Topical Ketoprofen Patch in the Treatment of Tendinitis: A Randomized, Double Blind, Placebo Controlled Study

BERNARD MAZIÈRES, STÉPHANIE ROUANET, YANNICK GUILLON, CLAUDIA SCARSI, and VALENTINA REINER

ABSTRACT. ***Objective.*** To evaluate the efficacy and tolerability of ketoprofen patch in the treatment of tendinitis.

Methods. A multicenter, 14 day, randomized, double blind placebo controlled trial of a once-a-day ketoprofen 100 mg patch in symptomatic tendinitis of recent onset, not requiring orthopedic or surgical treatment. Pain on daily activities scored on a 100 mm visual analog scale was the primary efficacy criterion. Other criteria were spontaneous pain at rest, pain on full passive motion, pain relief, and pain intensity assessed twice daily by the patient (calculation of total pain relief and summed time-weighted pain intensity difference). Statistical analysis was performed on the differences between the 2 groups in the intention-to-treat population.

Results. One hundred seventy-two patients were included. Good compliance was obtained in 98% of patients. Twenty-six patients (15%) discontinued the study mainly because of adverse events, inefficacy, or cure. Decrease in pain after one week of treatment (primary criterion) was –38.4 ± 25.6 mm (56%) and –25.8 ± 24.5 mm (37%) in the ketoprofen and placebo groups, respectively ($p = 0.0013$). The differences of the secondary criteria during the trial between the 2 groups were significant more often than not. Tolerance was considered satisfactory in both groups, most adverse events reported being local reactions: 47 versus 44 were possibly or probably related to treatment in the ketoprofen and placebo groups, respectively. These local skin reactions resolved spontaneously and rarely led to premature termination of treatment.

Conclusion. This trial suggested that a 3–14 day course of treatment by ketoprofen patch is useful in nonarticular rheumatisms, the duration of treatment depending on the results obtained. The safety profile revealed no unexpected adverse events. (J Rheumatol 2005;32:1563–70)

Key Indexing Terms:
TENDINITIS KETOPROFEN PATCH
NONARTICULAR RHEUMATISM RANDOMIZED CONTROLLED TRIAL

Nonsteroid antiinflammatory drugs (NSAID) have proved to be effective in the treatment of nonarticular rheumatisms[1-3]. Oral NSAID are often adjuncts to treatment but can cause serious systemic side effects. Applied topically, these drugs are formulated to penetrate the skin, subcutaneous fatty tissue, muscle, and intraarticular tissues in amounts sufficient to exert therapeutic effects, while plasma concentrations remain low[4-6]. Topical NSAID offer the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse events (AE), such as peptic ulcer disease and gastrointestinal hemorrhage[7].

A new dosage form, the topical delivery system (TDS) patch, containing ketoprofen as the active ingredient, has recently been developed*. The patch releases ketoprofen over 24 hours and the active substance is continually present at the injury site. Its once daily application is likely to ensure better compliance compared with creams, gels, and sprays that often require 3–4 applications per day[8-10] and currently available antiinflammatory patches that require application twice daily.

The aim of our randomized controlled trial was to assess the efficacy and tolerability of the ketoprofen TDS patch in the treatment of limb tendinitis, which was chosen as it is the most frequent nonarticular rheumatism.

MATERIALS AND METHODS

Study design. This prospective, randomized, double blind, placebo controlled, parallel-group, multicenter clinical trial was carried out in France and Belgium by 29 general practitioners with experience in clinical trials, from April 2002 to January 2003. The study was approved by independent ethics committees and conducted according to the Declaration of Helsinki and the European Good Clinical Practice guidelines. All patients gave writ-

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*The ketoprofen TDS patch has been developed by Applied Pharma Research SA, Balerna, Switzerland, and jointly patented with Labtec GmbH, Langenfeld, Germany; it will be marketed worldwide by Zambon Group, while it has been exclusively licensed to ProEthic LLC for the USA and Canada.

ten informed consent before the trial. An independent Data Monitoring Committee was set up from the outset of the study to verify it was properly conducted and that the completion review was performed under strictly blind conditions.

The overall design consisted of a 14-day treatment period followed by a 7-day posttreatment followup by telephone (for tolerance assessment only). After the inclusion visit, patients were examined at Days 3, 7, and 14. *Study objective.* The primary objective was to assess the clinical efficacy of the ketoprofen TDS patch versus placebo in the treatment of nonarticular rheumatisms. The secondary objective was to obtain information on the safety of locally applied ketoprofen compared to placebo.

