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MANAGEMENT OF UNCOMPLICATED ANKLE SPRAINS WITH TOPICAL OR ORAL KETOPROFEN TREATMENT

A REGISTRY STUDY

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Management of uncomplicated ankle sprains with topical or oral ketoprofen treatment. A registry study

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Ankle sprains mainly caused by accidents or strenuous sport activities can often be quite painful and impair motility. If not treated immediately and correctly, sprains may lead to severe complications. The aim of the present study was to compare the efficacy and safety of topically applied ketoprofen versus orally administered ketoprofen in 20 patients with grade I ankle sprain and 34 patients with grade II sprain. The patients were divide into in two treatment groups and received either topically applied ketoprofen treatment (ketoprofen 10% spray-gel; Prontoflex®; 360 mg/die) or orally administered ketoprofen treatment (ketoprofen tablets; 3x50 mg/die). Treatment duration was one week. After 3 and 7 days of treatment, reduction of spontaneous pain and pain on active movement in the Prontoflex® group was significantly bigger greater in the oral treatment group, irrespective of sprain severity. Regarding secondary parameters as mobility impairment and ankle swelling topically applied ketoprofen treatment turned out to be significantly superior to orally administered ketoprofen treatment. Additionally, Prontoflex® was well tolerated, whereas ketoprofen tablets caused gastrointestinal side effects in some patients. The good efficacy in pain reduction and absence of side effects in the present study distinguished the topically applied ketoprofen as a favorable treatment for patients with accidental or sport soft tissue injuries.

Key words: **Ankle injuries - Ketoprofen - Pain - Sport injuries.**

Conflicts of interest.—The authors have no financial interest with the companies quoted in this article. None of the authors has received or will receive any financial gain and involvement from/in the products quoted in this article.

Sprains, particularly those affecting the ankle or the knee are characterized by the stretching or tearing of stiff, non-elastic, non-contractile structures (ligaments or the joint capsule itself).

Ligament (sprain) and muscular (strain) injuries are classified according to the degree of functional impairment they cause.

Grade I sprain is caused by stretching (without tearing) of the ligament with clinical signs such as local tenderness, minimal edema, no significant instability at stress testing and firm end point. Grade II sprain is partial tear of the ligament, characterized clinically by moderate local tenderness and mild instability at stress testing. This lesion is moderately incapacitating. Grade III sprain is a complete tear of the ligament, with discomfort at manipulation, edema and swelling (from absent to conspicuous) and clear instability at stress testing (with a mushy end point) causing severe disability.

Immobility, and/or reduced activity, due to sprains may also be associated with venous thrombosis.[1]

Even though simple, uncomplicated Grade I and II sprains may be considered as a self healing illness, untreated sprains may recur and even cause severe complications.[2, 3]

Different treatments,[2-5] including locally or systemically active non-steroidal anti-inflammatory drugs (NSAIDs) are common treatment for patients with sprains, soft tissue injuries and sports traumata. Local treatments [6, 7] with topically applied NSAIDs offer the advantage of rather high local and low systemic bioavailability. Therefore, the risk of the incidence of systemic adverse events such as gastric discomfort or peptic ulcer or more severe ones, such as gastrointestinal hemorrhage or liver failure is reduced.[7-9]

Several studies have investigated the efficacy and tolerability of different doses of the NSAID ketoprofen.[8, 9] Studies have included patients with painful, benign (grade I) ankle sprains as a model of general traumatic soft tissue injuries [6] or patients with other soft tissue injuries.[10] The primary efficacy criterion was change of pain at rest after 7 days treatment.[6, 10] Studies clearly indicated, that the decrease in pain after 1 week treatment with ketoprofen was more remarkable than in the placebo group.[6, 10] Furthermore, as side effects have been mild, the tolerability of topically applied ketoprofen was regarded as good.[6, 10] According to published data, a 7-day course of treatment with a topically applied ketoprofen spray could be a useful therapeutic option for patients with benign ankle sprain, in soft tissue lesions, contusions and sports injuries, without causing adverse events.[6, 10]

The aim of the present study was therefore to evaluate the efficacy and safety of topically applied ketoprofen in patients with grade I and II sprains in comparison to orally administered ketoprofen.

Materials and methods

Patient population

This pilot study included 20 patients with ankle sprain grade I and 34 patients with ankle sprain grade II.

