

Topical diclofenac patch in patients with knee osteoarthritis: A randomized, double-blind, controlled clinical trial

P. Brühlmann, B.A. Michel

Department of Rheumatology and Physical Medicine, University Hospital Zurich Switzerland

Abstract

Objective

To assess the efficacy and safety of a diclofenac hydroxyethylpyrrolidine (DHEP) patch in the treatment of symptomatic osteoarthritis (OA) of the knee joint.

Methods

A double-blind, randomised, placebo-controlled trial was carried out on 103 outpatients for 2 weeks. The main efficacy parameters were spontaneous pain and Lequesne's Index. Secondary endpoints were walking time over a standard distance, global assessment of efficacy and tolerability, and paracetamol consumption.

Results

The active treatment group showed a significant improvement in pain, Lequesne's Index, and the physician's and patient's global assessment of efficacy. For these parameters the difference between groups was statistically significant in favour of the DHEP patch. Adverse reactions were seen in a small number of probands and were similar in both groups.

Conclusions

The results of this trial suggest that the DHEP patch appears to be an effective and safe treatment for patients suffering from symptomatic knee OA.

Key words

Knee osteoarthritis, diclofenac-hydroxyethylpyrrolidine, topical patch, Lequesne index.

P. Brühlmann, MD; B.A. Michel, MD,
Professor of Rheumatology.

Please address reprint requests and
correspondence to: P. Brühlmann, MD,
Department of Rheumatology and
Physical Medicine, University Hospital
Zürich, Gloriastrasse 25, CH-8091 Zürich,
Switzerland.

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Introduction

Osteoarthritis (OA) is the most common joint disorder in adults, affecting up to 50% of the population over the age of 65 (1). Pain is undoubtedly the most important symptom of OA (2). Whereas nearly all symptomatic OA patients report use-related pain, only some have rest or even night pain. Several possible causes of pain have been discussed, including mechanical factors, bone changes, synovitis and irritation syndromes stemming from periarthicular tissue.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of OA. However, NSAIDs are known to cause severe gastrointestinal side effects, especially in the elderly (3). To reduce these side effects many strategies have been proposed, including the use of analgesics (4), cyclooxygenase 2 inhibitors (COX-2) (5), capsaicin (6) and topical NSAID formulations (7, 8). In the revised ACR 2000 guidelines for the medical management of OA, the use of topical analgesics was recommended as either adjunctive treatment or monotherapy in patients with mild-to-moderate pain (9).

Topical NSAIDs have been investigated for the treatment of a wide range of clinical conditions, sport injuries (sprains, strains) (10, 11) and periarthicular disorders (tendinitis, bursitis) (12). Topical instead of systemic application of NSAIDs usually does not show any systemic side effects. This is most probably due to the much lower plasma concentrations resulting from topical versus oral administration (13). The penetration and adsorption of drugs through the skin is highly dependent on the chemical structure, dissolution properties and galenic formulation of the medication (14). Typical members of the NSAID class of drugs (e.g. naproxen, ibuprofen, diclofenac, indometacin etc.) display many common physicochemical properties such as weak acidity, low solubility in the non-ionised form and a high partition coefficient.

A new diclofenac salt [diclofenac-N-(2-hydroxyethyl)-pyrrolidine, known as diclofenac epolamine or DHEP] is much more soluble in water and non-

polar solvents than the other diclofenac salts. Its solubility is so high that the critical micellar concentration (CMC) (at 35 mM) for the diclofenac anion is exceeded. At concentrations above CMC, DHEP solutions can solubilise lecithins (15, 16). Thus, DHEP promotes its own absorption by interacting with components of the cell membranes. As a result topical pharmaceutical formulations appear to be particularly appropriate to exploit the unique properties of DHEP.

The Flector-EP Tissugel® patch containing 1.3% DHEP (corresponding to 1% of diclofenac sodium salt, DHEP-patch) is a special topical cutaneous formulation (medicated adhesive gauze), which has the advantage of being a semi-occlusive medication that allows continuous release of a standard dosage of diclofenac over 10-12 hours. Application of two patches per day allows the patient to obtain measurable levels of diclofenac in the underlying affected joint (17). In addition, the high water- and lipid-solubility of the DHEP salt allows the rapid transcutaneous absorption of the drug and therefore a rapid effect.

