiples of complete blocks of 4 units to ensure that a balanced number of patients was assigned to the 2 treatment arms within each site. The site investigator sequentially assigned randomization numbers to patients, as they qualified for study entry at the baseline visit. The 2 study solutions were identical clear, colorless liquids in opaque bottles with labels identical except for the individual patient identification number.

STATISTICAL ANALYSIS

Baseline demographic and clinical variables were analyzed by means of the \( \chi^2 \) or the t test. Safety analyses were performed on all patients randomized into the trial who applied at least 1 dose of study solution. Adverse event incidence was analyzed by the \( \chi^2 \) or the Fisher exact test.

An intent-to-treat (ITT) group was defined as a subset of all treated patients who met critical inclusion criteria\(^\text{35}^\) (primary OA by history and abnormal findings of the radiological study) and had any measured degree of pain at baseline. A per-protocol group was defined on the basis of stricter adherence to study conduct, including the requirement of a moderate flare of knee pain as described above, and treatment continuing for at least 83 days. Efficacy analyses (WOMAC, patient global assessment, and pain on walking) for the ITT and per-protocol data sets were performed by means of analysis of covariance, with baseline score as covariate. All statistical tests were 2 sided and were performed at the .05 level of significance.

RESULTS

PATIENT DISPOSITION

The Figure outlines the flow of patients through the study. After screening for 568 patients, 242 were excluded, leaving 326 who were randomized to receive treatment with topical diclofenac solution (n = 164) or the vehicle-control solution (n = 162). All randomized patients received at least 1 dose of their allocated intervention. Two hundred twenty-eight patients (70%) completed the study, with the groups comparable in total discontinuation rate (topical diclofenac group, 45/164 [27%]; vehicle-control group, 53/162 [33%]). Only 3 patients (topical diclofenac group) were lost to follow-up. Patient dropout owing to lack of effect was 28 (17%) of 164 for the topical diclofenac group and 42 (26%) of 162 for the vehicle-control group (\( P = .052 \)). Patient dropout owing to an adverse event was 8 (5%) of 164 for the topical diclofenac group and 4 (2%) of 162 for the vehicle-control group (\( P = .25 \)).

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The demographic and clinical characteristics of all patients randomized into the study were similar between treatment groups (Table 1). Mean age of all patients in the study was 64.1 years, and 67.8% of the patients were women. Radiographic analysis of joint space narrowing and marginal osteophytes showed no significant difference. Patients in the topical diclofenac group had a slightly longer mean duration of treatment (71.3 days) than patients in the vehicle-control group (64.1 days; \( P = .02 \)). Compliance with the treatment regimen was 90.4% for the topical diclofenac group and 90.8% for the vehicle-control group.

EFFICACY ANALYSES

In defining the ITT analysis group, 4 patients were dropped from the all-treated-patients group before blind breaking, per the guidelines of the International Conference on Harmonisation of Technical Requirement for Registration of Pharmaceuticals for Human Use,\(^\text{35}^\) as they did not meet ma-
Table 1. Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Topical Diclofenac (n = 164)</th>
<th>Vehicle-Control (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.4 (10.5)</td>
<td>64.9 (10.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>42-86</td>
<td>41-84</td>
</tr>
<tr>
<td>Women, %</td>
<td>68.9</td>
<td>66.7</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>86.6</td>
<td>91.4</td>
</tr>
<tr>
<td>Oriental</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Black</td>
<td>11.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>92.8 (21.8)</td>
<td>89.1 (20.3)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.6 (10.4)</td>
<td>165.9 (9.9)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>73.7 (8.8)</td>
<td>71.1 (8.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134.6 (15.6)</td>
<td>134.6 (17.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.5 (8.8)</td>
<td>78.7 (9.4)</td>
</tr>
<tr>
<td>Total radiographic score†</td>
<td>7.0 (3.9)</td>
<td>6.6 (3.4)</td>
</tr>
<tr>
<td>WOMAC‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain subscale</td>
<td>13.0 (3.3)</td>
<td>13.0 (3.4)</td>
</tr>
<tr>
<td>Physical function subscale</td>
<td>42.0 (11.7)</td>
<td>41.3 (11.5)</td>
</tr>
<tr>
<td>Stiffness subscale</td>
<td>5.2 (1.5)</td>
<td>5.2 (1.5)</td>
</tr>
<tr>
<td>Patient global assessment§</td>
<td>3.1 (0.7)</td>
<td>3.1 (0.7)</td>
</tr>
</tbody>
</table>

