

Pooled safety analysis of diclofenac sodium topical solution 1.5% (w/w) in the treatment of osteoarthritis in patients aged 75 years or older

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Background: This study aimed to determine the safety of diclofenac sodium topical solution 1.5% (w/w) in 45.5% dimethyl sulfoxide (TDiclo) for the treatment of knee or hand osteoarthritis in persons aged 75 years or older.

Methods: A pooled analysis of safety data from seven multicenter, randomized, blinded, Phase III clinical trials (4–12 weeks' duration) of TDiclo was conducted. The analysis focused on a subset of patients (n = 280) aged 75 years or older with a primary diagnosis of osteoarthritis of the knee (six trials) or hand (one trial). Patients received one of three topical treatments: TDiclo (n = 138); placebo (2.33% or 4.55% dimethyl sulfoxide, n = 39); or control (45.5% dimethyl sulfoxide, n = 103). Treatment groups were compared using Chi-square analysis, Fisher's Exact test, or analysis of variance.

Results: The most common adverse events involved the skin or subcutaneous tissue, primarily at the application site. The incidence of dry skin was higher in the TDiclo (36.2%; $P < 0.0001$) and dimethyl sulfoxide control (18.4%; $P = 0.0142$) groups than in the placebo group (2.6%); the incidence of other skin or subcutaneous tissue adverse events was similar between the groups. Relatively few patients (<18%) experienced gastrointestinal adverse events, and group differences were not detected. In the TDiclo group, constipation (3.6%), diarrhea (3.6%), and nausea (3.6%) were the most common gastrointestinal adverse events. Cardiovascular and renal/urinary adverse events were rare, and group differences were not detected. There was one case (0.7%) each of hypertension, spider veins, and vasodilation in the TDiclo group. Changes from baseline to the final visit in blood pressure and hepatic/renal enzyme levels were also similar between the groups.

Conclusion: TDiclo appears to be well tolerated for the treatment of osteoarthritis in persons aged 75 years or older.

Keywords: adverse events, analgesic, arthritis, gastrointestinal, nonsteroidal anti-inflammatory drugs, tolerability

Introduction

“The catastrophe of NSAID mortality is ultimately reduced to the individual collision of NSAID pharmacology conflated with the failure of host defences”

—Sanford H. Roth¹

Musculoskeletal disorders are the leading cause of disability in the United States and present a major economic burden as a result of lost work wages and direct health care costs, which together account for an estimated \$849 billion annually.² Of the various musculoskeletal disorders, arthritis is the most prevalent chronic condition. In the United States, 21.6% of the adult population aged 18 years or older is affected by arthritis.² Osteoarthritis is the most common form of arthritis and is characterized by cartilage

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degradation, osteophyte formation, synovial inflammation, subchondral sclerosis, and bone deformation of one or more joints, with the knees, hips, and hands more commonly affected than other joints, such as the ankles, wrists, or shoulders.^{3,4} Symptomatically, osteoarthritis is characterized by pain, stiffness, and an impairment or loss of function of the joint.^{3,4} Prevalence estimates vary depending on the criteria used to define the disease, but recent estimates indicate that 26.9 million American adults are affected by osteoarthritis in at least one joint.⁵ The prevalence of osteoarthritis is greater among female and elderly individuals; among adults older than 70 years of age, 26.2% of women and 13.3% of men have symptomatic osteoarthritis of the hand.⁶ The incidence of osteoarthritis is estimated to be 240 per 100,000 person-years for knee osteoarthritis and increases with age up to 80 years.⁷

There is no cure for osteoarthritis; its treatment is focused on alleviating signs and symptoms of the disease and improving overall quality of life. Multimodal treatment strategies are frequently employed; these approaches generally incorporate weight management and exercise programs, physical and occupational therapy, and other types of nonpharmacologic and nonsurgical therapies.^{8,9} Total joint arthroplasty is employed as a definitive treatment in advanced disease; total hip and knee replacements are the most common procedures.² Although often effective, these procedures confer significant health risks and economic costs.² Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common pharmacologic treatment utilized for alleviating the symptoms of osteoarthritis. However, use of these agents is associated with an increased risk of serious adverse effects, particularly among the elderly and those with increased cardiovascular and gastrointestinal risk.^{9–13} For example, cohort and case-control epidemiologic studies have shown an increase in NSAID-related upper gastrointestinal adverse events (aspirin and nonaspirin), with a 2–6-fold increase in risk over non-NSAID users.¹⁴

The most significant oral NSAID-related adverse events involve the gastrointestinal,^{15,16} cardiovascular,^{17,18} and renal^{19,20} systems. The Agency for Healthcare Research and Quality estimates that among adults aged 75 years or older receiving oral NSAIDs for osteoarthritis, 91 per 10,000 persons will experience a serious gastrointestinal bleed, 30 per 10,000 persons will experience a myocardial infarction from oral NSAIDs other than naproxen, and 20 per 10,000 persons will discontinue using oral NSAIDs due to renal dysfunction.²¹