The aim of this trial was to assess the efficacy and safety of the DHEP-patch in patients affected by symptomatic OA of the knee.

Materials and methods

The test drug formulations were supplied by IBSA (Institut Biochimique SA, Lugano, Switzerland). The Flector-EP Tissugel, hereafter called the DHEP-patch, is a medicated adhesive patch (10 x 14 cm) containing 180 mg of diclofenac-hydroxyethylpyrrolidine (diclofenac epolamine). The placebo-patch was identical in appearance, colour and odour to the DHEP-patch, but did not contain the active principle, diclofenac-hydroxyethylpyrrolidine. Paracetamol 500 mg tablets (Panadol®, SmithKline Beecham Consumer Healthcare AG, 3174 Thörishaus) were purchased from the local market and handed out to the patients as rescue medication if analgesics were needed. The trial was designed as a double-blind, randomised, placebo-controlled, parallel group study and received ethi-

cal approval prior to trial initiation. The study was conducted according to Good Clinical Practice (GCP) as set out in EEC Directive no. 111/3976/88-EN and the Declaration of Helsinki. All patients received complete information concerning the trial and gave their written informed consent prior to study entry. Inclusion criteria for enrollment were outpatients of both sexes, aged between 18 and 85 years, and affected by symptomatic OA of the knee. This had to be confirmed by X-ray according to the Kellgren and Lawrence criteria grade > 0 (18) and the spontaneous pain had to be rated more than 4 on a numerical scale ranging from 0 = no pain to 10 = severe pain. Exclusion criteria were a history of severe hepatic or hematological diseases, significant clinical or laboratory evidence of liver, kidney, or hematopoietic disorders, psychopathologies, a history of alcohol or drug abuse within the last year, and osteo-articular pathologies other than osteoarthritis. Furthermore, patients with significant skin disorders or skin trauma at the application site, a history of diclofenac allergy, hypersensitivity, or severe adverse reactions to aspirin or related compounds were excluded as well. Patients who had taken other NSAIDs during the three days before admission to the study, or one week if the drug was a steroid, or had participated in any other clinical trial during the previous two months were also excluded. Pregnant and lactating women were not considered as eligible for the study.

Enrolled patients were randomly assigned to one of the two treatment groups according to a computer-generated randomisation system: one group was treated with the DHEP-patch and the other with a placebo patch. Patients, investigators, monitors and statisticians were unaware of which study drug the patients were given (DHEP or placebo). The patch was to be applied topically twice a day, mornings at 8 a.m. and evenings at 8 p.m. for 14 days. In the case of bilateral symptomatic OA, the more symptomatic knee was chosen and exclusively treated. Follow-up visits took place on days 4, 7 and 14. From day 4, patients were allowed to

take daily up to 4 tablets Panadol® (containing 500 mg paracetamol) as rescue medication, and the consumption was recorded in the patient's study diary. Apart from the study drugs, no other analgesic or NSAID by whatever administration route was allowed during the entire study period.

The efficacy of the test preparation was assessed on the basis of the following parameters. Primary efficacy parameters were spontaneous pain as rated on a semi-quantitative numeric rating scale (NRS) from 0 (no pain) to 10 (severe pain) and Lequesne's algo-functional index (19). As a secondary efficacy parameter, walking time was assessed at baseline (day 0) and at all 3 follow-up visits in seconds over a distance of 20 m (standing start). The following parameters were recorded at the end of the study period on day 14: overall efficacy expressed by patients and the investigator (5-point scale: excellent, good, moderate, poor, or none), number of paracetamol tablets taken, and the investigators' and patients' judgement of global and local tolerability on a 5-point scale: excellent, good, moderate, bad or unbearable.

The safety of the test products was assessed clinically in relation to any adverse reactions reported by the patients or observed by the investigator.