Patients. Outpatients of both sexes, aged 18–70 years, with tendinitis of the upper or lower limbs were included. To be eligible, patients had to present with symptomatic tendinitis with pain at daily activities = 40 mm on a 100 mm visual analog scale (VAS)[11]. The tendinitis was defined by spontaneous pain and pain to palpation at the tendinous insertion into bone. The following sites were eligible: rotator cuff of the shoulder (i.e., supraspinatus, bicipital tendons); insertion of the wrist extensors (lateral epicondylitis, tennis elbow) and flexors (medial epicondylitis) at the elbow; patellar and popliteal tendons and iliotibial band at the knee; insertion of the posterior tibial tendon in the leg (shin splints); and Achilles tendon at the heel. Patients with fibromyalgia were excluded. Tendinitis associated with osteoarthritis or rheumatoid arthritis, articular chondrocalcinosis, rupture of the rotator cuff, shoulder capsulitis, or acute calcific tendinitis of the shoulder were also excluded (but small linear calcifications of the tendons with clinical presentation of regular tendinitis were not an exclusion criterion).

The tendinitis had to be of recent onset (≤ 15 days), not requiring orthopedic or surgical treatment, and without skin conditions affecting the site of patch application. Women of childbearing age had to be either surgically incapable of pregnancy or practising an acceptable birth control method (i.e., oral hormonal contraceptives or intrauterine device).

We excluded patients with known hypersensitivity or allergy to ketoprofen or other NSAID, including aspirin, or to paracetamol (rescue medication). Patients who had taken NSAID within 48 hours before inclusion, who had applied topical medications to the painful region, or used opioids within 7 days or steroids by any route within 30 days before inclusion were not randomized.

Randomization, drug administration, and concomitant treatments. For tendinitis, the recommended dose of ketoprofen gel is 200 mg given in 2 applications daily.

A bioavailability study in 24 healthy volunteers showed that the tested patch produced a higher blood concentration (peak plasma concentration 132 ng/ml) and area under the curve (1847 ng*h/ml) than the reference gel (peak plasma concentration and area under the curve 43 ng/ml and 517 ng*h/ml, respectively), when given for 8 consecutive days at a daily dose of 100 mg, in one application for the patch and 2 for the gel while maintaining plasma concentrations relevantly lower (about 1/100) than after oral dosing of ketoprofen and therefore reasonably devoid of systemic activity (Crestani S, *et al*, unpublished data). Thus a 100 mg daily patch was considered likely to relieve the pain in tendinitis and was selected as the dose for study.

Patients meeting the selection criteria were randomly assigned by a computer generated global randomization code to receive either ketoprofen or placebo (in a 1/1 ratio) in blocks of 4 (2/2 ratio). One group received a TDS patch (8.2 × 11 cm; surface 90 cm^2) containing 100 mg ketoprofen per patch (LTS Lohmann Therapie-System GmbH, Andernach, Germany). The placebo consisted of the same indistinguishable patch with no ingredient. The randomization list and code envelopes were prepared by the company appointed for clinical supplies packaging. At Visit 0 (baseline), the investigator was to assign to each new patient the next available patient number (in ascending chronological order) among the set of numbered medication boxes provided to him. The random code was disclosed only after study completion and database closure. No case of a compromise of blinding was reported. The first patch was applied during the first visit (Visit 0, Day 0). Patients were instructed to apply one new patch directly on the area of skin overlying the painful region every morning for the next 14 ± 2 days. Patients were asked to attend the clinic for 2 intermediate visits (Visit 1: Day 3–4 and Visit 2: Day 7 ± 1) and a final visit (Visit 3: Day 14 ± 2) followed by a followup telephone call after 7 days. Rescue medication (500 mg paracetamol tablets up to 3 g daily) was allowed, but was forbidden during the 12 hours preceding the control visits. Patients were allowed to withdraw for inefficacy after 7 ± 1 days of properly administered treatment.

Medication prescribed for a disorder other than tendinitis was authorized and reported in the case report form. All analgesics (including NSAID and opioids), or steroids by any route of administration, topical medications applied to the painful region, or any physical therapy (heat, infrared heat, shortwaves, ultrasound, cold, massage, or acupuncture) were forbidden during the trial. The patient recorded exact consumption in a self-report diary. Compliance was assessed by asking the patient at each visit if he/she had regularly taken the treatment and by an accurate count of patch packs and returned patches. Compliance was considered as acceptable at ≥ 85% (not more than one patch application missed) during the first 7–8 days and ≥ 70% (not more than 2 patch applications missed) during the last 7–9 days of treatment during the study.