Abbreviation: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
†Total maximum score possible was 27.
‡On a Likert scale pain scores ranged from 0 (no pain) to 20 (extreme pain); physical function, 0 (no difficulty) to 68 (extreme difficulty); and stiffness, 0 (no stiffness) to 8 (extreme stiffness).
§Patient global assessment score ranged from 0 (very good) to 4 (very poor).

Major entry criteria. One patient in the topical diclofenac group had undergone previous knee reconstructive surgery (not primary OA); 2 patients in the vehicle-control group had osteochondritis dissecans (not primary OA); and 1 patient in the vehicle-control group had a normal radiological examination. Exclusion of these patients left 322 patients [163 in the topical diclofenac group and 159 in the vehicle-control group] eligible for evaluation (numbers based on pain dimension). One patient was eliminated from the ITT analyses for physical function, stiffness, and patient global assessment, and another was eliminated from the ITT analysis for patient global assessment, owing to missing baseline scores.

Table 2 outlines the efficacy evaluation in the ITT group. There were significantly greater changes from baseline (improvement in score) in the topical diclofenac group compared with the vehicle-control group for pain (−5.9 vs −4.3; P = .001), physical function (−15.4 vs −10.1; P = .002), patient global assessment (−1.3 vs −0.9; P = .003), and stiffness (−1.8 vs −1.3; P = .005). In the topical diclofenac group, the largest effect was observed for the WOMAC pain subscale score, which improved by 45.7%. The WOMAC physical function and stiffness subscale scores improved by 36.7% and 35.1%, respectively, and the patient global assessment subscale score improved by 42.2%. A significant advantage for topical diclofenac solution compared with the vehicle-control solution was also observed for the separate efficacy variable pain on walking (P = .004), with an improvement in the score of 45.0% over baseline (Table 3).

Analysis of efficacy variable change scores in the per-protocol data set confirmed the superiority of topical diclofenac solution compared with the vehicle-control solution for pain (−7.1 vs −5.6; P = .02), physical function (−18.5 vs −14.3; P = .04), stiffness (−2.3 vs −1.6; P = .02), pain on walking (−1.42 vs −1.12; P = .03), and patient global assessment (−1.5 vs −1.2; P = .06). No significant difference was noted between groups in the mean±SD amount of rescue acetaminophen consumption (topical diclofenac group, 416±418 mg per patient-day; vehicle-control group, 468±473 mg per patient-day, P = .30).

SAFETY ASSESSMENTS

Most of the adverse events described were dermatological reactions at the application site (Table 4). Minor skin dryness and rash were the most frequent, occurring in a significantly greater number of patients in the topical diclofenac group (68 [41.5%] of 164 patients in the topical diclofenac group). Skin dryness and rash were the most frequent, occurring in a significantly greater number of patients in the topical diclofenac group (68 [41.5%] of 164 patients). These events led to dropout of only 5 patients in the topical diclofenac group and 1 patient in the vehicle-control group. All skin reactions resolved upon withdrawal of treatment.

There was no significant difference between groups in the incidence of adverse reactions in the GI tract (Table 4). The total number of patients reporting an adverse event in the GI tract was 19 (12%) of 164 in the topical diclofenac group compared with 15 (9%) of 162 in the vehicle-control group (P = .49). No related adverse event of the renal system was reported in any group. No significant difference between groups was noted for blood pressure or respiration. However, patients in the vehicle-control group had a slight increase in pulse, compared with a slight decrease in pulse for the topical diclofenac group (P = .03).