Statistical analysis

The sample size was calculated for the primary efficacy parameter Lequesne's algo-functional index assuming $\alpha = 0.05$ for a one-tailed test and a power of 80% ($\beta = 0.20$). All collected data was first analysed by determination of descriptive statistics and frequencies for each variable at each time. Inferential analysis was done using the tests considered most appropriate: Student's t-test was used for age, weight, and height, the chi-squared test for sex, side effects, and drop-outs. The Mann-Whitney U-test was applied for the duration of pain in months and paracetamol consumption, and analysis of variance (ANOVA) and Bonferroni's multiple comparison test for pain. Finally, a linear trend test was performed for assessments of efficacy and

safety. The analysis of efficacy included all 103 patients as the intention-to-treat group.

Results

Patients.

103 patients were enrolled in the study and randomly assigned to one of the treatment groups (51 DHEP and 52 placebo). The trial was completed by 48 patients treated with DHEP and 45 treated with placebo, respectively. Four patients (1 DHEP, 3 placebo) withdrew from the study at day 7 due to lack of efficacy, and 3 patients (1 DHEP, 2 placebo) quit the study prematurely because of side effects (pruritus, rash). Two patients in the placebo group were lost to follow up and one was terminated due to protocol violation (he applied the study medication to both knees).

Demographic data, clinical factors, and primary efficacy parameters at baseline (day 0) of the enrolled patients are shown in Table I. There was no significant difference between the groups at baseline regarding all data including demographic data, clinical factors, and primary and secondary endpoint parameters.

Lequesne's Index. There were two primary outcome measures defined by the protocol; however, sample size calculation was only based on the validated Lequesne's algo-functional index. During the course of the two-week treatment, the Lequesne's score decreased uniformly, reaching at day 14 a maximal reduction of 32% in patients treated with DHEP and 15% in patients treated with placebo (Table II, Fig. 1). The changes compared to baseline (day 0) were highly significant ($P < 0.01$) for all visits (day 4, 7, and 14) for DHEP. For the placebo group, the difference from baseline was found only for day 14 to be statistically significant ($P < 0.01$). There was a significant difference between the two groups on days 7 ($P < 0.05$) and 14 ($P < 0.01$).

Spontaneous pain. The second main outcome measure was the evaluation of spontaneous pain measured on a numerical rating scale from 0 (no pain) to 10 (severe pain). Patients treated with DHEP reported gradual pain relief during the first week of treatment, and

Table I. Demographic data, clinical factors and primary endpoint parameters at baseline given by group.

Variable		DHEP (n=51)	Placebo (n=52)
Demographic data			
Sex	Male	24 (47%)	19 (36%)
	Female	27 (53%)	33 (64%)
Age (years)		64.0 ± 10.7	64.8 ± 10.6
Weight (kg)		77.0 ± 12.9	78.7 ± 10.7
Height (cm)		167 ± 8	165 ± 9
Clinical factors			
Target knee	Left	28	19
	Right	23	33
Symptomatic involvement	Bilateral	25	20
	Unilateral left	11	11
	Unilateral right	15	21
Duration of pain (months)		32.8 ± 40.5	29.5 ± 33.6
Baseline values of primary endpoint parameters			
Spontaneous pain		5.7 ± 1.5	5.6 ± 1.5
Lequesne Index		10.2 ± 3.3	10.4 ± 3.5

Differences for all parameters measured were non-significant between groups.

Table II. Lequesne's algo-functional index, spontaneous pain (rated from 0-10) and walking time in seconds over a standard distance of 20 m [expressed as mean value (± SD)].

	Day 0	Day 4	Day 7	Day 14
Lequesne's Index				
DHEP (n=51)	10.2 (3.3)	8.7 (3.3)**	8.0 (3.3)** #	6.9 (3.2)** ##
Placebo (n=52)	10.4 (3.5)	9.8 (3.4)	9.5 (3.6)	9.0 (3.9)**
Spontaneous pain				
DHEP (n=51)	5.7 (1.5)	4.0 (1.7)** ##	2.6 (1.7)** ##	2.1 (1.8)** ##
Placebo (n=52)	5.6 (1.5)	5.0 (1.6)	4.5 (1.7)**	3.9 (2.1)**
Walking time (sec)				
DHEP (n=51)	16.3 (6.7)	14.6 (5.4)**	13.7 (5.3)**	13.3 (4.3)**
Placebo (n=52)	16.3 (4.2)	15.5 (3.6)	15.0 (3.7)*	14.5 (3.4)**

*p < 0.05 and **p < 0.01 within group compared to baseline (day 0); #p < 0.05 and ##p < 0.01 comparison between groups.

the results became stable during the second week ($P < 0.01$ between baseline and all follow-up visits). The placebo group showed slower but uniform pain relief throughout the observation period, reaching significance ($P < 0.01$ from baseline) only at days 7 and 14. When comparing the treatment groups, matching values were found at baseline, but there was a highly significant difference between groups ($P < 0.01$) at all treatment visits (Table II, Fig. 2).

