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Ketoprofen 2.5% gel: a clinical overview

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Abstract. – Ketoprofen (KP), a non-steroidal anti-inflammatory drug (NSAID), possesses analgesic, antipyretic and anti-inflammatory properties. Oral KP is widely used in musculoskeletal pain and inflammation in muscles and joints, including arthritis pain, osteoarthritis, stiffness of the joints, soft tissue rheumatism, and sports injuries. In common with all NSAIDs, oral KP has been associated with systemic adverse events and in particular gastrointestinal disorders. Topical application of the active ingredient is locally effective and at the same time minimises the risk of systemic adverse events. Pharmacokinetic studies show that serum levels of the active ingredient following topical KP 2.5% gel are less than 1% of those reported after oral dosing, thereby providing good levels of pain relief without the systemic adverse events normally associated with oral NSAIDs. In comparative studies, topical KP 2.5% gel twice daily showed clinical benefits in patients with a range of musculoskeletal conditions. KP 2.5% gel is generally well tolerated but the treated skin area should not be exposed to direct sunlight, including solarium (sunbeds), during the treatment and for 2 weeks afterwards as topical photosensitization has been reported. To our knowledge, this is the first overview on the use of topical KP (tKP) 2.5% gel which includes data from both clinical trials and from 'real-life' clinical practice.

Key Words:

Ketoprofen, Gel, NSAIDs, Pain, Topical treatment, Musculoskeletal.

Introduction

The use of topical non-steroidal anti-inflammatory drugs (NSAIDs) in relieving pain in patients with acute and chronic musculoskeletal disorders, including osteoarthritis (OA), tendonitis, and muscle strains is well established[1]. Topical formulations of NSAIDs have analgesic effects similar to that of oral formulations, but are associated with less systemic exposure and, therefore, with fewer serious adverse events (AEs)[2]. Current guidelines produced by the European League Against Rheumatism (EULAR) and the Osteoarthritis Research Society International (OARSI) suggest that topical NSAIDs are preferred over oral NSAIDs for patients with mild to moderate knee or hand OA with few affected joints, and/or a history of sensitivity to oral NSAIDs[3,4]. The favourable benefit/risk ratio of topical NSAIDs has been further confirmed by a recent Cochrane meta-analysis of 47 randomized studies[5]. Because there are a number of topical formulations of NSAIDs currently available, there is a need to summarize the evidence supporting the effectiveness and safety of each formulation. In fact, the results of a recent systematic review highlighted that topical NSAIDs may vary significantly in their pharmacokinetic and pharmacodynamic properties, as well as in their efficacy/safety profile[1].

Ketoprofen (KP), a widely used NSAID, is effective and well-tolerated in the treatment of acute and chronic pain, of both rheumatic and traumatic origin, as well as postoperative pain[6]. The clinical experience with this drug is extensive[6], and a number of different formulations are available - including capsules, suppositories, injectable solutions, sustained release formulations, and a topical gel[7]. To our knowledge, this is the first overview on the use of topical KP (tKP) 2.5% gel which includes data from both clinical trials and from "real-life" clinical practice.

Methodology

We first performed a systematic search using MEDLINE (last updated February 2011). The search terms included, but were not limited to, ketoprofen AND gel; topical NSAIDs AND pain were used. Articles were chosen based on their relevance, as judged by the Author and search results were supplemented with a search of Company reports held in a proprietary database, by manually searching the reference list of identified articles.

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Product Development and Indications

KP is a NSAIDs which belongs to the group of substituted 2-phenyl propionic acids [2-(3-benzoylphenyl)-propionic acid]. It was first synthesized in 1967 at Rhone-Poulenc Research Laboratories, Paris, and was approved for clinical use as an oral formulation in France and the United Kingdom in 1973. It is now available in more than 100 countries worldwide. There is a wealth of clinical experience with tKP and it is estimated that the therapeutic experience of KP exceeds 3 million patient/year[8]. In the 10 years from January 1998 to January 2008, more than 140 millions patients were treated with tKP gel.

The main indication for tKP 2.5% gel is the local treatment of musculoskeletal pain and inflammation in muscles and joints (contusions, distortions, strains, stiff neck, and lumbago). The topical release of the active molecule is locally effective, and because of the low systemic bioavailability is associated with fewer adverse events (AEs) than with systemic formulations[1]. Importantly, tKP should only be used on intact skin (as single or repeated application) to avoid any irritant action on mucosa and scarred skin.