The gastrointestinal effects of oral NSAIDs have been recognized for more than 20 years, yet remain a problem

despite the combined use of NSAIDs and gastroprotective agents.^{15,22–24} Recent studies have shown that even short-term use of oral NSAIDs can increase the risk of myocardial infarction and death among high-risk individuals. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is associated with an increased risk of myocardial infarction or death within 14–30 days of treatment.¹³ Rofecoxib, another selective COX-2 inhibitor, and ibuprofen, a nonselective COX inhibitor, are associated with increased risk of myocardial infarction or death within 7–14 days of treatment.¹³ The nonselective NSAID diclofenac is associated with increased risk of myocardial infarction or death immediately after initiation of treatment.¹³ In addition, NSAIDs increase blood pressure and can trigger blood pressure destabilization in hypertensive patients.^{25,26} These effects may be more pronounced in patients with compromised renal function, particularly the elderly, in whom renal function is compromised as a result of the normal aging process.^{10,19} The age-related compromise in renal function also confers greater risk of oral NSAID-induced renal toxicity in elderly patients.¹⁰ NSAID-induced hepatotoxicity is rare, but because NSAIDs are widely prescribed, their use accounts for a large proportion of cases of acute liver failure.²⁷ The elderly are at greater risk for NSAID-induced hepatotoxicity secondary to the increased risk of hepatotoxicity related to advanced age rather than to NSAID use per se.²⁷

Topical NSAIDs have the potential to reduce the risk of systemic adverse events associated with oral NSAIDs by reducing the plasma level of active drug and metabolites.²⁸ A number of professional organizations have included topical NSAIDs as a therapeutic option for the treatment of osteoarthritis, including the American Geriatrics Society,¹⁰ the European League Against Rheumatism,²⁹ the National Institute for Health and Clinical Excellence,³⁰ and the Osteoarthritis Research Society International.³¹ The American College of Rheumatology (ACR) recently updated its osteoarthritis treatment guidelines, using published data available through 2010 and a formal grading process implemented by a broad range of experts drawn from numerous disciplines.³² The new guidelines recommend topical NSAIDs as one option for first-line treatment of osteoarthritis of the knee or hand. For persons aged 75 years or older, the ACR guidelines recommend topical NSAIDs, rather than oral NSAIDs, as first-line treatment for osteoarthritis of the hand.

Currently, only two topical formulations of diclofenac have been approved by the United States Food and Drug

Administration for the treatment of osteoarthritis. Diclofenac sodium topical solution 1.5% (w/w) in 45.5% dimethyl sulfoxide (abbreviated herein as TDiclo), approved in 2009, is one such formulation. Because of the increased risk of NSAID-induced adverse events among the elderly, as well as the ACR recommendation regarding the use of topical NSAIDs for the treatment of hand osteoarthritis in the elderly, this study aimed to determine the safety profile of TDiclo in persons aged 75 years or older through pooled analysis of safety data from seven multicenter, randomized, blinded, Phase III clinical trials of TDiclo.

Materials and methods

Patients

Eligible patients were men and nonpregnant women who received a diagnosis, verified radiologically and scored for severity, of primary osteoarthritis in at least one knee (six trials) or hand (one trial), with regular pain in the affected joint. If patients had two affected joints, the joint with the highest pain score or the dominant joint was assessed in the trial. The age of eligible patients varied between trials, but all patients were at least 18 years of age. Exclusion criteria that were common to all trials included were: secondary arthritis; known sensitivity to diclofenac, other NSAIDs, dimethyl sulfoxide, or any other component of the vehicle; concomitant skin disease or use of another topical product at the targeted application site; corticosteroid use; oral use of analgesics, glucosamine, or chondroitin; and clinically significant renal, hepatic, or peptic ulcer disease. A one-week washout period preceded baseline measurements. The use of aspirin was permitted for prophylactic cardioprotection.

Study design

This study involved a pooled analysis of safety data derived from seven multicenter, randomized, blinded, Phase III clinical trials of TDiclo (Pennsaid®; Mallinckrodt Inc, Hazelwood, MO)³³ conducted in Canada and the United States, and focused on a subset of patients 75 years of age or older with a primary diagnosis of osteoarthritis in the knee or hand. The trials were similar in design, although the comparison groups and the duration of the trials (4–12 weeks) differed. Each trial was approved by the appropriate institutional review board, and all patients provided written informed consent before study enrollment.

Three treatment groups were examined in the pooled analysis: TDiclo (diclofenac sodium topical solution 1.5% [w/w] in 45.5% dimethyl sulfoxide; n = 138); placebo

(topical lotion consisting of 2.33% or 4.55% dimethyl sulfoxide; n = 39); and control (topical lotion consisting of 45.5% dimethyl sulfoxide; n = 103). The three lotions were identical in appearance. A small amount of dimethyl sulfoxide was included in the placebo lotion in order to control for the garlic odor produced by dimethyl sulfide when it is exhaled.³⁴ This blinding procedure was validated in earlier trials.³⁵ Patients were instructed to apply 40 drops (approximately 1.3 mL) of solution four times per day or 50 drops (approximately 1.55 mL) of solution three times per day to the affected knees or 5–40 drops of solution four times per day to the affected hands throughout the study period. Compliance was verified by weighing bottles at the start of each weekly visit and calculating the average dose applied per joint per day. Acetaminophen was permitted in these trials as a rescue medication.