Patients with grade III sprain, patients with other inflammatory/post-traumatic problems (strains, contusions, tendinitis, bursitis) as well as patients with multiple sprains/contusions or bleeding, limbs ulcerations and infections were excluded from the present study. Additionally, patients in need of immobilization, invasive orthopedic procedures or with complex lesions, as well as, patients subject to pharmacological treatment for any other disease were excluded.

Methods

The extension of the sprains as assessed by high resolution ultrasound at inclusion, was limited to 6x6 cm, with a thickness of the affected area (if haematoma was present) of not more than 1 cm.

All patients were included into the study within 48 hours post injury. Ice packs and non-medical local treatments were allowed only before inclusion. Complete joint immobilization was not done, only light elastic bandage was used in all patients.

Study medications

The present study compared the pain reducing efficacy of a topically applied ketoprofen 10% spray-gel (Prontoflex®, Medicom International, Czech Republic - other trade name: Ketospray®) and orally administered ketoprofen 50 mg tablets.

Prontoflex® is a stable solution of 10% ketoprofen, containing excipients facilitating skin penetration. Each pump actuation releases 20 mg of the active substance ketoprofen.

The patients were assigned either to topical or oral ketoprofen treatment.

Prontoflex® was applied three times per day, 5-6 spray puffs each (maximum daily dose have not had to exceed 360 mg of ketoprofen).

The recommended dose of ketoprofen tablets (Fastum, Menarini, Italy) was 3 times 50 mg per day.

The primary end-point was the assessment of pain reduction on active movement. The

TABLE I.—*Details of ankle sprain grade I patients. There were no drop-outs.*

	Total	M:F	Mean age (SD)
Topical ketoprofen (Prontoflex®) group	11	7:4	43.6 (3)
Oral ketoprofen group	9	7:2	44.2 (3.2)

secondary end-point was pain reduction at rest.

Secondary parameters of interest comprised disappearance of pain, percentage of patients with complete resolution, improvement of joint swelling and of impaired motility, patient's and investigator's assessment of efficacy, evaluation of safety and tolerability, frequency of adverse events and patient's and investigator's global assessment of tolerability.

The treatment lasted for one week. All clinical examinations were performed at baseline (inclusion), on day 3-4 and at the end of treatment (day 7-8).

Pain at rest, and upon active movement were measured using a visual analogue scale (VAS), a 100 mm horizontal line with "0=no pain" at the left side and "100=extreme pain" at the right side.

An effort test was performed to evaluate the impairment mobility due to the lesion, if possible, at inclusion and at the end of the treatment period. A 'minimal', walking treadmill assessment (velocity of 3 km/h with 10% inclination for 3 minutes) was used. The effects of pain and altered function on the exercise performance was recorded on a linear scale (0-10) where 10 was the best possible performance and 0 represented the total impossibility to initiate and complete the test (*i.e.* due to pain).

The presence of vascular problems (i.e. superficial thrombosis, haematoma) was excluded by an ultrasound investigation (particularly excluding venous thrombosis and peripheral vascular disease). The presence of local haematoma was also evaluated and quantified measuring its size and thickness.

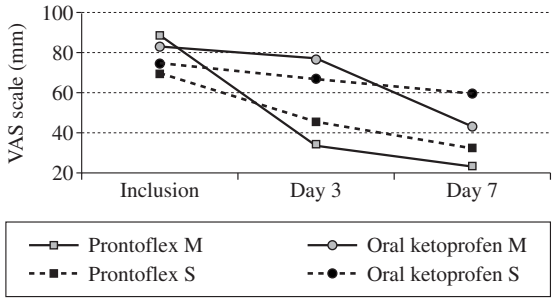

Figure 1.—Spontaneous pain and pain on movement in ankle sprain grade I patients at inclusion and after 3 and 7 days treatment with either Prontoflex® or orally administered ketoprofen.

TABLE II.—*Details of ankle sprain grade II patients. There were no drop-outs.*

	Total	M:F	Mean age (SD)
Topical ketoprofen (Prontoflex®) group	18	10:8	43.1 (5)
Oral ketoprofen group	16	9:7	44.7 (5.2)

Results

Ankle sprain grade I

The two groups of patients were comparable for age and sex, with higher proportion of males in both treatment groups (Table I).

