Seminars in Arthritis and Rheumatism 45 (2016) S18–S21

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Efficacy and safety of topical NSAIDs in the management of osteoarthritis: Evidence from real-life setting trials and surveys

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ARTICLE INFO

Keywords:
Hand osteoarthritis
Knee osteoarthritis
Topical non-steroidal anti-inflammatory drugs (NSAIDs)
Personalized medicine

ABSTRACT

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are recommended in international and national guidelines as an early treatment option for the symptomatic management of knee and hand osteoarthritis (OA), and may be used ahead of oral NSAIDs due to their superior safety profile. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends topical NSAIDs for knee OA in addition to the pharmacological background of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) and rescue analgesia with paracetamol and non-pharmacological treatment, if the patient is still symptomatic. Topical NSAIDs have a moderate effect on pain relief, with efficacy similar to that of oral NSAIDs, with the advantage of a better risk: benefit ratio. In real-life studies, topical and oral NSAIDs demonstrate an equivalent effect on knee pain over 1 year of treatment, with fewer adverse events due to lower systemic absorption of topical NSAIDs compared with oral NSAIDs. As a result, topical NSAIDs may be the preferred treatment option, especially in OA patients aged ≥ 75 years, and those with co-morbidities or at an increased risk of cardiovascular, gastrointestinal, or renal side effects. Furthermore, using topical NSAIDs in inflammatory rheumatic diseases leads to a 40% reduction in the need for concomitant oral NSAIDs. When selecting a topical NSAID, absorption and bioavailability are important because of heterogeneity among topical drug formulations. Molecules like etofenamate have a bioavailability of $>20\%$ and evidence for accumulation in synovial tissues, with efficacy demonstrated as improvement in pain and function in real-life studies of OA patients. Diclofenac also shows good efficacy alongside evidence that diclofenac accumulates in the synovium.

Introduction

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends topical non-steroidal anti-inflammatory drugs (NSAIDs) for knee osteoarthritis (OA) in addition to background pharmacological treatment with symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) and rescue analgesia with paracetamol and non-pharmacological treatment, if the patient is still symptomatic [1]. Topical NSAIDs are universally recommended across international and national guidelines for knee and hand OA (Table 1), generally ahead of oral NSAIDs or opioids for pain relief, due to their superior safety profile [1–5]. Topical NSAIDs have a moderate effect on pain relief, with efficacy similar to that of oral NSAIDs, but with a much better safety profile because of the lower systemic absorption [6]. The American College of Rheumatology (ACR) strongly recommends the use of topical rather than oral NSAIDs among people aged 75 years or older with knee OA [3], who often have co-morbidities or increased risk of cardiovascular, gastrointestinal (GI), or renal side effects. Lastly, ACR and NICE clinical guidelines recommend topical NSAIDs as first-line treatment for hand OA [3,5].

Examination of the evidence base for topical NSAID efficacy

The efficacy of topical NSAIDs has been established in randomized controlled trials (RCTs) and meta-analyses [6–9]. A 2011 comparative effectiveness review found comparable efficacy for topical and oral NSAIDs for knee OA. Head-to-head trials of up to 12 weeks' treatment showed no difference between topical and oral NSAIDs for efficacy in patients with localized OA, with lower risk of GI adverse events (AEs) but a higher risk of dermatological AEs with

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; SYSADOA, symptomatic slow-acting drugs for osteoarthritis.

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http://dx.doi.org/10.1016/j.semarthrit.2015.11.007

Table 1
Recommendations for the use of topical non-steroidal anti-inflammatory drugs (NSAIDs) for knee and hand osteoarthritis

Guideline committee	Recommendation for topical NSAIDs
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)	Recommended with paracetamol or SYSADOAs for knee OA when patients have insufficient pain relief
European League Against Rheumatism (EULAR)	Topical NSAIDs have efficacy in knee OA and are safe
American College of Rheumatology (ACR)	Conditionally recommended for initial therapy in hand and knee OA
Osteoarthritis Research Society International (OARSI)	Appropriate for individuals with knee OA only (with or without co-morbidities)
National Institute for Health and Care Excellence (NICE)	Consider ahead of oral NSAIDs or opioids; can be used with paracetamol in knee and hand OA

OA, osteoarthritis; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis.