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profile of tKP after topical application has been extensively studied *in vitro* and *in vivo*. In one of the first studies, tKP was applied to the entire surface of the knee once a day for three days in patients scheduled for surgical intervention. KP concentrations in the plasma, synovial fluid and tissue were determined by HPLC[9] KP was detected in the plasma 2 hours after the administration and its concentration remained constant for 12 hours. Local tissue concentrations at the site of application were about 100-fold higher than the plasma concentrations. KP levels in the knee joint were considered to be a result of a direct transcutaneous diffusion, rather than a plasma diffusion. In a 10-day study in 10 healthy volunteers, the total amount of KP in the urine following daily application of tKP was 2.6% of the initial dose applied and the apparent half-life of unchanged KP was 17.1 ± 9.1 hours, and no accumulation was reported[10]. Another study, conducted to determine the concentration of KP in the synovial fluid following topical application, showed that KP concentrations were comparable with those following intramuscular administration[11].

In 2002, KP 2.5% gel was used as a standard reference to measure the percutaneous absorption by human skin in two *in vitro* studies. The first study compared the percutaneous absorption (after a 24-hour contact) of KP 2.5% gel alone or in combination with sunscreen, through human skin compared with other two gel formulations (Table I)[12]. The second study was carried out using vertical Franz diffusion cells, and the extent of KP diffusion was determined using a validated HPLC method[13]. Systemic absorption of tKP 2.5% gel was relatively low, with the plasma levels about 100-fold lower, and the local tissue levels 100-fold higher than those reported following the oral administration.

In common with other NSAIDs, the pharmacodynamic activity of KP relies on the inhibition of the metabolism of arachidonic acid. KP is one of the most powerful inhibitors of cyclooxygenase (COX)[14] and the inhibition of prostaglandins synthesis gives it its anti-inflammatory, analgesic, and antipyretic effects[1]. In addition, KP is characterized by other pharmacological effects that may be relevant to its anti-inflammatory and analgesic activities. It is a powerful inhibitor of bradykinin (an important chemical mediator of pain and inflammation)[15]; it stabilises the lysosomal membranes against the osmotic damage[16] and it prevents the release of lysosomal enzymes that mediate the tissue destruction in the inflammatory reactions[8]. In an unpublished report, the effect of tKP 2.5% gel on prostaglandin concentrations in the synovial fluid and on the platelet output of tromboxane B2 (TXB2) was measured

Table I. Percutaneous absorption of tKP 2.5% (expressed as μg) gel alone or in combination with sunscreeen, through human skin in comparison with ethylhexyl methoxycinnamate 3% and phenylbenzimidazole sulfonic acid 3% after a 24-hour contact[12].

	Receptor fluid	Epidermis	Dermis	Total
Ethylhexyl methoxycinnamate 3%	17.16 ± 3.00	9.83 ± 1.85	1.31 ± 1.18	28.30 ± 3.34
KP 2.5% + sunscreen	6.19 ± 1.92	8.77 ± 1.43	0.66 ± 0.32	15.62 ± 3.27
KP 2.5% alone	10.13 ± 3.75	12.23 ± 3.30	0.86 ± 0.48	23.22 ± 5.07
Phenylbenzimidazole sulfonic acid 3%	12.56 ± 4.65	10.60 ± 3.51	1.00 ± 0.54	24.17 ± 9.29

in patients with joint effusion[17]. Inhibition of platelet COX activity was comparable to that observed after an oral administration of KP, with a significant reduction in the synovial concentrations of PGE_2 and 6-keto-PGF_{1alpha}.

Efficacy

The efficacy of tKP gel has been studied in a series of controlled trials versus placebo or other analgesic drugs such as diclofenac or etofenamate, in a broad range of patients, with acute and chronic painful conditions (sport lesions, low back pain, tendonitis, osteoarthritis of the knee and hand, soft tissue rheumatic pain). In general, in these studies, tKP 2.5% gel was applied twice daily at dosages ranging from 40-600 mg (typically 100–300 mg) for 2-42 days (typically 7–20 days). In addition, the effects of tKP 1– 5% gel were investigated in a number of open studies[18-26]. Marked improvements were observed in the severity of spontaneous and palpation pain; in both passive and active articular mobility and in the signs of inflammation. These improvements were significantly more marked with tKP 2.5% and 5% gel compared with tKP 1% gel, whereas statistical differences between the two higher concentrations were not reported for any of the parameters measured. Similar results were reported in another series of trials that assessed the efficacy of tKP in association with physical therapies including iontophoresis and sonophoresis[27-33].

The efficacy of tKP, as well as that of other topical NSAIDs has been confirmed in meta-analyses. Moore et al.[34] carried out a quantitative systematic review of 86 randomised controlled trials, involving 10,160 patients, and reported a significant advantage of tKP, with respect to placebo, in relieving pain in acute and chronic conditions (number needed to treat, NNT, 2.6) (Table II). In a subsequent meta-analysis by Mason *et al*. (35) of 26 double-blind, placebo-controlled trials in 2,853 patients, the indirect comparisons of individual topical NSAIDs showed that tKP was significantly better in the treatment of acute pain conditions than all the other topical NSAIDs studied (Table III). The efficacy of tKP was also confirmed by a recent Cochrane meta-analysis by Massey *et al*.[5], who concluded that topical NSAIDs when used to treat acute musculoskeletal conditions can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs.