This study demonstrates that topical diclofenac solution, a topical NSAID in a patented transdermal carrier that includes the penetration enhancer dimethyl sulfoxide, effectively treats symptoms of primary OA of the knee. Superior efficacy compared with the vehicle-control solution was demonstrated for all defined efficacy variables—WOMAC pain, physical function, and stiffness subscales; pain on walking; and a patient global assessment. The improvement in score for these efficacy variables after treatment with topical diclofenac ranged from 35% to 46% over baseline values. These results compare favorably with conventional oral diclofenac treatment of OA. In 2 trials, patients treated with 50 mg of diclofenac 3 times daily for 12 weeks showed improvement in visual analog WOMAC scores of 32% to 44% over baseline. In 2 trials using a Likert scale to assess WOMAC scores, treatment with diclofenac 50 mg twice daily for
little evidence supports a physiological and therapeutic benefit has been as-
documented previously using a standard in vitro model of human skin.44 Although many other physiological and therapeutic benefits have been ascribed to dimethyl sulfoxide, little evidence supports a clinical effect in rheumatic conditions.45 A previous 3-arm trial of topical diclofenac, similar in design to this study, demonstrated no clinical benefit of dimethyl sulfoxide as a vehicle-control solution, compared with a placebo solution (containing one tenth of the concentration of dimethyl sulfoxide as was in the vehicle-control solution).46

Safety analyses revealed no apparent, serious adverse effects, with only minor application-site skin reactions, mostly skin dryness, after treatment with this topical diclofenac solution. The slightly lower incidence in the vehicle-control group, as was noted in the previously cited

Table 2. Efficacy Evaluation*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Topical Diclofenac</th>
<th>Vehicle-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>163</td>
<td>159</td>
</tr>
<tr>
<td>Baseline score</td>
<td>13.0 (3.3)</td>
<td>12.9 (3.4)</td>
</tr>
<tr>
<td>Final score</td>
<td>7.1 (4.7)</td>
<td>8.6 (4.9)</td>
</tr>
<tr>
<td>Change in score</td>
<td>−5.9 (4.7)</td>
<td>−4.3 (4.4)†</td>
</tr>
<tr>
<td>% Change</td>
<td>−45.7</td>
<td>−33.3</td>
</tr>
<tr>
<td>WOMAC physical function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>162</td>
<td>159</td>
</tr>
<tr>
<td>Baseline score</td>
<td>42.0 (11.8)</td>
<td>41.3 (11.5)</td>
</tr>
<tr>
<td>Final score</td>
<td>26.6 (15.6)</td>
<td>31.2 (15.8)</td>
</tr>
<tr>
<td>Change in score</td>
<td>−15.4 (15.3)</td>
<td>−10.1 (13.9)†</td>
</tr>
<tr>
<td>% Change</td>
<td>−36.7</td>
<td>−24.5</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>161</td>
<td>159</td>
</tr>
<tr>
<td>Baseline score</td>
<td>3.1 (0.7)</td>
<td>3.1 (0.7)</td>
</tr>
<tr>
<td>Final score</td>
<td>1.8 (1.2)</td>
<td>2.2 (1.2)</td>
</tr>
<tr>
<td>Change in score</td>
<td>−1.3 (1.2)</td>
<td>−0.9 (1.2)†</td>
</tr>
<tr>
<td>% Change</td>
<td>−42.2</td>
<td>−36.4</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>162</td>
<td>159</td>
</tr>
<tr>
<td>Baseline score</td>
<td>5.2 (1.5)</td>
<td>5.2 (1.5)</td>
</tr>
<tr>
<td>Final score</td>
<td>3.4 (2.0)</td>
<td>4.0 (2.0)</td>
</tr>
<tr>
<td>Change in score</td>
<td>−1.8 (2.1)</td>
<td>−1.3 (2.0)†</td>
</tr>
<tr>
<td>% Change</td>
<td>−35.1</td>
<td>−24.1</td>
</tr>
</tbody>
</table>

Abbreviation: WOMAC, Western Ontario and McMaster Universities LK3.1 Osteoarthritis Index.