the topical NSAIDs [6]. A recent Cochrane review similarly found no difference in efficacy between topical and oral NSAIDs, but superior efficacy with topical NSAIDs compared with placebo for reducing pain due to chronic musculoskeletal conditions [10]. The most data available was for topical diclofenac in OA, where the number needed to treat (NNT) for at least 50% pain relief over 8–12 weeks compared with placebo was 6 for the solution and 11 for the gel formulation. The magnitude of the benefit for topical diclofenac in solution is similar to that found for oral NSAIDs (NNT: 5–8) in studies with similar duration and outcomes [11]. While there were insufficient data to compare the individual topical NSAIDs, other than diclofenac, with placebo, the NNT for all topical NSAIDs was estimated at 10 (range: 7–17) [10]. In RCTs of topical diclofenac application for 4–8 weeks, significantly greater changes from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales for pain, stiffness, and physical function were found compared with placebo, as well as for patient global assessment [12–14]. While similar effects on knee pain and disability, measured as global WOMAC score, have been observed for both oral and topical ibuprofen after 12 months' therapy in an RCT of 282 people aged over 50 years with knee pain [15].

An increase in local AEs, mostly mild skin reactions, was noted with topical diclofenac, with no increase in serious AEs and no increase in GI events compared with placebo [10]. While there are relatively few high-quality RCTs of interventions for hand OA published [16], topical diclofenac gel is demonstrated to be effective in primary hand OA with a reduction in pain intensity score of 42–45% and global rating of disease of up to 40% reported after 4–6 weeks' treatment [17].

Recent studies of topical ketoprofen formulations have failed to show a benefit for ketoprofen over the topical placebo treatment [18,19]. Surprisingly, in an active-control trial, both topical ketoprofen and ketoprofen-free vehicle were found to be superior to oral placebo and non-inferior to celecoxib for reducing knee OA pain at 12 weeks [19]. Both topical ketoprofen and the ketoprofen-free vehicle had a similar effect on reduction in WOMAC pain score at 12 weeks (at approximately 40% reduction compared with 29% for placebo). In another trial, ketoprofen was found to be inferior to ketoprofen-free gel in relieving moderate OA knee pain and improving joint function [18]. These reports are not totally incongruous with the evidence base, as a meta-analysis of RCTs in OA has reported a high placebo effect for pain, stiffness, and self-reported function [20]. In studies of topical NSAIDs, transdermal delivery of a placebo and previous pain relief experience with oral NSAIDs may provide an expectation for pain relief in participating patients that has potentially influenced the failure of many topically applied NSAIDs to demonstrate clinically significant benefit compared with topical placebo [21].

Evidence from real-life studies

The ESCEO algorithm recommends topical NSAIDs for knee OA in addition to background pharmacological treatment with SYSADOAs if the patient is still symptomatic [1], yet few studies have reported on the efficacy of the combination of topical NSAID plus SYSADOA. A real-life prospective, non-controlled study conducted in Russia recruited nearly 4000 patients with OA who were prescribed topical diclofenac (1% aerosol formulation, 3–4 times/day) for 2 weeks plus patented crystalline glucosamine sulfate (pCGS) formulated either as an intramuscular injection (ampule: 200 mg/ml, 2 ml 3 times/week) for 4 weeks or as an oral suspension (powder 1500 mg once/day) for 8 weeks [22]. After 8 weeks the median pain severity assessed on a numeric rating scale (NRS) had decreased significantly from 0.8 to 0.2 (interquartile range: ± 0.2; $p < 0.001$).

Few real-life trials have studied the use of topical NSAIDs over time periods longer than 12 weeks. A study of patients (aged ≥ 50 years) with chronic knee pain treated in primary care practice in the United Kingdom, recruited patients either into a randomized trial or patient preference study for up to 2 years [15]. In the controlled trial, patients ($n = 282$) were randomized to receive topical or oral NSAID treatment (approximately 1:1), while in the preference study three-quarters of patients ($n = 303$) chose to receive topical NSAID treatment. Overall, the study found that topical and oral NSAIDs were equivalent for effect on knee pain over 1 year, with no significant difference in changes in global WOMAC scores at 12 months for topical and oral NSAIDs. There was a slight increase in AEs and number of patients changing medication due to AEs for the oral NSAID group. In the topical group, more participants had chronic pain grade III or IV at 3 months, and more participants changed treatment due to ineffectiveness. The results were consistent across the randomized trial and patient preference study [15].