According to these results, and the overall improved efficacy/safety ratio when compared with oral administration, the topical treatment with NSAIDs, including KP, should be considered as a first-line treatment for the management of knee and hand osteoarthritis[3,4,36,37].

Safety and Tolerability

Overall tKP 2.5% gel is well tolerated[38]. Results of meta-analyses, conducted in a wide range of patients, consistently show that local and systemic adverse events associated with the administration of tKP are rare and in most cases mild[5,34,35]. In a double-blind, placebo controlled study no adverse effects were observed over a 7-day period[19]. These findings are consistent with those reported in other trials, in which the application of tKP was not associated with any local or systemic AEs[25,31]. In other trials, mild pruritus and erythema which did not lead to study a discontinuation were the only AEs reported[21,22,24]. Importantly the application of tKP gel did not alter the blood chemistry parameters[32].

Pooled data, collected in the context of post-marketing surveillance reports, from over 273 million patients treated with KP 2.5% gel from January 2001 to July 2010 showed a total of 624 reported serious adverse reactions (SDRs) in 437 patients (incidence: 0.16/100,000) (data on file). Most of the ADRs were cutaneous, such as hypersensitivity and photosensitivity reactions. Some cases of photosensitivity, potentially resulting in chronic dermatitis, have been documented following tKP gel treatment[39,40].

Drug interactions are not to be expected when using the topical route, and no cases of overdosage have been reported. tKP during pregnancy and in breastfeeding women should be avoided, as well as in children and adolescents under 15 years of age.

On the basis of the above, the most relevant safety issue for KP gel is its potential relationship with skin disorders, and in particular with photosensitivity reactions. To reduce the risk of these events, patients should be instructed not to expose treated skin to sunlight during the application period and for the following two weeks. In addition, tKP gel should not be applied near or over wounds and contact with the eyes should be avoided. Overall taking into account the wide clinical experience with tKP collated so far the overall safety profile of tKP is favourable and skin disorders are rare events[6].

Table II. Relative benefit and number needed to treat in randomized studies of topical NSAIDs in acute and chronic painful conditions (reproduced from[34]).

Condition/drug acute painful conditions	Total trials	Total patients	Average number of treated patients	Response* with placebo	Response* with active treatment (%)	Relative benefit (95% CI)	Number needed to treat (95% CI)
Combined efficacy data	37	3239	47	39	71	1.7 (1.5 to 1.9)	3.9 (3.4 to 4.4)
Local adverse effects				3.0	2.6	1.2 (0.8 to 1.7)	
Systemic adverse effects				0.7	0.8	1.0 (0.6 to 1.8)	
Withdrawal due to adverse effects				0.4	0.6	0.8 (0.4 to 1.4)	
Trials of quality score 3-5	30	2834	52	38	72	1.7 (1.5 to 1.9)	3.9 (3.4 to 4.4)
			Treatment group:				
< 40 patients (pts)	20	933	24	35	76	1.9 (1.6 to 2.2)	2.6 (2.3 to 3.1)
40-80 pts	8	810	51	44	66	1.6 (1.1 to 2.2)	5.0 (3.7 to 7.4)
> 80 pts	7	1496	123	41	67	1.6 (1.3 to 1.9)	4.6 (3.7 to 5.9)
Ketoprofen	9	724	43	36	74	2.0 (1.5 to 2.6)	2.6 (2.3 to 3.2)
Felbinac	3	413	70	32	66	2.0 (1.5 to 2.7)	3.0 (2.4 to 4.1)
Ibuprofen	4	284	36	34	70	1.9 (1.2 to 3.0)	3.5 (2.5 to 5.6)
Piroxicam	4	589	74	39	69	1.6 (1.2 to 2.2)	4.2 (3.1 to 6.1)
Benzydamine	4	245	31	62	84	1.4 (0.9 to 2.0)	6.7 (3.8 to 23)
Indomethacin	3	394	66	32	47	1.3 (0.9 to 1.8)	10 (5 to §)
			Chronic painful conditions				
Combined efficacy data	12	1097		30	65	2.0 (1.5 to 2.7)	3.1 (2.7 to 3.8)
Local adverse effects				5.3	5.9	0.9 (0.4 to 1.7)	
Systemic adverse effects				1.3	1.1	1.1 (0.5 to 2.3)	
Withdrawal due to adverse effects				0.7	0.7	1.0 (0.4 to 3.1)	
Trials of quality score 35	9	987	55	27	62	2.2 (1.5 to 3.1)	3.1 (2.6 to 3.8)
			Treatment group:				
< 40 pts	6	261	22	31	69	2.2 (1.5 to 3.1)	2.6 (2.0 to 3.6)
> 40 pts	6	836	70	29	61	2.0 (1.7 to 2.4)	3.3 (2.8 to 4.3)

*Response is either proportion of patients with successful outcome or of patients with adverse effect; §Indicates that there may be no benefit with treatment over placebo.