Safety assessments

Vital signs were recorded at the baseline and final visits. Urine and blood samples were collected at the baseline and final visits for four of the seven trials. These were used for routine laboratory measurements, including measurement of hemoglobin and key hepatic (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase) and renal (creatinine) enzymes. Patients were provided with a diary and instructed to record daily any adverse events that occurred. During each weekly clinic visit or telephone call, study personnel recorded adverse events using a standardized checklist containing common adverse events related to the use of NSAIDs. Study personnel verbally questioned patients using standardized open-ended questions and recorded any abnormalities in the checklist. Study personnel also assessed the affected joint at each weekly clinic visit and recorded any abnormalities using the same checklist.

Statistical analyses

All adverse events were categorized using the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms.³⁶ Serious and severe adverse events were defined according to the definitions provided by Spilker.³⁷ Descriptive statistics were calculated, and continuous variables were represented as mean, standard deviation, minimum, and maximum values. Categorical variables were represented as frequencies and corresponding percentages. For selected continuous variables, change scores were calculated from values measured at the baseline assessment to those measured at the final visit. Treatment groups were compared (TDiclo versus

placebo and control versus placebo) using the Chi-square or Fisher's Exact test for categorical variables and analysis of variance with a main treatment effect for continuous variables. For all statistical tests, $\alpha = 0.05$. All statistical analyses were conducted using SAS software (SAS Institute Inc, Cary, NC).

Results

Baseline demographics and clinical characteristics

Patients in the three treatment groups did not differ with respect to age, gender, or racial composition (Table 1). The baseline clinical characteristics of the patients were also similar among the three treatment groups (Table 2), except that the percentage of patients with a history of hypertension was higher in the TDiclo (60.9%; $P = 0.013$) and control (61.2%; $P = 0.015$) groups than in the placebo group (38.5%). However, mean blood pressure measurements were similar among the three treatment groups.

Treatment-emergent adverse events

Table 3 presents the incidence of skin or subcutaneous tissue and gastrointestinal adverse events affecting 1% or more of patients. The overall incidence of skin or subcutaneous adverse events was higher in the TDiclo (44.2%; $P < 0.0001$) and control (30.1%; $P < 0.0042$) groups than in the placebo group (7.7%). Among the specific skin or subcutaneous tissue adverse events, a significant difference between treatment groups was detected only for dry skin (Figure 1), and the percentage of patients with dry skin was higher in the TDiclo (36.2%; $P < 0.0001$) and control (18.4%; $P = 0.0142$)

groups than in the placebo group (2.6%). Other specific skin or subcutaneous tissue adverse events that were observed in the TDiclo group included erythema (5.8%) and contact dermatitis (5.1%); all other specific skin-related adverse events occurred in less than 3% of patients in the TDiclo group (Table 3).

The overall incidence of gastrointestinal adverse events was relatively low and did not differ between the TDiclo (17.4%), control (8.7%), and placebo (17.9%) groups (Table 3). Among the specific gastrointestinal effects observed in the TDiclo group, constipation (3.6%), diarrhea (3.6%), and nausea (3.6%) were the most frequently reported. All other gastrointestinal adverse events occurred in less than 3% of patients in the TDiclo group.

Cardiovascular adverse events occurred rarely, and the overall incidence of cardiovascular adverse events did not differ between the TDiclo (2.2%), placebo (2.6%), and control (0.0%) groups. Among the specific cardiovascular adverse events observed in the TDiclo group, there was one case (0.7%) of hypertension, one case (0.7%) of spider veins, and one case (0.7%) of vasodilation.

Renal or urinary adverse events were also rare and occurred with an incidence of 1.9% in the control group and 0.0% in both the TDiclo and placebo groups. One case (1.0%) of pollakiuria and one case (1.0%) of abnormal urine odor were reported in the control group.

Treatment-emergent serious adverse events

The overall incidence of serious adverse events was 0.7%, 0.0%, and 7.7% for the TDiclo, control, and placebo groups,

Table 1 Baseline demographics of patients

Parameter	Treatment group			P value ^a (versus placebo)	
	TDiclo (n = 138)	Placebo (n = 39)	Control (n = 103)	TDiclo	Control
Age (years)					
Mean (SD)	78.4 (2.8)	77.9 (2.8)	78.1 (2.6)	0.427	0.719
Minimum, maximum	75, 85	75, 84	75, 85		
Gender, n (%)					
Male	64 (46.4)	19 (48.7)	34 (33.0)	0.796	0.084
Female	74 (53.6)	20 (51.3)	69 (67.0)		
Race, n (%)					
White	131 (94.9)	36 (92.3)	95 (92.2)	0.577	0.915
Black	3 (2.2)	1 (2.6)	4 (3.9)		
Hispanic	1 (0.7)	1 (2.6)	1 (1.0)		
Asian	2 (1.4)	1 (2.6)	3 (2.9)		
Other	1 (0.7)	0 (0.0)	0 (0.0)		

Note: ^aP values were derived from Chi-square test or Fisher's Exact test for categorical parameters or from analysis of variance with a main treatment effect for continuous parameters.

