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

Sanford H. Roth, MD; J. Zev Shainhouse, MD

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.

Arch Intern Med. 2004;164:2017-2023
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; Dimetha 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 (osteoophytes) at the joint surface of the knee (medial, lateral, or 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 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.26 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; and other pain or disabling condition affecting the knee.

INTERVENTIONS

Patients were randomly assigned to 1 of the following 2 treatments: topical diclofenac solution, consisting of 1.5% (wt/wt) diclofenac sodium in a patented carrier containing dimethyl sulfoxide (45.5%, wt/wt), propylene glycol, glycerin, ethanol, and water; or a vehicle-control solution consisting of the complete carrier (including dimethyl sulfoxide; 45.5%, wt/wt) and no diclofenac. Study solution (about 1.3 mL) was applied around the affected knee (10 drops each to the front, back, medial, and lateral sides), without rubbing, 4 times daily for up to 12 weeks. Compliance was verified by weighing bottles at the start of each visit. If both knees were painful, both were treated and evaluated for safety, but efficacy analysis was performed only on the knee with the greater baseline pain score. If both knees had the same baseline pain score, the dominant knee was arbitrarily chosen. Rescue analgesia with acetaminophen (up to four 325-mg tablets per day) was permitted for residual knee or other body pain throughout the treatment period, except during the washout period before baseline and the 3 calendar days before the scheduled final assessment at week 12. Aspirin (≤325 mg/d) was permitted for cardiovascular prophylaxis.

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,27 the Osteoarthritis Research Society (OARSI),28 and the Group for the Respect of Ethics and Excellence in Science (GREEES).29 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?”), the only measure of pain in many NSAID trials, was assessed also as a separate efficacy variable. Pain on walking is referred to by GREEES30 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 probed with open-ended questions and with a checklist questionnaire of commonly seen adverse effects of NSAIDs.31 Dermatomal assessment of the knee was performed by the investigator at each clinic visit, and any abnormality was recorded as an adverse event. All adverse events were categorized according to Coding Symbols for Thesaurus of Adverse Reaction Terms.32 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 criteria35 (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

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=.02). 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-
A significant advantage for topical diclofenac 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 (60/164) compared with those in the vehicle-control group (41/162 [P = .03] and 8/162 patients [P = .04], respectively). However, these adverse 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.36-39 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.36,37 In 2 trials using a Likert scale to assess WOMAC scores, treatment with diclofenac 50 mg twice daily for

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographic and Clinical Characteristics†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Women, %</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Total radiographic score‡</td>
</tr>
<tr>
<td>WOMAC‡ Pain subscale</td>
</tr>
<tr>
<td>Physical function subscale</td>
</tr>
<tr>
<td>Stiffness subscale</td>
</tr>
<tr>
<td>Patient global assessment§</td>
</tr>
</tbody>
</table>

Abbreviation: WOMAC, Western Ontario and McMaster Universities LK3.1 Osteoarthritis Index.
†Study groups are described in the Figure legend. Unless otherwise indicated, data are expressed as mean (SD).
‡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).
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

<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>-30.4</td>
</tr>
</tbody>
</table>
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 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,7,47 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 tract50,51 and renal systems.10 Although cyclooxygenase-2–selective NSAIDs have been reduced to the incidence of GI tract complications,10,50 they have been linked to adverse renal effects6,30 and increased risk of cardiovascular morbidity.20 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 Roth52 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.35 Ten years later, Roth53 returned to the subject of NSAID gastropathy and indicated that, despite “newer understandings,” the morbidity and mortality continued. Despite attempts at expensive gastrosuppressive therapies and hoped-for benefits of selective cyclooxygenase-2 generations of NSAID therapy, the morbidity and mortality complications have still not been stopped.35 New alternatives on the horizon may produce a better answer.56 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.

Accepted for publication January 14, 2004.

This study was supported by Dimethaid Health Care Ltd, Markham, Ontario.

Preliminary data were presented at the Annual European Congress of Rheumatology; June 13, 2002; Stockholm, Sweden.

We thank all study investigators and support staff for their collaboration and commitment, without which the present study would not have been possible, including Herbert S. B. Baraf, MD, Wheaton, Md; Dennis E. Stone, MD, and David D. Gallagher, MD, Columbus, Ind; Alan J. Kivitz, MD, Duncansville, Pa; Selwyn A. Cohen, MD, Trumbell, Conn; Gary V. Gordon, MD, Wynnewood, Pa; Barry C. Lubin, MD, Virginia Beach, Va; John Reinhardt, DO, and D. Lawrence Levinson, MD, Altoona, Pa; Douglas C. Frankel, MD, Washington, DC; Terence Isakov, MD, Lyndhurst, Ohio; David L. Fried, MD, Warwick, RI; Raymond L. Malament, MD, Hagerstown, Md; Jonathan H. Horne, MD, Sandy, Utah; Mira Baron, MD, Cleveland, Ohio; Larysa Hun, MD, Great Neck, NY; Louise A. Donikyan, DO, Hackensack, NJ; Naomi de Sola Pool, MD, Huntington, NY; Louis J. Levy, Jr, MD, La Mesa, Calif; Dennis S. Riff, MD, Anaheim, Calif; J. Brannan Smoot, MD, Austin, Tex; Jacques R. Caldwell, MD, Gainsville, Fla; Karen R. Kutikoff, MD, West Palm Beach, Fla; Howard L. Offenberg, MD, Daytona Beach, Fla; Wendy Eider, MD, Yakima, Wash; Larry R. Popiel, MD, Ocala, Fla; Jeffrey B. Rosen, MD, Coral Gables, Fla; Stanley B. Cohen, MD, Dallas, Tex; Michael J. Ziter, MD, Cadillac, Mich; Christopher R. Morris, Johnson City, Tenn; and Thomas Chiambretti, DO, DeWitt, Mich.

Correspondence: J. Zew Shainhouse, MD, Dimethaid Health Care Ltd, 1405 Denison St, Markham, Ontario, Canada L3R 5V2 (medinfo@dimethaid.com).

References


52. Roth SH. Nonsteroidal anti-inflammatory drug gastropathy: we started it—it can we stop it? Arch Intern Med. 1986;146:1075-1076.


