Abstract. – Objective: The mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs), to which ketoprofen belongs, is based on their cyclo-oxigenase (COX) inhibiting action, concerning both subtype COX-1 constitutive isoform and COX-2 inducible isoform. Ketoprofen administration may be carried out by oral and parenteral routes as well as by topical application, which includes transdermic patch use. Following a synthetic description of the results obtained by several investigators on ketoprofen use, the Authors present a new formulation of the ketoprofen patch obtained by the so called DermaLight Technology.

Materials and Methods: According to such a technique, the active principle is dissolved in oil components and dispersed inside an anhydrous polymeric matrix made up of styrene-isoprene-styrene (SIS), which is an elastic and flexible material that provides a gentle adhesion to the skin, maintains an elevated ketoprofen concentration and induces a strong thrust that favours the crossing of the skin by the drug; in addition, the patch is fit to be applied to the various areas of the body, including the joints.

Results: Patch adhesiveness reduces skin irritation due to multiple applications and to long-term use, as the DermaLight Technology minimises keratinocytes exfoliation. In pharmacokinetic studies carried out on pigs ketoprofen has been demonstrated to reach deep tissues, where the drug was detected in much higher concentrations, with respect to plasma levels, 12 hours following its application. Experimental studies carried out on rats have shown that ketoprofen patch significantly reduces the edema induced by chronic inflammation.

Conclusions: The Authors conclude by stating that ketoprofen patch is both a good alternative and a safe modality of administration, with special reference to patients who are prone to gastrointestinal disorders.

Key Words: DermaLight Technology, Polymeric matrix, Keratinocytes.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are an important category of drugs widely used in treating musculo-skeletal disorders, such as rheumatoid arthritis and osteoarthritis, as well as some of the symptoms due to traumatic lesions. However, the use of systemic NSAIDs can result in an increased risk of serious side effects, especially with regard to gastrointestinal, renal and cardiovascular systems. Therapy involving topical application represents a valid and safe option. Even though topical treatments differ as regards to kinetics of absorption as well as to pharmacological effects and pharmaceutical preparations (foam, gel, patch, etc.), many studies report that they are effective in treating acute and chronic musculo-skeletal pathologies and display a security profile that is much better than that of orally administered NSAIDs.

Topical preparations combine the selective and rapid action at the site of application with a good degree of efficacy and limited or absent side effects. This is especially true in instances of treatment of acute musculo-skeletal disorders, and it appears to be in marked contrast with other forms of administration.
When choosing to administer an anti-inflammatory drug topically, the following considerations should be taken into account: the molecular weight of NSAIDs, the degree of lipophilia and the absorption-rate of active ingredients. In the case of topical patch, account is also to be taken of the “technology of the transdermic system” in which the drug is placed and whence it spreads into the tissues. In fact, a low molecular weight is associated with an elevated transdermic absorption. Amongst those NSAIDs commonly used, ketoprofen has a low molecular weight (260 dalton) as compared to diclofenac (325 dalton), piroxicam (330 dalton) and indomethacin (350 dalton). As a result, ketoprofen is especially suited for preparations involving its transdermic molecular passage. Ketoprofen, moreover, is one of the NSAIDs with the highest cutaneous permeability. It has a nearly optimal logarithm for the distribution coefficient (n-octanol/water) equal to 2.94. As a result, ketoprofen spreads through the skin far more quickly and intensely than other NSAIDs do since its percutaneous absorption takes place within 4 hours.

NSAIDs’ anti-inflammatory and analgesic action is due to the inhibition of cyclooxgenase (COX), an enzyme involved in production of prostaglandins. There are two subtypes of COX; subtype COX-1 occurs constantly in the body, while subtype COX-2 is induced by inflammation. Ketoprofen has shown a potent COX-1 inhibiting activity and therefore it increases the risk of gastrointestinal (GI) side effects if repeatedly taken by mouth.