Abbreviations: SD, standard deviation; TDiclo, diclofenac sodium topical solution.

Table 2 Clinical characteristics of patients

Parameter	Treatment group			P value ^a (versus placebo)	
	TDiclo (n = 138)	Placebo (n = 39)	Control (n = 103)	TDiclo	Control
Body mass index (kg/m ²) ^b					
Mean (SD)	29.7 (5.2)	27.2 (5.4)	28.0 (5.0)	0.077	0.575
Minimum, maximum	21, 45	22, 43	22, 44		
Hypertension, n (%)					
Yes	84 (60.9)	15 (38.5)	63 (61.2)	0.013	0.015
No	54 (39.1)	24 (61.5)	40 (38.8)		
Diastolic blood pressure ^c (mmHg)					
Mean (SD)	77.7 (9.4)	75.3 (10.2)	76.6 (8.5)	0.161	0.436
Minimum, maximum	50, 114	50, 94	52, 96		
Systolic blood pressure ^c (mmHg)					
Mean (SD)	137.9 (15.6)	133.1 (17.3)	138.7 (17.8)	0.101	0.094
Minimum, maximum	100, 182	108, 180	98, 210		

Notes: ^aP values were derived from Chi-square test or Fisher's Exact test for categorical parameters or from an analysis of variance with a main treatment effect for continuous parameters; ^bweight or height data were not available for 95 patients (68.8%) in the TDiclo group, 15 patients (38.5%) in the placebo group, and 55 patients (53.4%) in the control group; ^cblood pressure measurements were missing from one patient (2.56%) in the placebo group.

Abbreviations: SD, standard deviation; TDiclo, diclofenac sodium topical solution.

respectively. The incidence was significantly higher for the placebo group than for the TDiclo ($P = 0.034$) or control ($P = 0.020$) groups. One patient (0.7%) in the TDiclo group developed a malignant neoplasm, and three patients (7.7%) in the placebo group reported a total of seven serious adverse events, including one instance (2.6%) each of cerebrovascular accident, dizziness, allergic transfusion reaction, feeling hot, and nausea, and two instances (5.1%) of asthenia. No patients experienced serious cardiovascular or renal/urinary adverse events.

Treatment-emergent severe adverse events

The overall incidence of severe adverse events was also higher for the placebo group (10.3%) than for the TDiclo (4.3%; not significant) or control (1.0%; $P = 0.020$) groups. The severe adverse events reported by patients in the TDiclo group included dry skin (0.7%), contact dermatitis (0.7%), erythema (0.7%), upper abdominal pain (0.7%), constipation (0.7%), and paresthesia (0.7%). No patients experienced severe cardiovascular or renal/urinary adverse events.

Table 3 Incidence of treatment-emergent skin or subcutaneous tissue and gastrointestinal adverse events affecting $\geq 1\%$ of patients

Adverse event, n (%) ^a	Treatment group			P value ^b (versus placebo)	
	TDiclo (n = 138)	Placebo (n = 39)	Control (n = 103)	TDiclo	Control
Skin/subcutaneous tissue	61 (44.2)	3 (7.7)	31 (30.1)	<0.0001	0.0042
Dry skin	50 (36.2)	1 (2.6)	19 (18.4)	<0.0001	0.014
Erythema	8 (5.8)	2 (5.1)	3 (2.9)	>0.999	0.615
Contact dermatitis	7 (5.1)	0 (0.0)	0 (0.0)	0.350	–
Pruritus	4 (2.9)	1 (2.6)	6 (5.8)	>0.999	0.674
Bullous dermatitis	3 (2.2)	0 (0.0)	0 (0.0)	>0.999	–
Rash	3 (2.2)	0 (0.0)	3 (2.9)	>0.999	0.562
Gastrointestinal	24 (17.4)	7 (17.9)	9 (8.7)	0.936	0.121
Constipation	5 (3.6)	0 (0.0)	2 (1.9)	0.588	>0.999
Diarrhea	5 (3.6)	2 (5.1)	1 (1.0)	0.650	0.183
Nausea	5 (3.6)	2 (5.1)	3 (2.9)	0.650	0.615
Abdominal pain, upper	4 (2.9)	0 (0.0)	0 (0.0)	0.577	–
Dyspepsia	4 (2.9)	0 (0.0)	1 (1.0)	0.577	>0.999
Abdominal distension	3 (2.2)	0 (0.0)	1 (1.0)	>0.999	>0.999
Abdominal pain	1 (0.7)	1 (2.6)	2 (1.9)	0.393	>0.999

Notes: ^aPatients experiencing multiple episodes of a given adverse event were counted once within each row; ^bP values were derived from Chi-square test or Fisher's Exact test. Cases in which statistical testing was not possible due to the absence of adverse events are indicated by (–).