Outcome measures. The primary outcome measure was defined as change in global pain during daily activities, scored on a 100 mm VAS from baseline to Visit 2 (day 7 ± 1), as 7 days seemed the most accurate timepoint to assess efficacy in a disease in which spontaneous healing is usual. Secondary outcome measures at each visit included (1) change in pain with activity (100 mm VAS) from baseline to Visits 1 and 3 (day 3–4 and Day 14 ± 2, respectively); (2) change in spontaneous pain at rest (VAS); (3) pain on isometric contraction, on full passive motion, and on pressure, using a 4 point scale from 0: "no pain at all" to 3: "severe pain"; and (4) functional disability measured with a 4-point scale from 0: "no disability" to 3: "severe disability."

Finally, patients were asked to evaluate and note twice a day (8:00 AM and 8:00 PM) in their daily diary their pain intensity, pain relief, and paracetamol consumption determined by the number of tablets/day. Pain intensity was measured with a 4-point scale from 0: "no pain" to 3: "my pain is really bad and interferes with what I am doing," allowing calculation of the summed time-weighted pain intensity difference (SPID) by period (after 3, 7, and 14 days). Pain relief was measured with a 5-point scale from 0: "my pain has not improved at all" to 4: "all trace of my pain has gone," allowing calculation of the total pain relief (TOTPAR) for the same periods of time.

Safety was assessed by recording AE spontaneously reported by the patients on request at each visit. AE were analyzed with regard to number, seriousness, intensity, causal relationship with treatment, and outcome (corrective treatment, premature study withdrawal). AE were collected up to 21 days after the first patch application. Serious AE was defined according to international recommendations (any untoward occurrence that results in death or is life-threatening, or requires inpatient hospitalization, or results in persistent or significant disability). The intensity of non-serious AE was defined as follows: mild if the patient was aware of the sign or symptom, but found it easily tolerated; moderate if the patient had discomfort enough to cause interference with usual activities; and severe if the patient was incapacitated and unable to work or participate in many or all usual activities.

Global evaluations of the treatments according to 4-point scales were performed by the investigators (efficacy from 0: "unchanged or worse" to 3: "cured"; and tolerance from 0: "poor" to 3: "excellent") and the patients (overall assessments of the treatment received, from 0: "poor" to 3: "excellent") during the last visit.

Statistics. The sample size was calculated based on the primary outcome measure of change in global pain during activity, with an expected mean intergroup difference at Day 7 of 16 mm on the VAS in favor of the ketoprofen group, according to Dreiser, *et al*[12], a standard deviation of the mean distribution of 30 mm, an alpha level of 5%, and a beta level of 10%, giving a statistical power of 90%. With a predicted withdrawal rate of 17%, necessary sample size was estimated as 90 patients for each group.

Demographic and baseline data were compared within the 2 groups, including all the randomized patients, and using Student's t test for continuous variables and the chi-square test for noncontinuous variables.

Changes in variables at Visits 1, 2, and 3 were analyzed for both groups using Student's t test for quantitative variables, the chi-square test or Fisher exact test for nominal variables, and the Mann-Whitney test for ordinal variables. The principal analysis of efficacy was made on the intention-to-treat (ITT) population, which comprised all randomized patients who had received at least one patch and who were evaluated at least once during the trial, using the last observation carried forward method as the endpoint in case of missing data[13]. A secondary analysis was performed on the per-protocol population, which comprised patients who fulfilled the protocol requirements with no major deviation at inclusion or during followup, as determined by the Data Monitoring Committee at the blind review. Major deviations were defined as (1) patient wrongly included, (2) patient noncompliant, (3) time between last patch removed and last efficacy evaluation > 24 hours, (4) intake of paracetamol during the 12 hours preceding a visit, (5) missing data on the primary efficacy criterion, or (6) irregularities of dates of visits.

Safety analysis was performed on the safety population, consisting of all randomized patients who applied at least one patch, which corresponded to the ITT population.

Statistical analysis was performed using SAS version 8.2 software (SAS Institute, Cary, NC, USA). All statistical tests were 2-tailed at a 5% level of significance.