With respect to skin permeation, ketoprofen has shown to be well absorbed and was classified as one of the best NSAID drugs to be used percutaneously, while diclofenac and indomethacin showed a much lower skin absorption. Thus, transdermic administration can represent a significant alternative for patients who have problems in taking oral NSAID medications with potent anti-inflammatory activity, especially for the purpose of counteracting the development of GI side effects.

**Historical Overview**

There are 20 mg of ketoprofen contained within a styrene-isoprene-styrene copolymer-based transdermal matrix system of the “medicated” patch distributed in Italy. Ketoprofen release from the patch takes place over a 24-hour period; as a consequence one daily application only is necessary. Many studies conducted in the early 1990s investigated the effects of a 20 mg ketoprofen patch on musculo-skeletal disorders such as bursitis, tendinitis of the supraspinous ligament, epicondylitis, and lumbago; these studies showed the usefulness of using this topical preparation in treating musculo-skeletal pain.

A study conducted on 184 patients with lumbago compared the effects of 2% ketoprofen patch versus 25 mg ketoprofen capsules for oral administration. During a 2-week period one group of patients (group K) received one daily application of two patches measuring 7 cm x 10 cm and containing 2% ketoprofen (for a total of 40 mg of the drug) and a placebo capsule. Another group of patients (the control group) received the application of a placebo patch and the administration of two 25 mg ketoprofen capsules three times a day after meals (for a total of 150 mg daily). The main results of this study concern the efficacy and safety evaluations, which were carried out after 7 and 14 days. The respective analyses regarding efficacy display similar results for the study group (patch) and the control group (oral intake). The prevalence of side effects was 8.9% in the ketoprofen group and 20.7% in the control group. The overall safety of the drug was found to be far greater in the group treated with the ketoprofen patch (91.1%) than in the oral intake group (79.3%). These findings show that the patch preparation has an efficacy that is comparable with that of the oral preparation and shows a greater safety profile.

The benefit of topical administration of ketoprofen as opposed to oral intake was found to be particularly evident in treating knee pain in those patients in whom arthroscopy had been performed. A total of 100 patients were enrolled in the study and were divided into 3 groups. The first group consisted of 40 patients who underwent the single application of a 30 mg ketoprofen patch; the second group of 40 patients had the patch applied once a day for five consecutive days; the remainder of the patients received a single oral administration of 50 mg ketoprofen. The results obtained in this study showed that ketoprofen concentrations in the meniscal region were greater following topical administration as compared with the drug concentrations following oral intake. Similarly, greater concentrations of the drug were found in the articular cartilage, the synovial fluid and synovial tissue. Moreover, this study analysed ketoprofen plasma levels which were low with topical application, as opposed to plasma levels following oral administration.
Recently Kawai et al\textsuperscript{14} showed for the first time that the application of a 20 mg ketoprofen patch once a day for two weeks to a markedly painful wrist gives significant relief, as compared with placebo, to patients suffering from rheumatoid arthritis. These patients had suffered from persistent wrist pain for at least a month and had already brought under control the systemic illness by means of DMARD (Disease-modifying anti-rheumatic drugs) and/or oral therapy with corticosteroids for a period of more than 20 weeks.

**Topical Ketoprofen's Efficacy in Treating Sports Injuries**

Musculo-skeletal disorders deriving from sports activities can involve to a varying degree each of the components of the musculo-skeletal apparatus, i.e. muscles, bones, tendons and ligaments. In general the causes of the symptomatology are to be sought either in the accumulation of small-scale stress recurring over time\textsuperscript{15,16}, or in direct or indirect major accidents\textsuperscript{17}.

Two common characteristics are found in the various types of musculo-skeletal lesions. First of all, they involve in most instances superficial structures that are usually located beneath the cutaneous level and the subcutaneous tissue. Secondly, the inflammation itself represents an important pathogenetic moment, with respect to both the pathological process and the recovery.