Table III. Summary data and sensitivity analyses for placebo controlled trials of topical NDAIDs in acute painful conditions (reproduced from[35]).

Parameter	Trials	Patients	Success with		Relative benefit (95% CI)	NNT (95% CI)
			Treatment	Placebo		
All trials						
Trial quality	26	2853	993/1531	512/1322	1.6 (1.4 to 1.7)	3.8 (3.4 to 4.4)
Quality score ≥ 3/5	23	2551	893/1375	443/1176	1.6 (1.5 to 1.8)	3.7 (3.2 to 4.3)
Validity score ≥ 9/16	24	2793	969/1501	508/1292	1.5 (1.4 to 1.7)	4.0 (3.5 to 4.6)
Quality score ≥ 3 and validity score ≥ 9	22	2511	876/1355	440/1156	1.6 (1.4 to 1.8)	3.8 (3.3 to 4.4)
Trial size						
≥ 40 pts per group	15	2279	761/1234	400/1045	1.4 (1.3 to 1.6)	4.3 (3.7 to 5.2)
< 40 pts per group	11	574	232/297	112/277	1.9 (1.6 to 2.2)	2.7 (2.2 to 3.3)
Efficacy by outcome type						
Preferred outcomes	17	1941	676/1025	373/916	1.5 (1.3 to 1.6)	4.0 (3.4 to 4.8)
Lower preference outcomes	9	912	317/506	139/406	1.7 (1.5 to 2.1)	3.5 (2.9 to 4.5)
Efficacy by topical NSAIDs						
Ketoprofen	6	517	203/261	101/256	2.1 (1.7 to 2.5)	2.6 (2.2 to 3.3)
Ibuprofen	5	365	112/183	67/182	2.0 (1.5 to 2.6)	4.1 (2.9 to 6.9)
Felbinac	3	413	112/210	57/203	1.6 (1.2 to 2.2)	4.0 (2.9 to 6.2)
Piroxicam	3	563	179/283	118/280	1.4 (1.1 to 1.7)	4.7 (3.4 to 7.7)
Indomethacin	3	394	95/197	76/197	1.3 (0.99 to 1.6)	10 (5.2 to infinity)
Adverse events						NNH (95 % CI)
Local adverse events	23	2741	65/1464	60/1277	1.6 (1.0 to 2.5)	Not calculated
Systemic adverse events	23	2685	40/1437	30/1248	1.4 (0.9 to 2.0)	Not calculated
Adverse events withdrawals	24	3011	13/1601	10/1410	1.0 (0.8 to 2.4)	Not calculated

Conclusions

Oral KP has been widely in the treatment of patients with rheumatic and muscular pain and inflammation. As with all NSAIDs administered by this route, oral KP is associated with clinically relevant AEs, in particular gastrointestinal disorders. The topical application of the active ingredient is locally effective, but has the advantage lowering the risk of AEs. The efficacy and safety of tKP have been demonstrated in both clinical studies and in 'real-life' practice. It must be acknowledged that some of the studies which investigated the efficacy and safety of tKP 2.5% gel belong to the so-called "grey literature" – a term used by medical and research professionals to refer to a body of materials that cannot be found easily through conventional channels such as that published in international journals. However, these sources of information play a crucial role in conducting a full and comprehensive evaluation of the drug efficacy and safety[41].

Pharmacokinetic studies show that serum levels of the active ingredient following the application of tKP 2.5% gel are less than 1% of those reported after oral dosing, thus potentially lowering the risk of systemic AEs. In comparative studies, 5-15 cm (100-300 mg) of KP 2.5% gel applied twice daily produced a clinical benefit in the majority of patients with a broad range of symptoms. In addition, tKP was an useful adjunct to physical therapies in promoting a rehabilitation. KP 2.5% gel appears to be well tolerated, with a low potential for systemic adverse effects. Patients treated with tKP gel are advised not to expose the treated skin to direct sunlight, including solarium (sunbeds), during the treatment and for 2 weeks afterwards in light of recent reports of topical photosensitization, which in isolated cases can be severe and generalised.

In conclusion, a topical application of KP 2.5% gel appears to offer a more favourable therapeutic profile than oral NSAIDs in the management of soft tissue injuries. It provides a good symptom relief at low plasma concentration, a favourable risk/benefit ratio and a low incidence of AEs.

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