RESULTS

Study population. One hundred seventy-three patients were screened. The available intent-to-treat population comprised 172 patients. A total of 87 patients were randomized to the ketoprofen group and 85 to the placebo group. During the 14 days of followup, 26 patients (15%) withdrew: 9 and 6 for adverse events, 2 and 4 for lack of efficacy, and 4 and one for complete cure in the ketoprofen and control groups, respectively. After excluding the 22 major deviations (13 in the ketoprofen group, 9 in the placebo group), 74 and 76 patients remained in the ketoprofen and placebo groups, respectively, for the per-protocol population (Figure 1). Demographic characteristics, tendinitis history, and clinical status at baseline were similar in the 2 populations (Table 1). Compliance was good: over 97% of the patients were compliant at the end of the first week and over 87% at the end of the second week.

Efficacy. The primary criterion was decrease in pain from baseline at Visit 2 (Day 7 ± 1) for pain in daily activities during the previous 24 hours, calculated in the ITT population. These changes were –38.4 ± 25.6 mm (55.6%) and –25.8 ± 24.5 mm (36.8%) by VAS in the ketoprofen and placebo groups, respectively (p = 0.0013), giving an inter-group difference of 12.6 mm in favor of the ketoprofen patch.

The differences between the ketoprofen and placebo group in pain in daily activities were also significant at Visit 1 (Days 3–4) and Visit 3 (Days 14 ± 2) in favor of the ketoprofen patch (Figure 2, Table 2).

Globally, all efficacy measures improved during the study, for both treatment groups. Inter-group comparisons showed a statistically significant difference on most efficacy measures at at least one visit (Table 2). For measures where such a difference was not obtained for all visits, the improvement was, however, more marked in the ketoprofen than in placebo patients. The results for the secondary efficacy variables were therefore globally consistent with those concerning the main criterion.

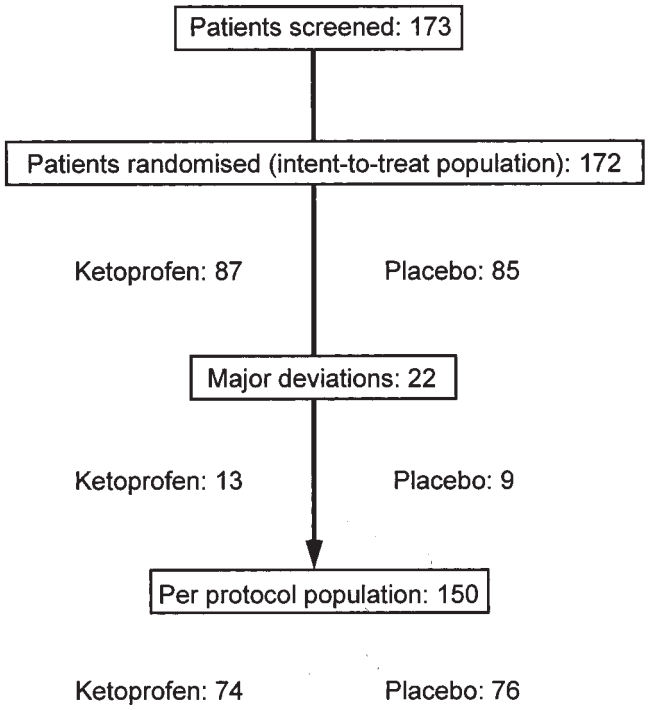


Figure 1. The study procedure.

Analysis of the per-protocol population supported the results obtained in ITT patients. In this population, SPID and paracetamol consumption (a mean total dose of 5.4 g and 8.6 g in the ketoprofen and placebo groups, respectively; p = 0.0488) decreased significantly in the ketoprofen group compared with the placebo group.