Non-steroidal anti-inflammatory drugs are often used in sports medicine on account of their well-known analgesic and anti-oedematous effects. In view of the fact that a certain amount of inflammation is needed to facilitate the repair of lesions, it is frequently emphasised that the use of NSAID should be limited to particular situations, such as fractures, stress fractures, chronic tendinopathies or chronic muscular lesions\textsuperscript{18}. Consequently, in recent years many Authors have suggested clinical guidelines for a cautious use of NSAIDs in sports medicine\textsuperscript{19,20}, notwithstanding the increasing evidence regarding the efficacy of systemic treatment of sports disorders by means of such drugs. Valid and safe alternatives to systemic NSAID therapy include paracetamol\textsuperscript{21} and topical NSAID application\textsuperscript{22,23} when analgesia is the primary objective of treatment.

A recent review of clinical studies carried out on this matter has analysed the efficacy and safety of topical NSAID therapy in instances of acute pain in adults\textsuperscript{5}. The Authors reviewed 47 randomised control trials (RCTs) in which the topical application of NSAIDs in the form of gel, spray or cream was compared with the use of placebo. The subjects enrolled in the study were adults who suffered from acute pain as a result of sprains, tears, and traumas due to sports or overload activity. In the final analysis, a total of 3.45% participants were investigated. In the group treated by topical NSAID application, the number needed to treat (NNT) in order to achieve a clinical success – which is assessed as a 50% reduction in pain level – was 4.5 (3.9 to 5.3) for treatment periods ranging from 6 to 14 days. The efficacy was found to be similar for diclofenac, ibuprofen, ketoprofen and piroxicam, whereas indomethacin and benzylamine were found to be similar to placebo. With a total of seven studies and 683 patients, ketoprofen represents the most studied molecule, with an NNT of 3.9, which is only slightly less than that found in the entire NSAID treated group\textsuperscript{5}.

Furthermore, this review analysed the development of adverse reactions to treatment with topical NSAIDs, in order to evaluating NSAIDs safety profile. It is interesting to note the nearly complete lack of systemic side effects with topical NSAIDs, whereas the local side effect most often reported was a cutaneous irritation (redness and itching); such an effect, however, was transitory. The percentage of local side effects was 6.3% in patients treated with NSAIDs; such a figure is not significantly greater than that found in patients treated with a placebo (5.9%). Even as regards to safety, ketoprofen appears to be the molecule most studied, with a total of eight studies carried out on 852 participants. The relative risk (RR) for adverse local events has been calculated for ketoprofen to be equal to 1.2 (0.83 to 1.7)\textsuperscript{5}.

As opposed to ketoprofen administered orally, the ketoprofen patch guarantees similar regional tissue concentrations of the active principle even when the plasma concentration is 17 times less\textsuperscript{23,24}, thus reducing the relative risk of systemic complications\textsuperscript{25}.

A randomized control trial (RCT)\textsuperscript{26} has been conducted on 163 patients suffering from a benign (grade I or II), acute (occurring <2 days) and painful (spontaneous pain ≥50 on a visual analogical scale [VAS] 0-100 mm) sprain of the ankle. Patients were randomly divided into two groups. The study group, consisting of 81 subjects, underwent treatment with a ketoprofen patch once a day. The control group (82 subjects) was treated with a patch that did not contain any
active ingredient. After a week treatment, the reduction in pain was found to be significantly greater for the study group with respect to the placebo group (−50 ± 20 mm vs −38 ± 24 mm respectively, \( p=0.0007 \)). Painful movements, functional performance and ability to maintain the single-pedal position in the affected side were found to be significantly improved in the group treated with the ketoprofen patch as compared with the placebo group. The Authors concluded that treatment with a ketoprofen patch for a period of 3-14 days is an effective treatment for painful post-traumatic lesions involving soft tissues and that ideal treatment should last an average of 7 days26.

The ketoprofen patch has shown to be effective also in the treatment of recently developed tendinitis. Indeed, in a group of 172 patients randomly treated with a ketoprofen patch or a placebo patch, the diminution of pain within a week time was found to be significantly greater for the former group as compared with the latter group (56% versus 37%; \( p=0.0013 \)), whereas the rate of local side effects – all spontaneously subsided – was found to be the same for both groups22.

