

Topical NSAIDs for Musculoskeletal Conditions

A Review Of The Literature

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Abstract

In recent years a growing number of topical nonsteroidal anti-inflammatory drugs (NSAIDs) have become available. This has been prompted in large part by the high incidence of serious gastrointestinal adverse events associated with the use of systemic NSAIDs, and the premise that minimisation of plasma concentrations of active drug may result in fewer systemic adverse effects. Evidence in humans and animals with topical NSAIDs demonstrates lower plasma concentrations than with systemically administered drugs, while those in soft tissues are still of a magnitude considered consistent with exerting an anti-inflammatory effect. In joints, however, the evidence is less strong, and there is still dispute whether in this case the drug reaches the joint predominantly via the transcutaneous or systemic route.

There has been a sufficient number of studies of soft tissue conditions to demonstrate the superiority of topical NSAIDs over placebo and to suggest equivalent efficacy in comparison with some oral NSAIDs. For arthropathies, however,

the literature is more sparse. Although several studies claim a benefit for topical NSAIDs against placebo, the results are less conclusive and further study is required. Trials of topical agents against intra-articular corticosteroids and rubefacients are either lacking or inconclusive. The adverse event profile of topical agents is reasonable: minor cutaneous effects occur in up to 2% of patients but tend to be self-limiting. Gastrointestinal events appear from the existing literature to be infrequent and minor, although long term studies are required. Bronchospasm and renal impairment have been reported and may be more frequent in patients who have experienced these effects with oral agents. The initial costs of topical agents tend to be higher than those of oral agents but a cost-effectiveness analysis suggests an overall benefit: this issue requires further clarification.

The extensive use of prescribed and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) associated with significant adverse effect profiles has prompted the search over recent years for solutions to this problem.^[1-4] Strategies have included attempts to minimise NSAID use by education or legislation, coadministration of other (usually gastroprotective) agents, development of potentially better tolerated drugs such as selective cyclo-oxygenase-2 (COX-2) inhibitors or NSAIDs incorporating nitric oxide, and modification of delivery systems.

The expectation of limiting direct gastric irritation by using topical formulations and thereby avoiding the oral route is appealing, but the question of efficacy looms large.

Inherent to the development of nonsystemic delivery of NSAIDs is the premise that minimisation of plasma concentrations may result in a reduction in serious toxicity. A number of studies note a correlation between salicylate concentrations and hearing loss.^[5,6] A relationship may also exist between plasma concentrations of NSAIDs and upper gastrointestinal bleeding.^[7,8]

In order to review the value of topical NSAIDs, it is helpful to consider mechanisms of action and transport, to examine the relationships between plasma and tissue concentrations in terms of efficacy and adverse reactions, and to assess relative efficacy and adverse reactions compared with other therapeutic options. Availability and cost are also relevant issues for consideration.

1. Pharmacology

1.1 Mechanism of Nonsteroidal Anti-Inflammatory Drugs

The major mechanism of action of NSAIDs is reduction of prostaglandin production by inhibition of COX.^[9] In recent years the relative importance of inducible COX-2 in mediating inflammation via prostaglandin production has been highlighted.^[10] Other postulated mechanisms by which NSAIDs suppress inflammation include inhibition of leucocyte adherence and function, reduction of platelet aggregation, modulation of lymphocyte responsiveness, inhibition of cytokine production and suppression of proteoglycan production in cartilage, amelioration of complement mediated cell-lysis and inhibition of free radical formation.^[11-13] Most NSAIDs are weak organic acids and tend to accumulate in inflamed tissues.^[8,14]

1.2 Principles of Transcutaneous Absorption

A successful topical NSAID requires not only efficacy at the target site but the ability to reach that site, which may involve delivery via the systemic circulation and direct penetration. An important question in determining the potential advantages of topical NSAIDs is whether any clinical effect is achieved by direct transport to the tissue or by systemic absorption and redistribution.

The skin layers through which any drug must be transported are the stratum corneum (being the uppermost layer of dead epidermal cells), viable

epidermis (devoid of blood vessels), the basement membrane and the dermis (containing blood vessels).^[15] Absorption into the systemic circulation or penetration into deeper tissues occurs from this point.^[16] The stratum corneum is largely lipophilic and is best traversed by un-ionised drug,^[15,16] while the viable epidermal layer is predominantly aqueous. Thus, for optimal penetration through both layers, the drug requires both hydrophilic and hydrophobic qualities. Drugs that are either extremely hydrophilic or extremely hydrophobic are poorly absorbed. The role of the molecular size of the compound in absorption is not well defined, but recent work suggests that a direct relationship exists between particle size and penetration.^[17]