At inclusion, all patients with grade I sprain experienced comparable severity of pain (VAS), though spontaneous pain of patients in the oral ketoprofen group was slightly, but not statistically higher than pain in patients in the topical treatment group. When pain on movement is considered, patients in the Prontoflex® group suffered from more pain at inclusion than patients in the oral ketoprofen group (P=0.092).

During the treatment period, Prontoflex® scored significantly better in pain reduction than ketoprofen tablets, regarding both, spontaneous pain and pain on movement. During the first 3 days of the study, the mean spontaneous pain in the Prontoflex® group decreased from 70.2 mm to 45.8 mm on a VAS scale, compared to a spontaneous pain

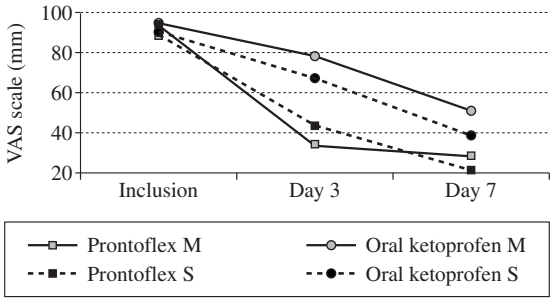

Figure 2.—Spontaneous pain and pain on movement in ankle sprain grade II patients at inclusion and after 3 and 7 days treatment with either Prontoflex® or orally administered ketoprofen. S: spontaneous; M: movement.

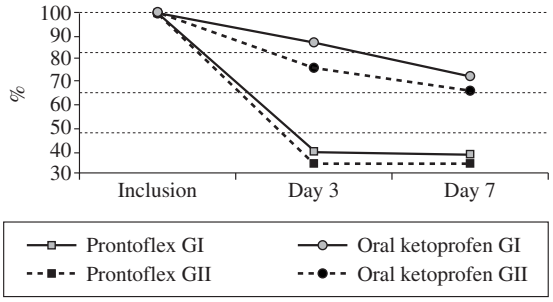

Figure 4.—Joint swelling in ankle sprain grade I and grade II patients at inclusion and after 3 and 7 days treatment with either Prontoflex® or orally administered ketoprofen.

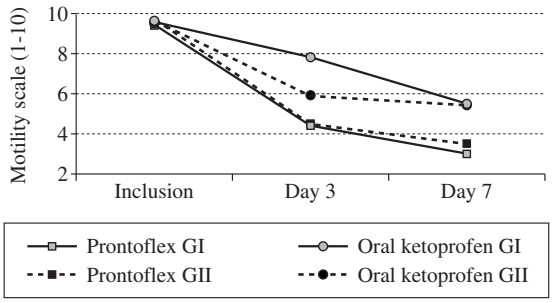

Figure 3.—Motility impairment in ankle sprain grade I and grade II patients at inclusion and after 3 and 7 days treatment with either Prontoflex® or orally administered ketoprofen.

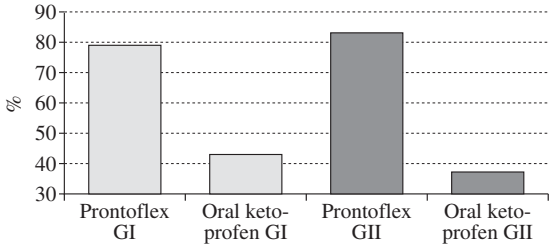

Figure 5.—Percentage of patients with complete resolution (ankle sprain grade I and grade II) after treatment with either Prontoflex® or orally administered ketoprofen.

decrease from 75.1 mm to 67.1 mm in the oral ketoprofen group (P<0.001). On day 7, the mean pain value in the Prontoflex® group was significantly lower than that in the oral ketoprofen group (32.5 mm *versus* 59.7 mm; VAS scale; P<0.001) (Figure 1).

Reduction of pain on movement was statistically significantly higher in the Prontoflex® group than in the oral ketoprofen group. On day 3 of the study, mean pain on movement was 34.2 mm (VAS scale) for Prontoflex®, compared to 77.2 mm (VAS scale) for the oral ketoprofen group (P<0.001). The difference between the two treatment groups remained pronounced on day 7 of the study as well. At this assessment point mean pain on movement values were 23.7 mm for Prontoflex® and 43.1 mm for orally administered ketoprofen, respectively (P<0.001) (Figure 1).

Ankle sprain grade II, primary parameters

The two groups of patients with ankle sprain grade II were comparable for age and sex (Table II).