Abbreviation: TDiclo, diclofenac sodium topical solution.

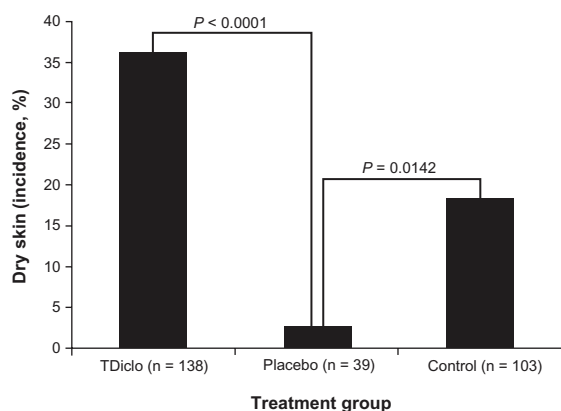


Figure 1 Incidence of dry skin among patients in the TDiclo, placebo, and control groups.

Note: Significant differences between groups are indicated.

Abbreviation: TDiclo, diclofenac sodium topical solution.

Treatment-emergent adverse events leading to study discontinuation

The overall percentage of patients who discontinued the study due to adverse events was higher in the placebo group (15.4%) than in the TDiclo (13.0%) or control (5.8%) groups, but these differences were not significant (Table 4). In the TDiclo group, dry skin (2.9%), erythema (2.9%), contact dermatitis (2.2%), and pruritus (2.2%) were the most common skin or subcutaneous tissue adverse events that resulted in study discontinuation. Gastrointestinal adverse events resulting in study discontinuation in the TDiclo group included upper abdominal pain (2.2%) and nausea (1.4%). Cardiovascular and renal/urinary adverse events were not associated with study discontinuation in the three treatment groups.

Application site–related treatment-emergent adverse events

The three treatment groups differed in overall incidence of application site–related adverse events, with a higher

incidence in the TDiclo (39.1%; $P < 0.0001$) and control (23.3%; $P = 0.014$) groups than in the placebo group (5.1%). Figure 2 shows the specific types of application site–related adverse events for the three treatment groups. Similar to the results for all adverse events, a significant difference between treatment groups was detected only for dry skin, and the percentage of patients with dry skin at the application site was significantly higher in the TDiclo (31.9%; $P < 0.0001$) and control (15.5%; $P = 0.041$) groups than in the placebo group (2.6%). Other application site–related adverse events in the TDiclo group included erythema (5.8%) and contact dermatitis (5.1%); all other events occurred in less than 2% of patients in the TDiclo group.

No patients experienced serious application site–related adverse events, but two patients (1.4%) in the TDiclo group experienced three severe application site–related adverse events (one case [0.7%] each of contact dermatitis, erythema, and paresthesia). The overall incidence of severe application site–related adverse events in the TDiclo (1.4%) and control (0.0%) groups was similar to that in the placebo group (0.0%).

The percentage of patients who discontinued study participation due to application site–related adverse events was higher in the TDiclo (5.1%) and control (1.9%) groups than in the placebo group (0.0%), but these differences were not significant. In the TDiclo group, the most common application site–related adverse events that resulted in study discontinuation were four cases (2.9%) of erythema and three cases (2.2%) of contact dermatitis.

Laboratory and blood pressure measurements

Table 5 shows changes in blood pressure and key laboratory parameters from the baseline to the final visit for the three

Table 4 Overall incidence of treatment-emergent skin or subcutaneous tissue and gastrointestinal adverse events that resulted in study discontinuation in $\geq 1\%$ of patients

Adverse event, n (%) ^a	Treatment group			P value ^b (versus placebo)	
	TDiclo (n = 138)	Placebo (n = 39)	Control (n = 103)	TDiclo	Control
Skin/subcutaneous tissue	10 (7.2)	0 (0.0)	1 (1.0)	0.120	>0.999
Dry skin	4 (2.9)	0 (0.0)	0 (0.0)	0.577	–
Erythema	4 (2.9)	0 (0.0)	0 (0.0)	0.577	–
Contact dermatitis	3 (2.2)	0 (0.0)	0 (0.0)	>0.999	–
Pruritus	3 (2.2)	0 (0.0)	1 (1.0)	>0.999	>0.999
Gastrointestinal	6 (4.3)	2 (5.1)	2 (1.9)	>0.999	0.303
Abdominal pain, upper	3 (2.2)	0 (0.0)	0 (0.0)	>0.999	–
Nausea	2 (1.4)	2 (5.1)	0 (0.0)	0.211	0.074

Notes: ^aPatients experiencing multiple episodes of a given adverse event were counted once within each row; ^bP values were derived from a Chi-square test or Fisher's Exact test. Cases in which statistical testing was not possible due to the absence of adverse events are indicated by (–).

Abbreviation: TDiclo, diclofenac sodium topical solution.