The use of topical NSAIDs may have a treatment-sparing effect on the use of oral NSAIDs in moderate-severe rheumatic disease. A real-life study of over 3500 patients with a range of rheumatic diseases, including OA ($n = 1288$), showed an average 40% reduction in the required dose of oral NSAIDs with the addition of topical etofenamate over 2–4 weeks in inflammatory rheumatic disease [23]. OA patients also reported a 46% improvement in pain and 34% improvement in function with topical etofenamate treatment. Lowering the oral NSAID dose due to addition of etofenamate led to a significant reduction in reporting of AEs, in particular a $>20\%$ reduction in AEs of the GI tract [23].

Bioavailability of topical NSAIDs

As the largest human organ, the skin forms a barrier between the organism and the environment. Its fundamental physiological functions include both the regulation of body temperature (homeostasis) and the regulation of water and substance exchange. The uppermost layer, the stratum corneum, forms the most important barrier to absorption in the epidermis, with a high lipid and very low water content, and is the rate-limiting step for epidermal drug transport [24].

There are great variations in the permeability of the skin to different substances. While both purely hydrophilic and purely

Table 2
Bioavailability of topical NSAIDs and analgesics [25]

Active agent	Active agent concentration (%)	Per-cutaneous absorption (%)
Benzydamine	3	1–4
Bufexamac	5	4–7
Diclofenac	1	6
Etofenamate	5	21
Flufenamic acid	2.5	2
Ibuprofen	5	5
Indomethacin	1	1
Ketoprofen	2.5	1
Salicylic acid	2	1–23

lipophilic substances are barely absorbed through the skin, there are very high absorption rates for predominantly lipophilic substances with a certain residual hydrophilia. The bioavailability of etofenamate following topical application is very high at >20% compared with 1–7% for other topical NSAIDs (Table 2) [25]. The physicochemical characteristics of etofenamate, i.e., pronounced lipophilia and residual hydrophilia, allow good penetration through the skin, irrespective of the pH value of the individual layers, and accumulation in the inflamed tissues [26].

Evidence of accumulation in target tissues

Penetration through the skin and accumulation of the active ingredient in the desired target tissues are important for the efficacy of topical NSAIDs. At the same time, low concomitant plasma levels will ensure low systemic burden and minimize systemic AEs. Studies with topical diclofenac have shown that the level attained in blood is 0.4–2.2% of the maximum serum concentration achieved with oral diclofenac, resulting in significantly lower systemic exposure [27].

Following topical application, studies in humans demonstrate that plasma levels of etofenamate are 10 times lower than tissue levels in fasciae, muscles, and periosteum [28]. A study has measured the distribution of etofenamate in intra-articular and periarticular tissue following the application of 10% etofenamate gel to the affected knee 3 times daily on 3 days before surgery on the anterior cruciate ligament (n = 13) [29]. Samples of the following tissues and fluids were taken during the operation: blood, synovial fluid, synovial membrane, muscle, patella, condyle of the femur, infrapatellar fat pad, patellar ligament, and cruciate ligament. In 12 h following application, the lowest concentrations (approximately 20 ng/ml) of etofenamate and flufenamic acid, a metabolite, were found in the blood and synovial fluid, while the highest concentrations (125–327 ng/ml) were found in the synovial membrane, muscle, patella, patellar tendon, and cruciate ligament (Fig.) [29].

In a recent trial, patients with joint effusions and scheduled for total knee arthroplasty (TKA) received diclofenac sodium 4% spray gel with 2- or 3-times daily application for 3 days prior to surgery (n = 39) [30]. Within 8 h of the last application, TKA was conducted and the diclofenac concentrations were found to be 10–20-fold higher in the synovial tissue in a dose-dependent manner, compared with the synovial fluid and blood plasma concentration (Table 3). Treatment-related AEs were limited to skin reactions recorded in 2 patients.

The potential benefits (and harms) of topically applied NSAIDs at the chondrocyte level are yet to be fully elucidated. *In vitro* studies have shown that several NSAIDs (such as sodium salicylate and indomethacin) inhibit the synthesis of cartilage matrix components, whereas others (such as aceclofenac and meloxicam) increase matrix synthesis and protect chondrocytes against apoptosis [31]. Studies in animal models of OA show diverse effects of the same NSAIDs on articular cartilage in different animal models. Nonetheless, clinical data support a local mechanism of action for topical NSAIDs at the application site [32].

Conclusions

Topical NSAIDs are recommended in international and national guidelines, including the ESCEO treatment algorithm, as an early treatment option for the symptomatic management of knee and hand OA. While the level of evidence for the effectiveness of topical NSAIDs is lower than with other treatments due to a lack of appropriate studies, the effectiveness of topical NSAIDs is comparable to oral NSAIDs with the advantage of a superior risk: benefit ratio. The quasi-effect size of NNT for topical diclofenac in knee OA over 8–12 weeks was calculated as 6 for the solution and 11 for the gel formulation.