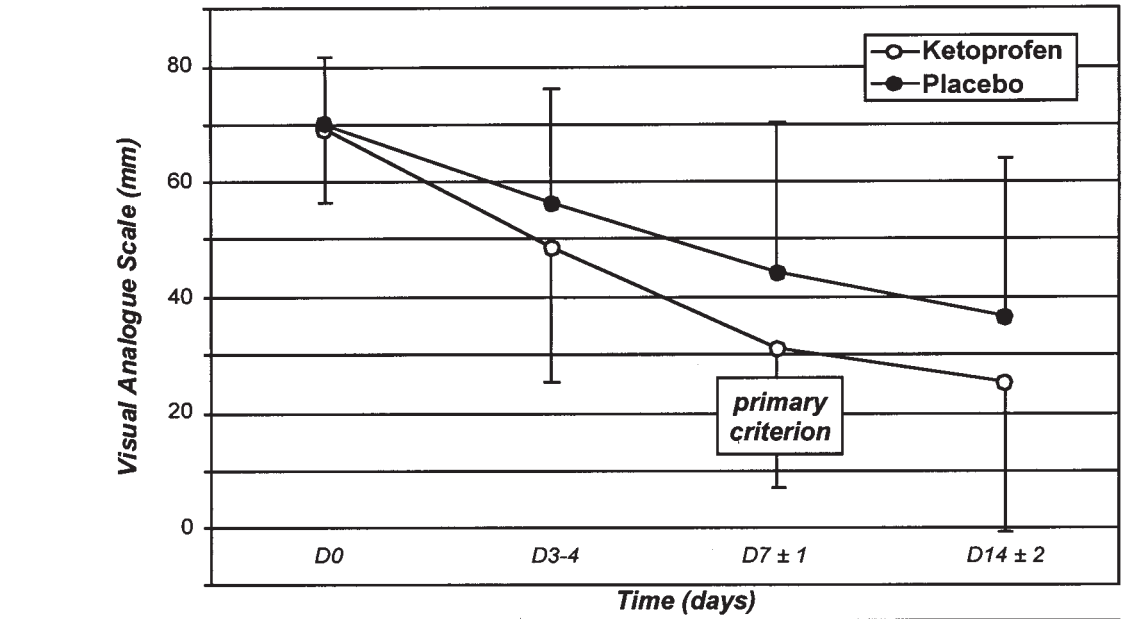
Tolerance. The ITT and the safety populations were the same and comprised 172 patients, all having applied at least one patch (ketoprofen or placebo). One hundred thirty-seven AE were observed in 74 patients (43.0% of the total). The number of AE in the 2 treatment groups was similar: 69 AE occurred in 46% of ketoprofen patients and 68 AE in 40% of placebo patients. No serious AE occurred (Table 3).

Local cutaneous AE were the most frequent (66.4% of all AE, involving 33.3% of ketoprofen patients and 31.8% of placebo patients), and involved conditions such as erythema/redness, irritation, pruritus/itching, and burning. There was no statistical difference between treatment groups for the number of reported local AE or the number of patients involved. The occurrence of local AE was studied in both groups (Kaplan-Meier technique). No statistically significant difference between the 2 groups was found (log-rank test, p = 0.8201). Further, these local AE were studied according to the date of their first occurrence; no difference was noted between the 2 groups. All AE had resolved spon-

Table 1. Demographics and disease characteristics at baseline.

Measures*	Ketoprofen, n = 87	Placebo, n = 85	p
Demographics			
Age, yrs	48.5 ± 12.5	45.5 ± 13.2	0.1315
Sex female, %	55.2	61.2	0.4249
Body mass index, kg/m^2	24.9 ± 4.0	25.7 ± 4.9	0.2764
Disease characteristics			
Location of tendinitis			
Upper limb, n (%)	65 (75)	59 (69)	
Rotator cuff of shoulder	31	28	
Lateral and medical epicondylitis	30	22	
De Quervain syndrome	4	9	
Lower limb, n (%)	22 (25)	26 (31)	
Hip (gluteus medius and adductor tendons)	4	5	
Patellar and popliteal tendons	15	17	
Achilles tendon at the heel	3	4	
Duration of symptoms, days	7.1 ± 3.5	6.9 ± 3.4	
Pain on daily activity, VAS, mm	69.1 ± 12.9	70.1 ± 11.5	0.5876
Spontaneous pain at rest, VAS, mm	58.3 ± 21.7	56.2 ± 22.4	0.5288
Pain on isometric contraction (0–3 scale)	2.2 ± 0.8	2.0 ± 0.8	0.2489
Pain on full passive motion (0–3 scale)	1.9 ± 0.8	1.8 ± 0.9	0.5506
Pain on pressure (0–3 scale)	2.6 ± 0.6	2.4 ± 0.6	0.1319
Functional disability (0–3 scale)	2.2 ± 0.7	2.2 ± 0.8	0.8247

* Expressed as mean ± SD; otherwise, as indicated.