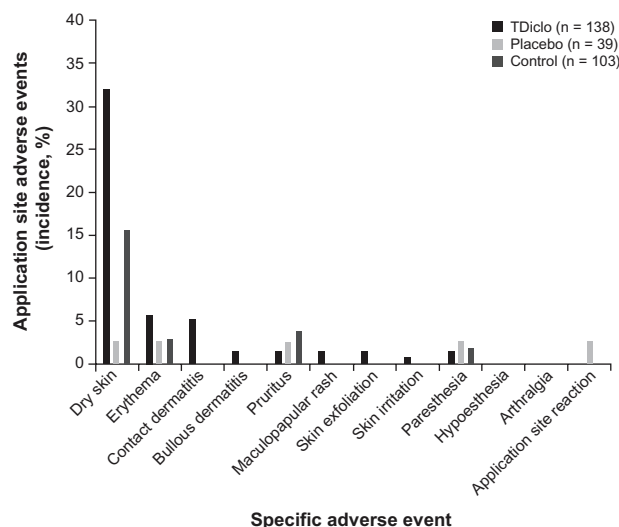


Figure 2 Incidence of application site-related adverse events among patients in the TDiclo, placebo, and control groups.

Abbreviation: TDiclo, diclofenac sodium topical solution.

treatment groups. Of the 280 patients who were analyzed in this dataset, only 239 had both baseline and final readings (125 in the TDiclo group, 28 in the placebo group, and 86 in the control group). Changes in blood pressure from the baseline to the final visit did not differ between groups. Changes in levels of hepatic and renal enzymes and hemoglobin were similar between the TDiclo and placebo groups and between the control and placebo groups.

Discussion

Osteoarthritis is a prevalent chronic disorder among the elderly.⁵ NSAIDs are the most common drugs prescribed to the elderly, and they are often used to treat the symptoms associated with osteoarthritis.³⁸ The elderly deserve special consideration when prescribing NSAIDs due to the natural effects of aging on the gastrointestinal, cardiovascular, renal, and hepatic systems, the presence of comorbid conditions, and the potential for polydrug use.^{9–11} Topical NSAIDs are associated with less systemic bioavailability than oral NSAIDs²⁸ and thus may impart a particular benefit to the elderly.¹⁰

TDiclo is a topical formulation of diclofenac that is approved for the treatment of osteoarthritis.³³ Several multicenter, randomized, blinded, Phase III clinical trials have demonstrated the efficacy of TDiclo in the treatment of osteoarthritis of the knee.^{35,39–42} In addition, the efficacy of TDiclo has been demonstrated to be equivalent to that of oral diclofenac.⁴¹

NSAID-induced gastrointestinal adverse events range from mild events such as heartburn and dyspepsia to

more serious events such as gastric and duodenal ulcers, bleeding, and perforation.^{15,16,22–24} The risk of NSAID-induced gastrointestinal injury increases with age.¹⁶ NSAIDs injure the gastrointestinal tract by blocking the production of prostaglandins in the gut, and this decreases mucosal blood flow, inhibits the secretion of mucus and bicarbonate, and decreases epithelial cell proliferation.^{20,43} In a pooled safety analysis comparing oral diclofenac with TDiclo, gastrointestinal adverse events were significantly more frequent with oral diclofenac than with TDiclo (39.0% versus 25.4%, $P < 0.0001$). The most common adverse events that occurred in the oral diclofenac group were dyspepsia (18.4%), diarrhea (13.4%), upper abdominal pain (12.1%), and abdominal distension (10.6%).⁴⁴ In the current study, 17.4% of patients in the TDiclo group experienced treatment-emergent gastrointestinal adverse events, with the most common being constipation (3.6%), diarrhea (3.6%), and nausea (3.6%). No serious gastrointestinal events were observed, and severe gastrointestinal events were rare in the TDiclo group. The incidence of gastrointestinal adverse events in the TDiclo group was similar to that in the placebo group. These results suggest that use of TDiclo by the elderly is not associated with a significant risk of gastrointestinal adverse events.

NSAID-induced cardiovascular adverse events are more common with selective COX-2 inhibitors than with non-selective NSAIDs,^{17,18} although one study using hospital registry data found that patients admitted to hospital with an initial myocardial infarction and treated subsequently with oral diclofenac had the greatest risk of subsequent myocardial infarction and death compared with patients treated with other NSAIDs.¹³ The risk of NSAID-induced cardiovascular injury generally increases with age.^{10,45} NSAIDs adversely affect the cardiovascular system in part through their well established ability to increase blood pressure (about 5 mmHg)²⁵ and in part through their effects on renal function.¹⁹ In the current study, cardiovascular adverse events were observed in 2.2% of patients in the TDiclo group, with one case (0.7%) each of hypertension, spider veins, and vasodilation, but the incidence of cardiovascular adverse events in the TDiclo group did not differ from that in the placebo group, and no serious or severe cardiovascular adverse events were reported among patients receiving TDiclo. No differences were detected between the TDiclo group and the placebo group in baseline blood pressure measurements or in mean change in blood pressure from the baseline to the final visit. These findings suggest a minimal risk of cardiovascular toxicity after TDiclo treatment in the elderly.