Walking time. In the group receiving the active anti-inflammatory drug, walking time was significantly reduced

at all follow-up visits compared to baseline. Changes were significant ($P < 0.01$) within groups compared to day 0 for all visits for the test drug, and on days 7 ($P < 0.05$) and 14 ($P < 0.01$) for placebo. There was no significant difference between groups (Table II).

Paracetamol consumption. Eleven patients (22%) in the DHEP group took paracetamol. The mean consumption was 2.3 tablets (± 5.2 SD) for the whole permitted period (from day 4 to day 14). On the other hand, 19 patients (37%) in the placebo group took the rescue medication with a mean total

consumption from day 4 to day 14 of 3.4 tablets (± 8.6 SD). These differences were not statistically significant (data not shown).

Overall efficacy. The efficacy of the study drugs was assessed by both the physician and the patients. The patients' judgement of efficacy was found to be in favour of the DHEP-patch: 24.5% patients considered it "excellent", whereas the same assessment was given only by 8.9% of patients treated with placebo. Of the DHEP group 10.2% patients judged the treatment to be "with no efficacy" compared to 17.8% patients in the placebo group. The linear trend test showed a significant difference ($P < 0.05$). The assessment of efficacy by the physician as well was in favour of DHEP: the results of DHEP were found to be excellent in 10.2% cases compared to placebo, which was considered excellent in 8.9% cases. DHEP was judged to be of no efficacy in 8.2% cases, whereas placebo was found to have no efficacy in 20% cases. The linear trend test showed a significant difference between treatments ($P < 0.01$).

Tolerability. Tolerance of treatment was assessed as "good" or "excellent" by 91.8% of the patients using DHEP, and by 93.4% of patients using the placebo. The physicians expressed the same opinion in 95.9% and 93.5% of cases, respectively. Seven patients complained of adverse reactions, four in the DHEP group (2 rash, 1 pruritus, 1 nausea) and 3 in the placebo group (1 rash, 1 feeling of local heat, 1 weakness/dizziness). None of the adverse events described was judged as severe, all symptoms resolved spontaneously, and only two events in the placebo group led to a breaking off of treatment.

Discussion

The use of topical anti-inflammatory and analgesic drugs has been proposed to be appropriate as either adjunctive treatment or monotherapy in patients with OA of the knee (6-9). Previous studies reported pain relief and a positive effect on physical function (8, 20). In comparison to the systemic use of NSAIDs, adverse events of the gastrointestinal tract were significantly lower

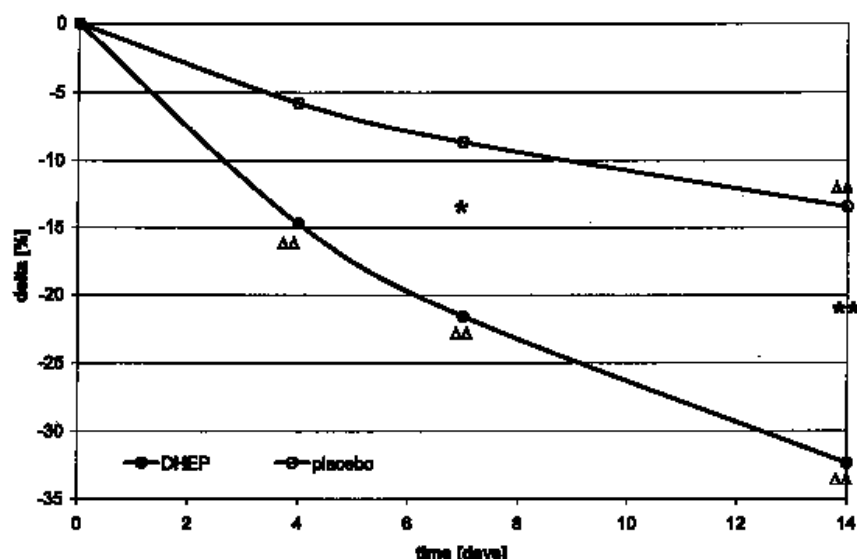


Fig. 1. Reduction in Lequesne's algo-functional index in percent [%] over the course of time. The baseline value was arbitrarily set at zero.

