Editorial

Topical Nonsteroidal Antiinflammatory Drugs Are Effective in Osteoarthritis of the Knee

Until publication of the large randomized comparison of topical with oral diclofenac in this issue of *The Journal*[1], the title of this editorial would have been written as a question rather than a statement. Although circumstantial evidence existed, proof was lacking. This trial fulfils criteria of quality, validity, and size, and, together with supporting evidence, proves topical nonsteroidal antiinflammatory drug (NSAID) efficacy.

THE TRIAL

The study is properly randomized, with concealment of allocation, and properly blinded using a double-dummy technique, so bias is highly unlikely. It was designed and conducted accorded to OARSI recommendations[2,3], and as a formal equivalence study. It used outcomes specified by OMERACT (Outcome Measures in Rheumatology Clinical Trials)[4], lasted for 12 weeks, and, crucially, directly compared topical diclofenac with 150 mg oral diclofenac. There was no massage, so any beneficial result with topical diclofenac could not have been due to rubbing. It was large, randomizing 622 patients, much bigger than oral NSAID-trials in the pre-coxib era[5,6].

Topical and oral diclofenac produced equivalent improvements in pain, physical function, and patient global assessment of 36–44% and 42–49%, respectively: a little more with oral than topical diclofenac, but rarely significantly so. The number of responders was 66% and 71%.

Equivalent effect came with different adverse events. Topical diclofenac had more skin-related problems, like dry skin, pruritus, and rash, usually mild, and resolving on withdrawal. Oral diclofenac had more gastrointestinal adverse events (48% vs 35% for topical diclofenac). These were classified as severe in 10% of patients taking oral diclofenac, compared with 2.6% with topical. Laboratory adverse events were also worse with oral diclofenac, including liver enzyme elevations, creatinine clearance, and hemoglobin changes. The magnitude of the difference was often quite large, with abnormal hemoglobin, for instance, in 10% of subjects taking oral diclofenac compared with 2% on topical.

Overall, 28% of patients discontinued oral diclofenac because of adverse events (25%) or lack of efficacy (3%). With topical diclofenac the overall numbers were similar (30%), with 21% discontinuing because of adverse events and 9% because of lack of efficacy.

SCIENTIFIC BUTTRESSES

To be effective, topical NSAID have to penetrate the skin, and either enter the circulation or additionally be absorbed into underlying tissue to inhibit cyclooxygenases.

Depending on the molecule and delivery system, NSAID dermal penetration can be extensive. A comprehensive review[7] indicated that a balance between lipid and aqueous solubility was needed to optimize permeation. An *in vitro*-based index of topical antiinflammatory activity combined dermal penetration with cyclooxygenase inhibitory effect[8]. It indicated that ketoprofen, ketorolac, and diclofenac had acceptable efficiency for external use.

Plasma concentrations after topical NSAID are low[9-12], much lower than after oral. For instance, after 400 mg oral ibuprofen, peak plasma concentrations of 30–60 µg/ml occur within 1 hour[13]. Maximum concentrations after topical were less (mostly much less) than 2 µg/ml. With topical diclofenac or ketoprofen, plasma concentrations were generally under 100 ng/ml. Topical application produces plasma concentrations 5% or less than the maximum oral concentration.

Synovial fluid concentrations are similar after topical and oral administration[9-12,14]. Tissue concentrations can be very high after topical administration[9,10,12], with concentrations of tens of µg/g, and perhaps one or 2 orders of magnitude higher than in plasma or synovial fluid.

CLINICAL BUTTRESSES

Systematic reviews of randomized trials in acute and chronic pain have shown topical analgesics to be effective:

See Equivalence study of a topical diclofenac solution compared with oral diclofenac in the symptomatic treatment of OA of the knee, *page 2002*

NSAID[11,15-17], rubefacients[18], and capsaicin[19]. Trials were randomized and double-blind, but were short, generally no longer than 4 weeks, and samples were small.

Evidence on rubefacients and capsaicin was limited (Table 1). These agents were statistically better than placebo, but clinically unimpressive. The rubefacient result was compromised because 3 trials with adequate quality and validity scores had no statistically significant effect[18]. With capsaicin, 37% of patients benefited, but local adverse events affected almost half[19].

A review of topical NSAID in acute and chronic conditions[15] included salicylates. Updated without salicylates[16], topical NSAID were effective in strains and sprains over one week with an overall number needed to treat (NNT) of 3.8 (3.8 to 4.4) compared with placebo in 26 trials with 2853 patients; local and systemic adverse events were no different from placebo. Ketoprofen was significantly better than other topical NSAID.

An updated systematic review of topical NSAID in chronic musculoskeletal[17] pain produced an overall NNT of 4.6 (3.8 to 5.9) compared with placebo for all NSAID. This analysis included 14 trials with 1502 patients in placebo comparisons, and produced similar results for 5 trials in knee osteoarthritis (OA) as in other musculoskeletal conditions. Only 3 trials compared topical with oral NSAID in patients with OA of the knee or finger joints, where the oral NSAID was 1200 mg ibuprofen or 100 mg diclofenac daily. In these trials with 764 patients there was no statistically significant difference between routes of administration[19].

COMMENT

What we have is a pyramid of evidence. The lowest layer is of laboratory and pharmacokinetic studies supporting skin penetration of NSAID and uptake into blood and high levels in underlying tissue. The middle layer is from systematic reviews of small, less valid short trials that demonstrate better efficacy than placebo, and probably equal efficacy with oral NSAID. The pinnacle is this new trial[1], demonstrating equivalence of topical and oral diclofenac in a large, valid, high quality trial.

Equivalent effect comes with fewer severe gastric adverse events, and lower rates of abnormal hemoglobin, a possible marker for lower bowel blood loss. The challenge now for topical NSAID is to confirm safety and economic benefit, and define the patients for whom they are the best choice.

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Table 1. Systematic reviews of trials of topical analgesics.

Reference	Topical Analgesic	Comparator	Condition	Duration, weeks	No. of Trials	No. of Patients	Successful Treatment, % Analgesic	Successful Treatment, % Comparator	NNT (95% CI)
17	NSAID	Placebo	Chronic MSK	2	14	1502	48	26	4.6 (3.8 to 5.9)
17	NSAID	Oral NSAID	Chronic MSK	2+	3	764	37	37	NA
1	NSAID	Oral NSAID	Knee OA	12	1	622	66	71	NA
18	Salicylate	Placebo	Chronic MSK	2	6	429	54	36	5.3 (3.6 to 12)
19	Capsaicin	Placebo	Chronic MSK	4	3	368	38	25	8.1 (4.6 to 34)

NNT: number needed to treat. CI: confidence interval. MSK: musculoskeletal. NA: not available.

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