Table 5 Changes in blood pressure and key laboratory measurements from baseline to the final visit

Measurement ^a	Treatment group			P value ^b (versus placebo)	
	TDiclo (n = 138)	Placebo (n = 39)	Control (n = 103)	TDiclo	Control
Δ Diastolic blood pressure (mmHg)	(n = 125)	(n = 28)	(n = 86)		
Mean (SD)	-1.13 (10.24)	-3.11 (7.81)	0.24 (8.88)	0.338	0.077
Minimum, maximum	-30.0, 25.0	-24.0, 11.0	-38.0, 26.0		
Δ Systolic blood pressure (mmHg)	(n = 125)	(n = 28)	(n = 86)		
Mean (SD)	-3.61 (15.16)	-0.32 (16.14)	-2.37 (19.27)	0.307	0.613
Minimum, maximum	-44.0, 40.0	-32.0, 30.0	-52.0, 50.0		
Δ Alanine aminotransferase (IU/L)	(n = 76)	(n = 27)	(n = 31)		
Mean (SD)	2.61 (12.61)	-0.26 (3.93)	1.87 (13.67)	0.250	0.438
Minimum, maximum	-18.0, 96.0	-8.0, 9.0	-10.0, 64.0		
Δ Aspartate aminotransferase (IU/L)	(n = 76)	(n = 27)	(n = 31)		
Mean (SD)	2.34 (8.97)	0.19 (3.13)	2.94 (14.30)	0.225	0.332
Minimum, maximum	-16.0, 53.0	-7.0, 6.0	-7.0, 72.0		
Δ Creatinine (μmol/L)	(n = 76)	(n = 25)	(n = 31)		
Mean (SD)	0.53 (11.43)	2.60 (13.67)	3.81 (11.67)	0.456	0.723
Minimum, maximum	-28.0, 33.0	-25.0, 53.0	-32.0, 29.0		
Δ Gamma-glutamyltransferase (IU/L)	(n = 62)	(n = 16)	(n = 15)		
Mean (SD)	5.23 (27.04)	0.50 (6.69)	-2.87 (7.03)	0.492	0.182
Minimum, maximum	-29.0, 182.0	-12.0, 15.0	-19.0, 6.0		
Δ Hemoglobin (g/L)	(n = 75)	(n = 27)	(n = 31)		
Mean (SD)	-0.72 (7.52)	2.04 (6.48)	-0.84 (7.53)	0.094	0.127
Minimum, maximum	-19.0, 32.0	-12.0, 19.0	-14.0, 15.0		

Notes: ^aValues shown represent the change in each measurement from baseline to the final visit. First or final visit blood pressure measurements were missing for 13 patients (9.4%) in the TDiclo group, 11 patients (28.2%) in the placebo group, and 17 patients (16.5%) in the control group. Laboratory data were available for four of the seven pooled trials (80 patients in the TDiclo group, 31 patients in the placebo group, and 34 patients in the control group). Of those trials for which laboratory data were available, baseline or final visit data were missing for 4–18 patients (5.0%–22.5%) in the TDiclo group, 4–15 patients (12.9%–48.4%) in the placebo group, and 3–19 patients (8.8%–55.9%) in the control group. Adjusted sample sizes are listed for each measurement in the column headings; ^bP values were derived using analysis of variance (with a main treatment effect).

Abbreviations: SD, standard deviation; TDiclo, diclofenac sodium topical solution.

NSAID-induced renal adverse events are relatively uncommon, but can be serious. They include sodium retention and edema, acute tubular necrosis, acute renal failure, hyperkalemia, interstitial nephritis, and renal papillary necrosis.^{19,20} The risk of NSAID-induced renal toxicity increases with age due to a natural age-related decrease in the rate of glomerular filtration, which results in decreased urine excretion.^{9–11,19} No renal adverse events were found among elderly patients in the TDiclo group in this analysis. Furthermore, the mean change in creatinine levels from the baseline to the final visit was similar in the TDiclo and placebo groups. These results suggest that the risk of TDiclo-induced renal dysfunction may be low among the elderly.

Hepatotoxicity related to NSAIDs is rare; however, because oral NSAIDs are so widely prescribed, particularly among the elderly,³⁸ they represent a major overall cause of drug-related hepatotoxicity.^{27,46} Hepatotoxicity related to the use of oral diclofenac is especially high,²⁷ and acute liver injury is estimated to occur in 6.3 per 100,000 oral diclofenac users.⁴⁷ Diclofenac-induced hepatotoxicity is not well understood, but it is believed to result from direct toxicity related to diclofenac

metabolites and indirect toxicity related to inflammation; both effects result in a hepatocellular pattern of liver injury.²⁷ The risk of NSAID-induced hepatotoxicity increases with age.^{10,27} An examination of key hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase) at the baseline and final visits showed a similar mean change in hepatic enzyme levels for the TDiclo and placebo groups. These findings suggest minimal hepatotoxicity associated with TDiclo treatment in the elderly.