Studies in which various NSAIDs have been applied directly to rat dermis, with the major epidermal barrier removed, show almost equal penetration between drugs to deeper tissues,^[16] indicating that most of the variability between drugs in terms of transcutaneous absorption relates to their relative ability to negotiate the superficial layers. A number of substances have been investigated as penetration enhancers, including solvents, lecithin gels, liposomes and submicron emulsions.^[18,19] Submicron emulsions consist of oil droplets in water, which allow incorporation of relatively hydrophobic drugs. Studies in rats show encouraging enhancement of activity of topical NSAIDs when incorporated in submicron emulsions, with acceptable tolerability in humans.^[18]

1.3 Pharmacokinetics of Transcutaneous Administration

1.3.1 Animal Models

The relative contributions of direct penetration versus systemic delivery of topical NSAIDs are the subject of much study in both animal and human models. Direct penetration is thought to occur predominantly to a depth of 3 to 4mm, with a logarithmic reduction of concentration below that level.^[16] In several rat studies of topically applied NSAIDs, the concentration in tissues appeared to peak at 2 to 4 hours and again at 10 hours, thought to reflect direct absorption and systemic delivery peaks,

respectively.^[16,20,21] For salicylic acid applied directly to rat dermis, the later peak was somewhat higher than the earlier peak for all tissues below the dermis except fat. A study in rat dermis assessing relative maximum tissue absorption of aqueous solutions of different NSAIDs showed salicylic acid to have the highest tissue concentration followed by piroxicam, naproxen, indomethacin and diclofenac.^[16] This hierarchy, however, is somewhat artificial because most commercial formulations are not in aqueous form.

Ishihama et al.^[22] undertook a study of indomethacin applied as ointment to guinea pigs. They demonstrated stabilisation of concentrations in skin and superficial muscle after 5 applications, and in deep muscles after 10 twice-daily applications at levels considered consistent with exerting an anti-inflammatory effect.

McNeill et al.^[21] performed a study in rats which had received either intravenous or topical piroxicam over one shoulder to examine tissue concentrations in ipsilateral and contralateral shoulder muscles, in addition to plasma concentrations, at time points up to 48 hours. For intravenous administration, tissue concentrations closely paralleled those in plasma over 16 hours and beyond, producing a relatively constant tissue/plasma (T/P) ratio over this period. For topical administration, T/P ratios were markedly elevated until >6 hours, with gradual stabilisation after that time. For periods of <8 hours, concentrations in ipsilateral muscles were higher than for contralateral muscles or for plasma concentrations achieved with intravenous administration. The authors concluded that the concentration in local tissue could not be explained by systemic delivery alone, and referred to this phenomenon as 'local enhanced topical delivery'.

A comparison of plasma and tissue concentrations in dogs following single doses of radioisotope-labelled oral aspirin or salicylate cream showed that higher local drug concentrations were achieved by topical administration in muscle, tendon, cartilage and synovium and lower concentrations (of the order of 60%) were measured in synovial fluid.^[23] Plasma concentrations at 60 and

120 minutes were less than 1% of those obtained from oral doses.

The effect of topical indomethacin on carrageenin-induced inflammation in rats has been studied.^[24] Inhibition of oedema in the treated paw, but not in the contralateral, untreated paw was observed. Concentration of drug in muscle underlying the site of application was 10 times higher than that in the muscles of the contralateral paw and 7 times higher than that in plasma, after once-daily application for 5 days.

It should be noted that most of the evidence in animals suggesting enhanced topical delivery applies to soft tissues rather than to joints, and this may have implications for the relative efficacy of topical NSAIDs for soft tissue complaints and arthropathies.

1.3.2 Human Models

Peak plasma concentrations of individual NSAIDs vary widely, and plasma elimination half-lives of orally administered NSAIDs vary between 0.5 hours for aspirin and 60 hours for tenoxicam.^[8] Synovial concentrations are more stable than those in plasma.^[8,25] Plasma concentrations achieved via topical delivery are 1 to 10% of those achieved by systemic delivery.^[23,26,27] There is conflicting evidence^[16,27] as to whether local tissue concentrations are higher than can be accounted for by systemic delivery, with the implication that topical preparations may produce similar tissue concentrations with lower plasma concentrations compared with orally delivered forms. Studies of plasma concentrations of topically applied versus orally administered drug generally show very low relative concentrations^[26,28] considered by some to be sub-therapeutic and unlikely to explain efficacy.

A study of diclofenac regularly applied to the hands of 8 arthritic patients for 3 days before surgery demonstrated synovial fluid and synovial tissue concentrations several times greater than that in plasma, at the time of surgery.^[29] The possibility that synovial tissue and fluid concentrations were achieved by systemic redistribution was not discussed in this study. The pattern of urinary excretion appeared to be similar to that of the oral for-

mulation. Although this study is often cited as evidence that topical NSAIDs may penetrate superficial joints well, we are not aware that this work has been confirmed elsewhere.