Ketoprofen (n = 87)	69.1 ± 12.9	48.6 ± 23.2	30.8 ± 23.8	25.1 ± 25.9
Placebo (n = 85)	70.1 ± 11.5	56.1 ± 20.0	44.3 ± 25.6	36.4 ± 27.6
Differences (P)	0.5876	0.0491	0.0013	0.0146

Figure 2. Changes from baseline in pain on daily activity (100 mm VAS) in ketoprofen and placebo patients (ITT population). The primary efficacy criterion was the difference in improvement from baseline to one week (Day 7 ± 1) between the 2 groups. This difference was also statistically significant at Days 3–4 and Days 14 ± 2 (secondary criteria).

taneously at the followup telephone call 7 days after removal of the last patch, except for 2 cases (placebo group) that resolved at 2 and 8 weeks, respectively, after the end of the study. Other systems were also affected, such as gas-

Table 2. Secondary efficacy variables at the different timepoints and statistical significance of their differences for the 2 groups (ITT population).

Variable	Visit 1 (Day 3–4)	Visit 2 (Day 7 ± 1)	Visit 3 (Day 14 ± 2)
Spontaneous pain at rest*, VAS, mm			
Ketoprofen	34 ± 26	21 ± 21	18 ± 21
Placebo	41 ± 26	33 ± 26	27 ± 26
p	**0.0119**	**0.0005**	**0.0120**
Pain on isometric contraction** (0–3 scale)			
Ketoprofen	1.6 ± 0.9	1.1 ± 0.9	0.8 ± 0.9
Placebo	1.6 ± 0.8	1.3 ± 0.9	1.0 ± 0.9
p	0.8083	0.2539	0.0660
Pain on full passive motion** (0–3 scale)			
Ketoprofen	1.3 ± 0.8	0.9 ± 0.9	0.6 ± 0.9
Placebo	1.4 ± 0.9	1.1 ± 0.9	0.9 ± 0.8
p	0.6401	0.2231	**0.0178**
Pain on pressure** (0–3 scale)			
Ketoprofen	1.8 ± 0.8	1.2 ± 0.9	1.0 ± 0.9
Placebo	2.0 ± 0.8	1.5 ± 0.9	1.1 ± 0.9
p	0.1177	**0.0429**	0.1648
Functional disability** (0–3 scale)			
Ketoprofen	1.5 ± 0.8	1.1 ± 0.9	0.8 ± 0.8
Placebo	1.7 ± 0.8	1.4 ± 0.9	1.0 ± 0.9
p	0.2348	**0.0447**	0.1497
Total pain relief (TOTPAR)*			
Ketoprofen	85 ± 69	260 ± 166	656 ± 359
Placebo	67 ± 63	208 ± 149	551 ± 319
p	0.0753	**0.0324**	**0.0491**
Summed time-weighted pain intensity difference (SPID)*			
Ketoprofen	51 ± 49	161 ± 119	396 ± 260
Placebo	37 ± 41	126 ± 103	330 ± 227
p	0.0712	0.0651	0.1112
Paracetamol consumption*, total g			
Ketoprofen			5.90 ± 6.40
Placebo	—	—	8.95 ± 9.00
p			0.0663

Figures in bold type represent statistically significant differences. * p for 2-tailed Student t at 5% level of significance. ** p for 2-tailed Mann-Whitney test at 5% level of significance.

Table 3. All adverse events (AE) reported in the intent-to-treat population (n = 172).

Adverse Events	Ketoprofen, n = 87		Placebo, n = 85	
	No. of AE	No. of Patients Affected (Prevalence)	No. of AE	No. of Patients Affected (Prevalence)
Total number of AE (%)	69	40 (46)	68	34 (40)
Local skin reactions* (%)	47	29 (33.3)	44	27 (31.8)
Gastrointestinal** (%)	7	7 (8.0)	7	5 (5.9)
Musculoskeletal† (%)	5	5 (5.7)	3	2 (2.4)
Central nervous system †† (%)	3	3 (3.4)	6	5 (5.9)
Miscellaneous (%)	7	5 (5.7)	8	6 (7.1)

* Erythema/redness, irritation, pruritus/itching, burning skin, subcutaneous bleeding spot, eczema. ** Nausea, vomiting, diarrhea, dyspepsia (no perforation, ulcer, bleeding). † Arthralgia, myalgia, low back pain. †† Headache, paresthesia, vertigo, insomnia.

trointestinal, nervous, or musculoskeletal (Table 3). Most of these incidents were considered not related to the study drug.