As noted previously, the ACR recently updated its osteoarthritis treatment guidelines to include the recommendation that topical NSAIDs be considered as one option for first-line treatment of osteoarthritis of the hand or knee.³² The new guidelines do not specifically address treatment recommendations for osteoarthritis in persons at increased risk for NSAID-induced gastrointestinal, cardiovascular, renal, or hepatic adverse events. However, the updated guidelines do include the recommendation that topical rather than oral NSAIDs be used to treat knee osteoarthritis in persons aged 75 years or older. Presumably, this recommendation is based on the increased risk of gastrointestinal,¹⁶ cardiovascular,^{10,45}

renal,^{9–11,19} and hepatic^{10,27} adverse events with oral NSAID use in the elderly.

Published short-term trials of TDiclo in the adult population report that the incidence of application site–related skin dryness ranges from 18.2% to 39.3%.^{35,39–42} Paresthesia and rash are additional adverse events related to TDiclo.^{39–41} The rate of study withdrawal due to application site–related adverse events ranges from 3.2% to 6% in the published trials.^{35,39,40,42} A long-term (52-week) study of TDiclo in adults found that application site–related skin irritation is the most common type of adverse event after TDiclo treatment for primary osteoarthritis of the knee, with dry skin (25.3%) and contact dermatitis (22.5%) being the most common specific adverse events.⁴⁸ A systematic literature review on the use of topical NSAIDs in the elderly showed that application site–related adverse events are the most common type, with dry skin, erythema, dermatitis, rash, paresthesia, pruritus, and urticaria occurring frequently in the reviewed studies.¹² The same review found a high rate (0%–21%) of study discontinuation due to adverse events, although the rate of study discontinuation due specifically to application site–related adverse events was not reported. A study by Baraf et al compared the adverse event profile of diclofenac sodium gel 1% among persons aged 25–64 years and those aged 65 years or older, and for both groups, application site–related dermatitis was the most common treatment-emergent adverse event, affecting 4.0%–5.8% of patients.⁴⁹ The rate of study discontinuation due to application site–related dermatitis was low (2.0%–2.2%) and did not differ between the two age groups. The findings of the current study show that dry skin was the most common adverse event in the TDiclo group, affecting 36.2% of patients and occurring primarily near the application site. Erythema and contact dermatitis occurred in less than 6% of patients in the TDiclo group. Serious skin or subcutaneous adverse events were not reported by patients in the TDiclo group, and severe skin or subcutaneous adverse events were rare in the TDiclo group. Together, the current and previous findings suggest that the majority of adverse events after treatment with TDiclo are related to the application site, primarily involve the skin or subcutaneous tissue, and are minor, even among the elderly.

Of note is the fact that the incidence of skin or subcutaneous tissue adverse events in the control group, which received the TDiclo vehicle (45.5% dimethyl sulfoxide), was significantly higher than in the placebo group. This finding suggests that dimethyl sulfoxide was responsible for or contributed to the adverse events observed after TDiclo treatment. Indeed, the dermatologic effects of dimethyl

sulfoxide, including skin rash and pruritus, are well established and have been exploited for the medical treatment of several dermatologic conditions.³⁴ The current finding confirms previous trial results suggesting that dimethyl sulfoxide likely contributes to some of the skin and subcutaneous tissue adverse events observed after treatment with TDiclo.^{35,39}

This study has several limitations that should be considered when interpreting its results. First, the data were derived from a retrospective pooled analysis based on relatively short-term (4–12-week) trials. Long-term trials are needed to confirm the results of the current study, although a recent 52-week, open-label study of TDiclo⁴⁷ reported results that are similar to those reported here. Also, this analysis included only one study involving hand osteoarthritis, which limits the ability for these findings to be generalized beyond knee osteoarthritis. Another limitation is that sample sizes were relatively low, particularly for the placebo group. This limitation is a consequence of the study design, which involved a pooled analysis of data from a subgroup of patients aged 75 years or older. Only a subset of the studies in this pooled analysis included laboratory measurements, hence reducing the sample sizes for those measurements. This may have limited the observation of the most serious upper gastrointestinal bleeds, which are most often asymptomatic in nature. Another limitation is that blood pressure measurements were not strictly controlled, and blood pressure variability was not examined. Finally, indirect measures of hepatic and renal toxicity were used for analysis.

Conclusion

TDiclo appears to be well tolerated in persons aged 75 years or older. The current findings suggest that TDiclo may be an appropriate treatment choice, particularly for patients who are resistant to or tolerant of application site–related skin or subcutaneous tissue adverse events. These findings support the new recommendation by the ACR that topical NSAIDs be used for the treatment of hand or knee osteoarthritis in the elderly.³²

Disclosure

SHR has served as a consultant/advisory board member and speaker for Covidien. He holds stock in Transdel Pharmaceuticals. PF is an employee of Mallinckrodt Inc, which sponsored the study and the preparation of this manuscript. Technical editorial and writing support for the preparation of this manuscript was provided by Karamarie Fecho, Synchrony Medical, LLC, West Chester, PA.

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