Taburet and colleagues' study^[26] in humans of twice-daily flurbiprofen patches showed plasma concentrations on the order of 4% of those achieved with oral administration of 50mg of the same drug after single doses, with the topical peak more than 48 hours after application. Repeated 12-hourly application of the topical formulation demonstrated maximum concentrations 2.5 times higher than that of a single topical dose, peaking at day 5. Plasma concentrations between patients showed an up to 10-fold variability. Plasma concentrations continued to rise after removal of a single patch, suggesting that the skin may act as a drug reservoir in this situation. There was no increase in plasma concentration after removal of the patch in this study once steady-state had been achieved. Urinary excretion had ceased in the majority of patients by 60 hours after the removal of the last patch. Similarly, the plasma concentrations of naproxen in 15 healthy volunteers after application of single doses of 5 and 10% gel were examined.^[30] Bioavailabilities of 2 and 1%, respectively, were measured and peak plasma concentrations for both strengths occurred between 24 and 48 hours, again suggesting a role for soft tissue as a reservoir.^[30]

Dawson and coworkers^[31] examined plasma and synovial fluid concentrations of felbinac following topical application in 9 patients with rheumatoid arthritis, and found no statistically significant difference in plasma/synovial concentrations between the treated and untreated knees, concluding that synovial concentrations were achieved via systemic redistribution. In addition, plasma concentrations were considered to be well below that required for a therapeutic effect. Therapeutic effects were not reported in this study.

In 10 patients with inflammatory or degenerative effusions, plasma and synovial fluid concentrations of total and unbound diclofenac, after application to a single knee, were measured.^[27] Concentrations achieved in synovial fluid and plasma

in this study were estimated to be about 20% of the peak observed after a single oral dose of diclofenac 75 to 100mg. The diclofenac knee synovial fluid had a mean total concentration 15% higher than that in the placebo knee, a difference reaching statistical significance, but this difference was not apparent for free drug. Furthermore, plasma versus synovial concentrations for free drug were not significantly different. The authors concluded that the majority of drug reached the joint via the systemic circulation.

Dominkus et al.^[32] examined plasma, subcutis, muscle, fascia and synovial fluid ibuprofen concentrations in patients with degenerative knee disorders undergoing knee surgery, in whom 12 had received 3 days of topical ibuprofen 375mg and 5 had received 3 days of twice-daily oral ibuprofen 600mg. The authors found no significant differences in concentrations in plasma, synovial fluid, fascia and muscle between patients receiving oral versus topical ibuprofen, although mean concentrations were higher for the first 3 regions mentioned. Concentrations in all regions reached or exceeded what is considered the minimum therapeutic concentration.

A study of flurbiprofen reported similar concentrations in subcutaneous fat after administration of topical versus oral flurbiprofen, but lower concentrations in serum, muscle and synovial fluid.^[33] A small study evaluating topical flurbiprofen in patients undergoing arthroscopy showed highest concentrations in skin, with synovial fluid and plasma values being one-fiftieth and one-thousandth of those achieved in skin after 6.5 days of twice-daily application.^[34]

One study examined the relative plasma ibuprofen concentrations achieved by 3 vehicles, namely gel with ibuprofen in aqueous-alcoholic hydrophilic solution, emulsion cream with ibuprofen in the oily phase and hydrophilic ointment.^[35] Gel application resulted in highest and quickest concentrations, and the ointment in lowest and slowest.

A study of diclofenac applied as plaster to the knees of 8 patients with osteoarthritis and effusions showed synovial concentrations after the ninth 12-

hourly application to be 36% of plasma concentrations at the same time.^[36] Although the authors concluded that this result indicated direct transport across the skin to the joint, it seems premature to exclude the possibility that this concentration was achieved by systemic redistribution.

Absorption presumably depends to some extent on the amount applied, surface area, enthusiasm with which the preparation is rubbed in and local factors such as skin thickness and integrity. The extent to which these factors affect absorption has not been well documented.^[37] Certainly, most studies in humans document wide variations in concentrations despite attempts to strictly regulate application regimens, and this may be due in part to differences in application techniques. It has been suggested that the elderly may have increased relative plasma concentrations because of reduced clearance, thin skin and extensive and frequent use.^[38] The development of a fixed-dose patch allows some standardisation of dose.

In summary, there is considerable evidence that substantial concentrations can be achieved in soft tissues with topical application of NSAIDs, but the evidence that such application results in clinically significant synovial fluid concentrations is scant.^[39]

2. Efficacy

2.1 Soft Tissue Conditions

2.1.1 Trials Against Placebo

The results of randomised, double-blind studies investigating the response of patients with soft tissue complaints are presented in table I. It should be noted that the table summarises results in terms of statistically significant differences at final review only. In many cases nonsignificant trends were evident, usually in favour of the active agents. In addition, benefits evident early on in treatment had sometimes disappeared at last review. Potentially important results evident at intermediate time points are noted below.