However, since the efficacy of treatment by topical application is influenced not only by the pharmacological characteristics of the active ingredient, but also by the technology of the transdermic system employed (release of the molecule over time and in space, adhesiveness of the patch)2, it is worth comparing not only the different molecules, but also the different topical preparations.

Esparrza et al27 compared the use of ketoprofen TDS patch and diclofenac gel in treating acute post-traumatic pain following minor lesions involving soft tissues as a result of sports activities. A total of 114 patients were treated with a ketoprofen patch once a day, whereas 109 patients were treated with 2-4 g of diclofenac gel three times a day. By means of a 0-100 mm visual analogical scale (VAS), all patients included in the study were evaluated for the presence of pain as they went about doing their daily activities as well as at rest. Both treatments were found to be effective in reducing pain during daily activities, although with a difference of −1.17 mm in favour of the ketoprofen patch (95% CI −5.86 to 3.52). Patients treated with ketoprofen patch showed also a rate of healing significantly more elevated at the seventh day of treatment as compared with patients treated with diclofenac gel (64% versus 46%; \( p=0.004 \)). It is interesting to note that even patients’ opinions regarding the comfort of treatment were significantly better for the ketoprofen patch as opposed to the diclofenac gel.

**Development of a New Ketoprofen Patch**

When developing a patch formulation many factors must be taken into consideration, such as the physicochemical properties and the potency of the active principle, the interaction between the active principle and the other ingredients, the selection of the release liner where the active drug is going to be applied and the adhesive materials needed for applying the patch onto the various body areas (i.e., knee, shoulder, elbow, etc.). In synthesis, the following objectives should be kept in mind:

1. Reduction in skin irritation subsequent to long-term use;
2. Improvement of the patch adherence to the various body areas; and
3. Enhancement of local NSAID absorption.

With such objectives in mind a new technology has been developed and has been denominated “DermaLight Technology”.

**DermaLight Technology**

The ketoprofen patch consists of a micro-domain structure, which is illustrated in Figure 1. The major adhesive polymer is realised by an anhydrous matrix made up of styrene-isoprene-styrene (SIS) block, which is an elastic and flexible material. The active principle is dissolved into oil components and dispersed inside the polymer network. Such a structure adheres gently to the skin, keeps a high drug concentration inside the micro-domain and induces a strong thrust aimed at delivering the drug through the skin into the underlying body structures. Moreover, the supporting flexible and stretchable material of the patch is designed to fit all the body joints.

Patch adhesiveness is an important feature as it prevents detachment during the prolonged application period. Skin irritation consequent to multiple applications and to long-term use is reduced. One of the factors inducing skin irritation is the exfoliation of the corneous layer when the patch is removed. DermaLight Technology minimises keratinocytes exfoliation (Figure 2).

Absorption studies carried out on guinea pigs8 showed that ketoprofen concentrations in fascia, muscles and plasma were higher following patch or cataplasm application as compared with oral administration; and patch application brought
about a higher tissue concentration as compared to cataplasma. Experimental studies carried out on Mexican hairless pigs demonstrated that the active principle contained inside a 2% ketoprofen patch was detected in the skin, the subcutaneous fat, fascia, superficial and deep muscles, 12 hours following its application on the laboratory animals back; furthermore, it was observed that tissue concentrations were much higher than plasma concentrations (Figure 3).

In order to evaluate the pharmacological efficacy of ketoprofen patch two experimental chronic inflammation models were used in rats, namely the adjuvant arthritis model and the collagen arthritis model. In both models the ketoprofen patch showed significant edema-suppressing effects (Figure 4).

The ulcerogenic effect induced by the ketoprofen patch as well as by ketoprofen oral administration was investigated in rats. An ulcerogenic effect was clearly found in the group treated with 10% ketoprofen patch and in the group undergoing oral administration of ketoprofen 5 mg/kg (Table I). The value of UD50 for the ketoprofen patch was found to be 49.9 mg/kg and 48.9 mg/kg for the stomach and the small intestine, respectively, whereas the value of UD50 for the orally administered ketoprofen was found to be 3.6 mg/kg and 3.7 mg/kg, respectively. These results indicate that in rats the ulcerogenic doses are about 13 times higher with ketoprofen patch as compared with ketoprofen oral administration, and consequently it may be assumed that ketoprofen patch may attenuate the risk of gastrointestinal disorders in clinical use.