Table 3. Analysis of Pain on Walking*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Topical Diclofenac</th>
<th>Vehicle-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score</td>
<td>2.62 (0.82)</td>
<td>2.66 (0.83)</td>
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<tr>
<td>Final score</td>
<td>1.44 (1.09)</td>
<td>1.79 (1.11)</td>
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<tr>
<td>Change in score</td>
<td>−1.18 (1.11)</td>
<td>−0.87 (1.06)†</td>
</tr>
<tr>
<td>% Change</td>
<td>−45.0</td>
<td>−32.7</td>
</tr>
</tbody>
</table>

Abbreviation: COSTART, Coding Symbols for Thesaurus of Adverse Reaction Terms.

Table 4. Incidence of Adverse Events (as Coded by COSTART)*

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Topical Diclofenac (n = 164)</th>
<th>Vehicle-Control (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (3.0)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (4.9)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (2.4)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Melena</td>
<td>0</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (2.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Application-site skin reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>60 (36.6)</td>
<td>41 (25.3)†</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (11.0)</td>
<td>8 (4.9)†</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1 (0.6)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vesiculobullous rash</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Other reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>3 (1.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>4 (2.4)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (5.5)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Haltitus</td>
<td>0</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>3 (1.8)</td>
<td>5 (3.1)</td>
</tr>
</tbody>
</table>

*Study groups are described in the Figure legend. Data are expressed as number (percentage) of patients with at least 1 episode.

†P < .05 vs the topical diclofenac group.
3-arm study, suggests that little of the irritation was due to the diclofenac. Dimethyl sulfoxide is commercially used as a potent solvent, and when applied as a topical penetrant, it dissolves normal skin surface oils and dries the skin. Thus, common skin lubricants should prevent most of the adverse effects to the application site noted. Such lubricants were not permitted in this trial, to detect the maximum adverse effect profile of the product. Despite the substantial incidence of skin-related adverse events in the topical diclofenac group (41.5% of patients), the low dropout rate owing to these events (5 patients [3%]) suggests that these were tolerable, minor reactions. Although allergic contact dermatitis has been reported with topical NSAIDs, they have been linked to adverse renal effects and increased risk of cardiovascular morbidity. These adverse effects commonly observed with oral NSAIDs were not detected in this trial, despite the regular questioning of patients by the investigator using a checklist of common NSAID-related adverse events.

There is a tangible trade-off between risk and benefit when treating OA with oral NSAIDs or cyclooxygenase-2–selective NSAIDs. Treatment with oral NSAIDs carries a substantial risk of clinically significant adverse effects, particularly on the GI tract and renal systems. Although cyclooxygenase-2–selective NSAIDs have been reported to reduce the incidence of GI tract complications, they have been linked to adverse renal effects and increased risk of cardiovascular morbidity. These adverse effects commonly observed with oral NSAIDs were not detected in this trial, despite the regular questioning of patients by the investigator using a checklist of common NSAID-related adverse events.