As in the group affected by Grade I ankle sprain, in patients with Grade II injury, the efficacy of Prontoflex® was significantly better compared to orally administered ketoprofen.

At inclusion, patients of the oral ketoprofen group and of the Prontoflex® group showed comparable pain values for both spontaneous pain (P<0.733) and pain on movement (P<0.794). Regarding spontaneous pain, already on day 3 of the study, patients in the Prontoflex® group had lower mean pain values (43.7 mm VAS scale as compared to 67.2 mm in patients receiving ketoprofen orally (P<0.001)). Also on day 7 of the study spontaneous pain values were significantly lower in the Prontoflex® group than in the oral ketoprofen group (P<0.001) (Figure 2).

In terms of pain on movement, the same tendency was observed. On both assessment points (days 3 and 7 of the study), patients in the Prontoflex® group experienced significantly lower pain compared to patients taking ketoprofen orally (P<0.001, each; Figure 2).

Ankle sprain grade I and II, secondary parameters

In addition to the primary endpoint of the study, a number of secondary parameters were analyzed as well. In both ankle sprain grade groups, patients treated with Prontoflex® suffered pain for fewer days (P=0.307 for ankle sprain grade I; P<0.001 for ankle sprain grade II). Both, patients (P=0.023 in case of ankle sprain grade I and P<0.001 in case of ankle sprain grade II) and investigators, (P=0.029 sprain grade I and P<0.001 sprain grade II, respectively) rated Prontoflex® treatment as more efficient than the oral ketoprofen treatment.

Regarding impairment of motility, both treatment groups were comparable at inclusion. On day 3 and on day 7 as well, patients treated with Prontoflex® experienced statistically significantly better improvement of motility than patients taking ketoprofen orally (P=0.027 and P=0.011 for ankle sprain grade I, respectively, Figure 3; P=0.039 and P=0.040 for ankle sprain grade II, respectively, Figure 3).

Joint swelling was reduced in the Prontoflex® group irrespective of the sprain grade. After 3 days treatment an average 60% reduction of swelling was observed. In the oral ketoprofen group, however, about 20% swelling reduction was observed. In comparison to sprain grade I, in sprain grade II patients, only minimal reduction of swelling was observed after administration of ketoprofen tablets (Figure 4).

Furthermore, topical application of ketoprofen resulted in a much higher percentage of patients with complete resolution of symptoms compared to oral treatment irrespective of the sprain severity (Figure 5).

Additionally, patients and investigators evaluated Prontoflex® to be well tolerated. In the oral ketoprofen group gastrointestinal discomfort was reported in 3 out of 9 grade I patients and in 5 out of 16 grade II patients. Nevertheless the treatment was not changed or stopped. The average consumption of ketoprofen tablets, obviously driven by symptoms and patient's personal needs, was 98.4 (SD 24) tablets within the seven days of treatment.

Discussion

In sport and in general practice, distortions, contusions, sprains and strains are among common diagnoses mainly caused by accidents or strenuous sports activities. Symptoms of such traumatic injuries are severe pain, edema and hematoma and in case of joint injuries extensions of the capsule, strains or even fissures. Pain and swelling which impair the functional motility tend to increase due to advancing inflammation.

The severity of ankle sprain is classified as grade I to III (or stage I to IV according to Castaing.[11] Even small injuries can often be quite painful, alter mobility and delay the rehabilitation programs.[3, 12, 13] Acute ankle trauma is common and costly due to its frequency and need for visits to physicians or emergency departments and may finally result in significant loss of working days.[8, 14] Symptomatic treatment consists of rest, ice, compression and elevation. The currently most commonly prescribed drugs are NSAIDs and paracetamol.[8, 14]

If the sprains are not immediately and correctly treated, severe complications and disabilities may resul.[15-18] Venous thrombosis, more severe lesions and other fractures may occur in subjects with an unstable ankle after sprains. The outcome is more severe with prolonged course of healing, when patients with existing arterial or venous disease are affected. In these subjects, ankle sprains may generate serious complications, i.e. venous thrombosis or pulmonary embolism, venous or arterial ulcerations. These are primarily caused by reduced functional mobility.