The AE in the 2 treatment groups did not really differ in intensity: severe AE were rather rare in both groups, but seemed more frequent in patients using ketoprofen [15 (21.7%) and 6 (8.8%) of the total number of AE, in the ketoprofen and placebo groups, respectively]. These were expe-

rienced by 11 and 4 patients, respectively. Fourteen of the 15 AE (10 patients, 11.5%) in the ketoprofen group and 4 out of the 6 AE (3 patients, 3.5%) in the placebo group were judged as possibly or probably related to the study drug.

One case of myalgia in the ketoprofen group and one case of bronchitis and one of insomnia in the placebo group were judged as unlikely to be related to the study drug.

Among severe local events in the ketoprofen group, 6 episodes of irritation, 5 episodes of erythema, 2 episodes of burning skin, and one episode of pruritus were described. In the placebo group, 2 episodes of irritation, one of eczema, and one of fissure were described.

In 5 cases in the ketoprofen group the study drug was temporarily interrupted, while in 7 and 3 cases in the ketoprofen and placebo groups, respectively, the study drug was permanently interrupted. In 6 and 2 cases in the ketoprofen and placebo groups, respectively, it was necessary to apply a treatment.

As to causality assessment, there was no evidence of an inter-group difference, and most AE reported as possibly or probably related to study treatment were local events (Table 4). Concerning premature withdrawals, 26 patients (15%) discontinued the study, mainly because of AE (9 in the ketoprofen group vs 6 in the placebo group), lack of effectiveness (4 in the placebo group, 2 in the ketoprofen group), or cure (4 in the ketoprofen group, one in the controls). Mean duration of treatment at the time of withdrawal due to local AE was 9.22 ± 2.91 and 8.17 ± 2.56 days in the ketoprofen and placebo groups, respectively.

Global therapeutic response. Sixty-nine percent of ketoprofen patients were declared by the investigators either improved or cured, versus only 53.0% of placebo patients. These results were consistent with those obtained in the efficacy analysis. Tolerability results provided by the investigators were also satisfactory, with 81.2% of good/excellent tolerance scores for placebo patients and 78.2% for ketoprofen patients: high percentages and a small difference.

As for patients' global evaluation, the therapeutic response to ketoprofen was assessed as good or excellent by 57.5% of patients, versus 48.2% of patients for the placebo patch.

DISCUSSION

The active component of the ketoprofen TDS patch is a well established NSAID, ketoprofen. Ketoprofen gel is a relevant therapeutic approach for symptomatic nonarticular rheumatisms such as tendinitis, if the disease does not require orthopedic or surgical treatments and if the skin at the site of application is normal. The use of a patch was selected because it is more convenient to apply to the skin than ketoprofen gel, especially in terms of better control of dosage and ease of use. An *in vitro* based index to topical antiinflammatory activity predicts topical efficiency of ketoprofen[14]. Pharmacokinetic data for ketoprofen suggest the 100 mg ketoprofen TDS patch once daily was similar to 50 mg ketoprofen gel bid[12]. The results of this clinical trial confirm the usefulness of this dosage.

Efficacy. The primary goal of this study was to judge the efficacy assessment of once daily application of the 100 mg ketoprofen TDS patch in the treatment of tendinitis. The primary efficacy criterion was decrease in pain during daily activities in the first 7 days of treatment in the intent-to-treat population. Based on this criterion, the ketoprofen patch was found to be significantly more effective than the placebo patch. This change of about 13 mm is considered clinically relevant in studies concerning acute pain[15,16]. This is obviously a quite different setting and type of patient, but we found nothing in the literature concerning the minimal clinically relevant change to be obtained in soft tissue disorders. Further, almost all the secondary criteria tested (including TOTPAR or total pain relief, a criterion for assessing relief from acute pain) were also improved during the trial, sometimes achieving statistically significant difference after 3 days.

As nonarticular rheumatisms resolve spontaneously, the main criterion was assessed after 7 days of treatment, which seems the best endpoint. Data were collected before (3–4 days) and after (2 weeks) this endpoint. The differences between groups were also most often positive at these 2 endpoints. These results agree with other reports concerning the treatment of the same conditions with topical NSAID[17]. A recent review, which is a revision of the report by Moore, *et al*[17], concluded that indirect comparisons of individual topical NSAID showed that ketoprofen was significantly better than all other topical NSAID[18]. In the ITT population of this trial, at Day 7, 57.5% and 40.0% of the patients had improved pain (primary criterion) of at least 50% in the ketoprofen and placebo groups, respectively. Similarly, 63.2% and 49.4% improved at Day 14. The number needed to treat[19] was 5.7 (95% CI 5.6–5.9) at 7 days and 7.3 (95% CI 7.1–7.4) at 14 days. The effect size[20] calculated for pain at Day 7 was 0.55, which is considered as medium.