In real-life studies, topical and oral NSAIDs demonstrate an equivalent effect on knee pain over 1 year of treatment, with fewer AEs recorded for topical NSAIDs and fewer patients changing medication due to AEs with topical NSAIDs compared with oral treatments. Given the option, three-quarters of patients chose to use a topical NSAID rather than an oral NSAID. Furthermore, using

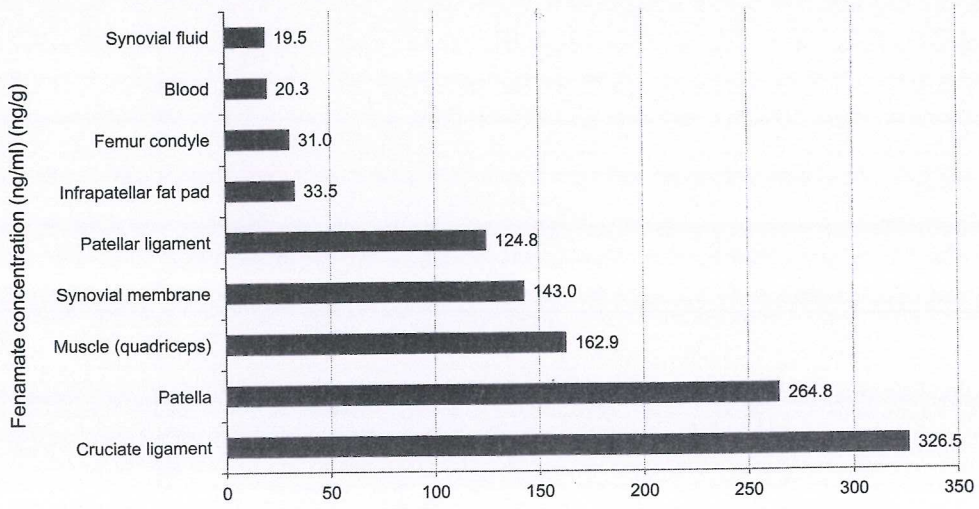

Fig. Fenamate concentration (etofenamate plus flufenamic acid) in intraarticular and periarticular tissue of the knee joint approximately 12 h after the last application of 10% etofenamate gel. (Adapted from Walde [29].)

Table 3
Penetration of topical diclofenac sodium (4% spray gel) into the synovial tissue and synovial fluid of the knee [30]

Median diclofenac concentration (range)	Diclofenac (2 × 40 mg/day) (n = 20)	Diclofenac (3 × 40 mg/day) (n = 19)
Plasma (ng/ml)	3.9 (1.3–302.2)	4.1 (1.1–23.0)
Synovial fluid (ng/ml)	2.6 (0.4–408.5)	2.8 (0.2–47.1)
Synovial tissue (ng/g)	36.2 (1.2–1232.0)	42.8 (0.8–594.0)

topical NSAIDs in inflammatory rheumatic diseases leads to a 40% reduction in the need for concomitant oral NSAIDs, with a reduction in the reporting of GI side effects.

When selecting a topical NSAID, absorption, that is to say bioavailability, matters. It should be noted that there is some heterogeneity between different topical drug formulations. Molecules like etofenamate have a bioavailability of greater than 20%, and evidence for accumulation in synovial tissues, with efficacy demonstrated as improvement in pain and function in real-life studies of OA patients. Good data also exist for the effectiveness of diclofenac in hand and knee OA alongside evidence that diclofenac accumulates in the synovium. Conversely, recent studies fail to demonstrate a benefit for topical ketoprofen and demonstrate a high placebo effect for topical sham treatments used in these studies.

For safety reasons, topical NSAIDs may be used in preference to oral NSAIDs due to their lower peak plasma concentration, and consequent lower propensity to cause unwanted side effects. Due to their non-inferiority and superior safety profile, topical NSAIDs may be the preferred treatment option, especially in OA patients aged 75 years or older, and those with co-morbidities or at an increased risk of cardiovascular, GI, or renal side effects.

Acknowledgments

All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Editorial assistance in the preparation of this manuscript was provided by Lisa Buttle, PhD, of Medscript Ltd., which was funded by the ESCEO asbl, Belgium.

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