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REFERENCES

per gastrointestinal toxicity of rofecoxib and naproxen in patients with rheuma-
18. Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Gastrointes-
tinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib
compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch
19. Wright JM. The double-edged sword of COX-2 selective NSAIDs. CMAJ. 2002;
167:1131-1137.
20. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with
21. Shimp LA. Safety issues in the pharmacologic management of chronic pain in the
22. Moore RA, Tramer MR, Carroll D, Wiffers PJ, McQuay HJ. Quantitative system-
atic review of topically applied non-steroidal anti-inflammatory drugs [pub-
radiographic features in osteoarthritis. Osteoarthritis Cartilage. 1995;3(suppl A):
3-70.
don Health Sciences Centre; 1995.
measures for future phase III clinical trials in knee, hip and hand osteoarthritis:
patients with osteoarthritis: recommendations from a task force of the Osteo-
29. Group for the Respect of Ethics and Excellence in Science (GREES) Osteoarthri-
tis Section. Recommendations for the registration of drugs used in the treat-
30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study
of WOMAC: a health status instrument for measuring clinically-important patient-
relevant outcomes following total hip or knee arthroplasty in osteoarthritics. J Or-
31. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study
of WOMAC: a health status instrument for measuring clinically important patient
relevant outcomes to antirheumatic drug therapy in patients with osteoar-
32. Bellamy N. Osteoarthritis clinical trials: candidate variables and clinimetric prop-
33. Canadian Pharmacists Association. Compendium of Pharmaceuticals and Special-
34. US Food and Drug Administration. COSTART: Coding Symbols for Thesaurus of
Adverse Reaction Terms. 4th ed. Springfield, Va: National Technical Informa-
Geneva, Switzerland: International Conference on Harmonisation of Technical Re-
quirements for Registration of Pharmaceuticals for Human Use: 1998. Available at:
http://www.ich.org/UrGpServer.jsr?i@ID=2788&_@TEMPLATE=254. Ac-
and diclofenac in patients with osteoarthritis of the knee. J Rheumatol. 1993;
20:999-1004.
Group. Rofecoxib, a specific inhibitor of cyclo-oxygenase 2, with clinical effi-
cacy comparable with that of diclofenac sodium: results of a one-year, random-
38. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P, for the Meloxi-
cam Osteoarthritis Investigators. Safety and efficacy of meloxicam in the treat-
ment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-
coxib versus diclofenac in the management of osteoarthritis of the knee. Scand
40. Bellamy N, Buchanan WW. Outcome measurement in osteoarthritis clinical trials:
41. Nishihata T, Kamada A, Sakai K, et al. Percutaneous absorption of diclofenac in
42. Obata Y, Takayama K, Okabe H, Nagai T. Effect of cyclic monoterpenes on per-
cutaneous absorption in the case of a water-soluble drug (diclofenac sodium),
43. Kligman AM. Topical pharmacology and toxicology of dimethyl sulfoxide—part I.
44. Hewitt PG, Poblete N, Wester RC, Maibach HI, Shainhouse JZ. In vitro cutane-
ous disposition of topical diclofenac lotion in human skin: effect of a multi-dose
45. Council on Scientific Affairs. Dimethyl sulfoxide: controversy and current status—
46. Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solu-
tion for relieving symptoms of primary osteoarthritis of the knee: a randomized
controlled trial. CMAJ. 2004;171:333-338.
47. Halpern SM. Topical non-steroidal anti-inflammatory drugs: a review of their use
48. Ophaswongse S, Maibach H. Topical nonsteroidal antiinflammatory drugs: al-
lergic and photoallergic contact dermatitis and phototoxity. Contact Dermati-
tics. 1993;29:57-64.
49. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal com-
50. Lichtenstein DR, Syngal S, Wolfe MM. Nonsteroidal antiinflammatory drugs and
the gastrointestinal tract: the double-edged sword. Arthritis Rheum. 1995;38:
5-18.
51. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: fo-
655-70S; discussion 708-715.
52. Roth SH. Nonsteroidal anti-inflammatory drug gastropathy: we started it—can we
53. Roth SH, Bennett RE. Nonsteroidal anti-inflammatory drug gastropathy: recog-
54. Roth SH. NSAID gastropathy: a new understanding. Arch Intern Med. 1996;156:
1623-1628.
55. Roth SH. Etoricoxib: a viewpoint by Sanford H Roth. Drugs. 2002;62:2652-
2653.
56. Roth SH. Arthritis therapy: a better time, a better day. Rheumatology (Oxford).