Table 4. Severity of adverse events (AE) and their relation to treatment, as assessed by investigators (intent-to-treat population).

Adverse Events	Ketoprofen, n = 69	Placebo, n = 68
Moderate to severe, n (% of total AE)	41 (59)	34 (50)
Possibility or probably related*, n (% of total AE)	49 (71)	45 (66)

* All local events were reported as possibly or probably related to the treatment.

These results were confirmed by the fact that the number of patients withdrawn for lack of efficacy was twice as high in the placebo group (4 placebo vs 2 ketoprofen patients). The balance was again in favour of the ketoprofen group in patients who withdrew because they recovered (one placebo vs 4 ketoprofen patients). Rescue paracetamol consumption was also lower and of shorter duration in the ketoprofen group.

Tolerance. Topical NSAID are prescribed in soft tissue disorders to reduce systemic exposure to the drug[5] and subsequently to decrease the risk of gastrointestinal adverse events, which are frequent and sometimes severe with oral NSAID. We observed only 7 gastrointestinal adverse events in the 2 groups, none of them severe (no perforation, ulcer, or bleeding). Without considerable postmarketing surveillance data, it is difficult to definitely associate topical NSAID administration and systemic AE, since many events may occur independently and patients may have been taking oral NSAID at the time of their illness. A case-controlled study demonstrated that when adjustments were made for the confounding effects of concomitant oral NSAID use, topical NSAID administration was not significantly associated with upper gastrointestinal bleeding or perforation[21].

Most AE during the study were related to local tolerance, and all were assessed as being drug related in both groups. The frequency and severity of AE (local or otherwise) were quite similar in both groups, suggesting relation to the patch itself, rather than the active ingredient, and the safety profile revealed no unexpected events. There were slightly more ketoprofen patients than placebo subjects withdrawn because of local AE, but no serious AE occurred during this trial. Skin reactions with topical ketoprofen have been reported[22], especially photosensitization, possibly related to benzophenone chromophore[23-25]. A recent review of trials studying other topical NSAID[7] stated that adverse drug reactions leading to dropout occurred in 12% of the patients of the reviewed studies (range 0 to 85%) and roughly 75% of the events were cutaneous, mainly rash and/or pruritus at the application site. The mean percentage of patients reporting AE after topical placebo was 14.4% (range 0 to 52%). Again, these events were primarily rash and pruritus, suggesting that the vehicle itself may be responsible for a significant portion of the adverse cutaneous reactions. Another possible factor contributing to occurrence of local events is that the NSAID patches, as well as the ketoprofen patch, must always be applied on the same skin area, which is therefore occluded for some days. The Spanish System of Pharmacovigilance[26] reviewed 194 adverse reaction reports attributed to topical NSAID. Of these, 95% were dermatological and the remaining 5% were systemic reactions. Again, the System of Pharmacovigilance of Midi-Pyrénées (France) collected all reported cases of adverse drug reactions in topically applied drugs over a 5 year period (1993–97). One hundred twenty-eight cases were reported, of which only 20 (16%) were related to topical NSAID, and all were local reactions[27].

Overall therapeutic response. Assessment of overall therapeutic response by investigators and patients was in good agreement with the efficacy and tolerability profile reported above.

From our study, the following facts emerge: (1) most symptoms were adequately controlled after 7 days of treatment using ketoprofen patches; (2) placebo patients recovered fairly satisfactorily after a longer period (one to 2 weeks); (3) the mean duration before treatment interruption due to AE was 9.2 days in the ketoprofen group; (4) the ketoprofen patch was generally well tolerated, with AE that were mainly mild or moderate, mostly local, and no serious events; (5) the efficacy of the ketoprofen patch as assessed by investigators and patients was better than that of the placebo patch. This trial suggests that a 3–14 day treatment course with the once daily 100 mg ketoprofen TDS patch is useful in nonarticular rheumatisms, the duration depending on the results obtained, although 7 days seems optimal.

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