**Conclusions**

Non-steroidal anti-inflammatory drugs (NSAIDs) can be administered through the oral,
Figure 3. Ketoprofen concentrations 12 hours following application of ketoprofen patch on the back of Mexican hairless pigs. Mean ± SD (n = 4). (From Horie M, Sekiya I, Nakamura T, et al).

Figure 4. Anti-inflammatory effect induced by ketoprofen patch in experimental arthritis models induced in rats by adjuvant (A) and collagen (B). Mean ± SD (group a: n=8, **p < 0.01 vs. control group; group b: n=10, ***p < 0.001 vs. control group). (Modified from Tanida N, Sakurada S).

Table I. Ulcerogenic effect on rats’ stomach induced by ketoprofen patch at various concentrations and by orally administered ketoprofen at different dosages.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (cm)</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Ulcer index</th>
<th>Ulcer rate (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.25 ± 0.16</td>
<td>0/8</td>
</tr>
<tr>
<td>KPT base</td>
<td>3 × 3</td>
<td>–</td>
<td>Topical</td>
<td>0.75 ± 0.16</td>
<td>0/8</td>
</tr>
<tr>
<td>1% KPT</td>
<td>3 × 3</td>
<td>–</td>
<td>Topical</td>
<td>0.50 ± 0.27</td>
<td>1/8</td>
</tr>
<tr>
<td>2% KPT</td>
<td>3 × 3</td>
<td>–</td>
<td>Topical</td>
<td>0.75 ± 0.25</td>
<td>1/8</td>
</tr>
<tr>
<td>3% KPT</td>
<td>3 × 3</td>
<td>–</td>
<td>Topical</td>
<td>1.13 ± 0.35</td>
<td>2/8</td>
</tr>
<tr>
<td>10% KPT</td>
<td>3 × 3</td>
<td>–</td>
<td>Topical</td>
<td>1.75 ±0.45</td>
<td>5/8</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>–</td>
<td>1</td>
<td>Oral</td>
<td>0.75 ± 0.25</td>
<td>1/8</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>2</td>
<td>Oral</td>
<td>1.25 ± 0.53</td>
<td>2/8</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>5</td>
<td>Oral</td>
<td>1.75 ± 0.37</td>
<td>5/8</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>10</td>
<td>Oral</td>
<td>2.25 ± 0.16</td>
<td>8/8</td>
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</table>

Each ketoprofen topical (KPT) patch was applied on rats’ dorsal region for a 6-hour period. The ulcerogenic effect was assessed 6 hours following each drug administration. UD$_{50}$ and 95% confidence interval (C.I.) were calculated according to the number of rats that developed an ulcer. Ulcer index: indicates mean ± standard error (SE) on 8 rats. (From Taniguchi Y, Inui K, Furuta K, et al).
Physical characteristics, pharmacological properties and clinical efficacy of the ketoprofen patch

the parenteral, the rectal and the topical routes, all of which appear to be effective, although in various degrees, against a large variety of painful and inflammatory acute and chronic conditions, of rheumatic as well as of traumatic type. NSAIDs, however, may induce a number of side effects that in the majority of instances involve the gastrointestinal tract. The use of topical NSAIDs preparations may remarkably reduce both intensity and frequency of such side effects, while the pharmacologic action of the active medication remains unaltered.

The development of a new ketoprofen patch appears to be a welcome progress for the therapy of all the inflammatory and rheumatic disorders as well as for a variety of traumatic lesions involving practically all the areas of the body, including the joints. In addition, the use of the ketoprofen patch structured according to the DermaLight Technology may represent the administration of choice for patients suffering from gastrointestinal disorders, since ulcerogenic effect induced by the patch is minimised as compared with that produced by oral administration of the active principle.

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