p < 0.01 compared to baseline (day 0) within group; *p < 0.05 and ** p < 0.01 comparison between groups

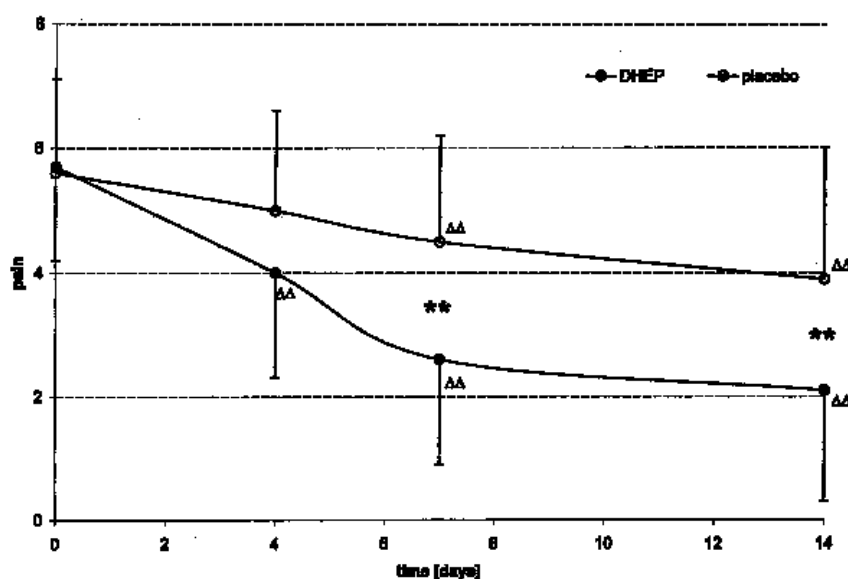


Fig. 2. Reduction in the mean value (± SD) of patients' spontaneous pain during the treatment period is depicted.

p < 0.01 compared to baseline (day 0) within group; **p < 0.01 comparison between groups.

(21).

The results of this trial confirm the efficacy of a patch formulation of percutaneously administered diclofenac (DHEP patch) in the treatment of knee OA with respect to pain and physical function as assessed by Lequesne's Index. Although both groups improved, a significant difference was found between the DHEP and placebo groups in the extent of change in the Le-

quesne's algo-functional index. This disease-specific questionnaire is able to detect improvement of symptoms and physical function as a result of a therapeutic modality. Corresponding to previous trials using the same (20) or a comparable questionnaire, the WOMAC (Western Ontario and Mc Master Universities) (8), the efficacy of the tested approach was confirmed. Spontaneous pain measures showed a signif-

icant difference between the treatment groups, as well. Both parameters, spontaneous pain and Lequesne's algo-functional index, showed in the DHEP group an initially (day 4) greater improvement than placebo. This picture reflects the local drug's activity attained by the transdermal delivery of the medication. Based on pharmacokinetic studies, the local concentration of the drug seems to be much more responsible for the therapeutic effect than the systemic one (22). Despite pain relief there was no significant change in walking time, indicating that OA patients continue to be disabled by impaired physical functioning.

The patient's and investigator's global assessment of efficacy showed similar results in comparison to previous studies with topical anti-inflammatory drugs (20,21). The low frequency and mild severity of the side effects caused by the patch are also in accordance with previous reports (8,20). Usually there is no difference between placebo and different topical diclofenac delivery modalities regarding the reported number and type of adverse reactions. Local skin reactions were dominant and systemic effects were very rare (8, 20).

In conclusion this double blind, randomised, placebo-controlled study suggests that the DHEP patch may be an effective and safe treatment modality for symptomatic OA of the knee. Further studies should be conducted to compare the DHEP patch with other topical drugs and delivery systems and investigate the results and side effects of its long-term use.

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