Early mobilization particularly in younger subjects, is considered very important for

optimal healing. In addition to rapid pain relief, an essential starting point for therapy is the inhibition of inflammation at the site of injury.[19-21]

Local therapy with NSAIDs has become increasingly important. The main advantage of the topical application of NSAIDs is the reduction of incidence and severity of undesirable side effects such as gastrointestinal disturbances which are quite frequent after oral administration of NSAIDs.

The present study, in general, showed good tolerability and safety of topically applied ketoprofen assessed by patients and investigators, in contrast to gastrointestinal side effects reported by some patients in the oral ketoprofen group.

Bioavailability studies suggest that NSAIDs administered topically achieve 1-5% systemic absorption compared to oral administration.[14, 22] Local concentrations are apparent within hours with certain formulations. Local tissue concentrations depend on many factors e.g. formulation, duration, and frequency of treatment, anatomical site, age of the individual, inflammatory state, and the type and thickness of the skin.[14, 22, 23]

Several efficacy studies on topical NSAIDs including ketoprofen have been published up to now. A recent systemic review of 13 placebo-controlled randomized trials concluded that topical NSAIDs [14] are effective in relieving the pain associated with acute soft tissue injury without systemic adverse reactions. Local skin reactions were rare (average 3.6%) and systemic events even more rare (less than 0.5%).[14] Another review of 37 published comparative studies confirmed the effect of topical treatment in acute injuries of soft tissue, sprains and strains.[9]

The results of our pilot study presented herein are in accordance with the studies mentioned above. Prontoflex®, a topical ketoprofen spray, showed efficacy in controlling pain and improving mobility in patients with sprained ankle grade I and II. Primary parameters (pain on motion), as well as, secondary parameters (swelling, mobility impairment) were improved after topical application of Prontoflex®, whereas the improvements observed in the groups treated with oral ketoprofen 50 mg three times a day were significantly less.

On the one hand, the remarkable symptom improvements with topical ketoprofen treatment are highly likely due to the galenic composition of Prontoflex®. In fact, the incorporated penetration enhancer facilitates the migration of the active substance ketoprofen towards the target tissue. On the other hand, comparatively lesser improvements in the oral ketoprofen groups might raise the assumption that ketoprofen orally administered did not result in a sufficient high concentration of the active substance on the injured tissue.

Conclusions

Therefore, taking into account the good efficacy in pain reduction and also absence of side effects, the quality of topically applied ketoprofen seems to be highly favorable as a valuable treatment of choice for patients with accidental or sport soft tissue injuries.

Riassunto

Management delle distorsioni non complicate della caviglia con ketoprofene per via topica o orale: registry study

Le distorsioni della caviglia provocate principalmente da incidenti o da attività sportive estreme possono spesso essere molto dolorose ed influenzare la mobilità. Se non trattate immediatamente e in modo corretto, le distorsioni possono andare incontro a gravi complicanze. L'obiettivo di questo studio è stato quello di confrontare l'efficacia e la sicurezza del ketoprofene applicato per via topica rispetto alla somministrazione orale in 20 pazienti con distorsione della caviglia di grado I e in 34 pazienti con distorsione di grado II. I pazienti sono stati assegnati a due gruppi di trattamento: uno trattato con ketoprofene per via topica (ketoprofene spray-gel 10%; Prontoflex®; Medicom International, Repubblica ceca; 360 mg/die) e l'altro trattato con ketoprofene per via orale (ketoprofene compresse; 3 x 50 mg/die). La durata del trattamento è stata di una settimana. Al 3° giorno di trattamento, così come al 7°, la riduzione del dolore a riposo e del dolore a seguito di movimento attivo nel gruppo trattato con Prontoflex® è stata significativamente maggiore rispetto al gruppo trattato per via orale, indipendentemente dalla gravità della distor-

sione. Per i parametri secondari (la riduzione della mobilità e il gonfiore della caviglia) la somministrazione per via topica di ketoprofene si è dimostrata significativamente più efficace di quella orale. Inoltre, Prontoflex® è stato ben tollerato, mentre le compresse di ketoprofene hanno provocato in alcuni pazienti effetti collaterali gastrointestinali. In questo studio, la buona efficacia relativamente alla riduzione del dolore e l'assenza di effetti collaterali hanno sottolineato come l'applicazione per via topica di ketoprofene rappresenti un trattamento favorevole per i pazienti con lesioni dei tessuti molli accidentali o legate all'attività sportiva.

Parole chiave: Lesioni delle caviglie - Ketoprofen - Dolore.

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