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 McMaster Universities LK3.1 OA 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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Nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium are recommended for the treatment of the symptoms of osteoarthritis (OA),

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Dr Shainhouse owns stock in Dimethaid Health Care Ltd.
within the previous 3 months,²⁴,²⁵ and (2) a flare of pain after
bone (osteophytes) at the joint surface of the knee (medial,
lar cartilage (joint space narrowing) and/or formation of new
diological findings of deterioration and abrasion of the articu-
85 years with primary OA in at least 1 knee defined by (1) ra-
exclusion interview and was eligible to proceed to washout if
the surrounding community. After providing written, in-
tients were recruited from the physician’s private practice or
approval by the appropriate institutional review boards. Pa-
18, 2001, at 39 medical centers across the United States after
aminophen and wish to avoid systemic therapy.¹ At
cal analgesics in patients who do not respond to acet-
tomatic OA. In this study, we report on the results of a
12-week trial of this topical diclofenac solution, com-
pared 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
85 years with primary OA in at least 1 knee defined by (1) ra-
diological findings of deterioration and abrasion of the articular
tilage (joint space narrowing) and/or formation of new bone
osteoarthrosis) at the joint surface of the knee (medial, lateral,
patellofemoral) at an examination performed within the previous 3 months,²⁴,²⁵ 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 Universi-
sites LK3.1 OA Index (WOMAC) pain subscale, scored on a
5-point Likert scale where 0 indicates none; 1, mild; 2, mod-
erate; 3, severe; and 4, extreme.²⁶ A flare was defined as an in-
crease 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/ ques-
tions 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 arthri-
tis, psoriatic arthritis, postinfectious arthritis, metabolic ar-
thritis, and traumatic arthritis or surgical joint replacements;
sensitivity to diclofenac, aspirin or any other NSAID, di-
methyl sulfoxide, propylene glycol, glycerin, or ethanol; clin-
cally active renal, hepatic, or peptic ulcer disease; a history of
alcohol or other drug abuse; lactation; concomitant skin dis-
ease 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 antide-
pressant; 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

Rheumatology.²⁷ On the other hand, the American Col-
lege of Rheumatology has recommended the use of topical
analgesics in patients who do not respond to acet-
aminophen and wish to avoid systemic therapy.¹ 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 con-
taining dimethyl sulfoxide (Pennsaid; Dimethaid Health
Care Ltd, Markham, Ontario) was approved in Canada
and several European countries for the treatment of symp-
tomatic OA. In this study, we report on the results of a
12-week trial of this topical diclofenac solution, com-
pared with a vehicle control solution, in the treatment of the symptoms of primary OA of the knee.

OUTCOME MEASURES

The primary efficacy variables were the change from baseline
to final assessment in pain and physical function, as measured by the WOMAC²⁶ subscales, and in the patient global assess-
ment (“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 car-
ried forward. The secondary variable was the change in stiff-
ness. This core set of outcome measures follows the recom-
mendations of Outcome Measures in Arthritis Clinical Trials
(OMERACT) III,²⁷ the Osteoarthritis Research Society (OARS),²⁸
and the Group for the Respect of Ethics and Excellence in Sci-
ence (GREES).²⁹ The WOMAC is a validated question-
naire³⁰-³² 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 walk-
ing on a flat surface?”), the only measure of pain in many NSAID
trials, was assessed also as a separate efficacy variable. Pain on
walking is referred to by GREES³² as “use-related pain,” dis-
tinct 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 probed with open-ended questions and with a check-
list questionnaire of commonly seen adverse effects of NSAIDs.³³
Dermatological assessment of the knee was performed by the
investigator at each clinic visit, and any abnormality was re-
corded as an adverse event. All adverse events were catego-
rized according to Coding Symbols for Thesaurus of Adverse
Reaction Terms.³⁴ Vital signs were recorded at baseline and at
final assessment.

SAMPLE SIZE

Based on a power of 80% and a type I error rate of α = .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 nonevaluable 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 χ² 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 χ² or the Fisher exact test.

An intent-to-treat (ITT) group was defined as a subset of all treated patients who met critical inclusion criteria31 (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,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>42-85</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.

‡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 additional 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 (81 of 164 patients in the topical diclofenac group compared with 15 of 162 in the vehicle-control group) eligible for evaluation (numbers based on pain dimension). One additional 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.

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
12 weeks or 50 mg 3 times daily for 6 weeks produced improvements ranging from 35% to 42%. The results of these earlier studies, compared with those of the present study, suggest that topical administration of this diclofenac solution can relieve the symptoms of OA in a manner and extent similar to that of traditional oral dosing with diclofenac.

The reliability of these efficacy results is enhanced by the rigorous design of this study. Extensive reviews of topical NSAIDs indicate that many studies have an inadequate trial design, with outcome measures of poorly defined or undefined reliability, validity, and responsiveness and brief duration ranging from 7 to 14 days.

The present study was a large, randomized, vehicle-controlled trial with appropriate powering, standardized radiological and clinical entry criteria, validated efficacy variables, and 12 weeks’ duration that parallels investigations of oral NSAID treatment for OA.

A limiting factor in topical NSAID therapy is penetration of the skin barrier. Percutaneous topical penetration of diclofenac in this topical diclofenac solution is enhanced by the carrier containing dimethyl sulfoxide, as has been documented previously using a standard in vitro model of human skin. Although many other physiological and therapeutic benefits have been ascribed to dimethyl sulfoxide, little evidence supports a clinical effect in rheumatic conditions. 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).

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 noted in the previously cited
3-arm study,46 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 pen- etrant, 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,57,58 that problem was not found, when specifically sought in a previous trial.46 The halitosis and taste perversion infrequently reported in this trial result when dimethyl sulfoxide is metabolized to a volatile gas that gives the breath a garlic-like taste.

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 tract49,50 and renal systems51–53. Despite attempts at expensive gastroprotective therapies and hoped-for benefits of selective cyclooxygenase-2–selective NSAIDs have been reported to reduce the incidence of GI tract complications,10,16,18 they have been linked to adverse renal effects52 and increased risk of cardiovascular morbidity.53 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.

Upper GI tract bleeding related to NSAIDs comprises the most serious and often fatal complications reported for any group of drugs. Since the first report by Roth54 of the extent of NSAID gastropathy in 1986 that stated, “we started it—can we stop it?” a subsequent report described the unique features of NSAID gastropathy.55 Ten years later, Roth54 returned to the subject of NSAID gastropathy and indicated that, despite “newer understandings,” the morbidity and mortality continued. Despite attempts at expensive gastroprotective therapies and hoped-for benefits of selective cyclooxygenase-2 generations of NSAID therapy, the morbidity and mortality complications have still not been stopped.55 New alternatives on the horizon may produce a better answer.30 The success of this topical diclofenac solution in this rigorous study reported herein—positive efficacy results and a minor profile of adverse effects—could be a step in that important direction.

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