The disappearance of treatment differences with longer follow-up reflects the natural history of many soft tissue conditions. Similarly, the pla-

Table I. Double-blind trials of topical nonsteroidal anti-inflammatory drugs (NSAIDs) vs topical placebo for soft-tissue conditions. When the trial also involved an oral agent, only the results relating to the topical agent and placebo are shown

Reference	No. of patients	Condition	NSAID	Formulation	Dosage of active drug	Duration of treatment (days)	Result ^a				% of adverse reactions (% of adverse reactions causing withdrawal)	
							pain	function	overall assessment		agent	placebo
									patient	physician		
Airaksinen et al. ^[52]	56	Acute soft-tissue injury	Ketoprofen	2.5% gel	125mg bd	7	ND	ND	Ketoprofen	NA	17 (?)	15 (?)
Akermark & Forsskah ^[53]	70	Acute soft-tissue injury	Indomethacin	1% spray	5-15mg 3-5 times/day	14	ND	NA	ND	ND	38 (5)	0 (0)
Campbell & Dunn ^[42]	51	Acute ankle sprain	Ibuprofen	5% gel	Variable	Variable, 7-14	ND	ND	NA	NA	2	?
Diebschlag et al. ^[43]	25	Acute ankle sprain	Ketorolac	2% gel	60mg tid	14	Ketorolac	NA	NA	NA	15 (0)	0 (0)
Dreiser et al. ^[40]	131	Acute ankle sprain	Flurbiprofen	40mg patch	40mg bd	7	Flurbiprofen	ND	ND	ND	3 (0)	0 (0)
Dreiser et al. ^[41]	60	Acute ankle sprain	Niflumic acid	2.5% gel	375mg tid	7	Niflumic acid	Niflumic acid	ND	Niflumic acid	0	10
Dreiser et al. ^[47]	59	Tendinitis	Niflumic acid	2.5% gel	12.5g tid	7	Niflumic acid	Niflumic acid	Niflumic acid	Niflumic acid	7 (0)	0 (0)
Ginsberg & Famaey ^[46]	30	Periarthritis or tendinitis	Indomethacin	4% spray	5mg 3-5 times/day	14	Indomethacin	Indomethacin	NA	NA	7 (0)	0 (0)
Mattara et al. ^[45]	80	Scapulohumeral periarthritis	Flurbiprofen	40mg patch	40mg bd	14	ND	ND	ND	ND	20 (0)	8 (0)
McLatchie et al. ^[49]	231	Acute soft-tissue injury	Felbinac	3% gel	? tid	7	Felbinac	NA	Felbinac	Felbinac	2.5 (0)	1.8 (0)
Poul et al. ^[48]	104	Soft tissue complaint	Flurbiprofen	40mg patch	40mg bd	14	ND	NA	ND	Flurbiprofen	15 (4)	3 (2)
Russell ^[50]	200	Sprain or tendinitis	Piroxicam	0.5% gel	5mg qid	7-21	Piroxicam ^{b,c}	Piroxicam ^b	Piroxicam ^b	NA	7 (1)	15 (8)
Thorling et al. ^[51]	120	Acute soft-tissue injury	Naproxen	10% gel	? 2-6/day	7	Naproxen	Naproxen	Naproxen	ND	2 (0)	0 (0)

a Statistically significant (p < 0.05) benefit at last measurement.

b Statistically significant (p < 0.05) benefit at day 8, when most data were available.

c Only in the tendinitis group.

bd = twice daily; **NA** = not assessed; **ND** = no difference; **qid** = 4 times daily; **tid** = 3 times daily; **?** = unknown.

cebo response associated with topical treatment in these conditions is in some cases up to 60 to 80%, considerably higher than that observed with other routes of administration. The natural history of healing of most soft tissue injuries may account for most of this response. In some cases the placebo patches contain menthol and the cooling action or odour of this may influence the response. It has been suggested that the concept of applying treatment to the area that actually hurts may contribute to this significant effect. The rubbing of the affected area may itself increase local blood flow and speed healing.

Acute Ankle Injuries

Dreiser et al.^[40] investigated 131 Caucasian patients with acute ankle strain, comparing flurbiprofen 40mg versus placebo patch (both containing menthol) over 7 days in a randomised, double-blind study. Efficacy criteria were visual analogue scale (VAS) pain at 3 and 7 days, and physician assessment of periarticular oedema, pain at rest/active tension/passive tension/palpation, functional and weight-bearing capacity and overall physician and patient evaluation. Tolerability was assessed by patient and physician on a 4-point scale. At day 7, statistically significant differences were noted between flurbiprofen and placebo groups with regard to spontaneous pain and periarticular oedema only. No differences were noted at 3 days. Supplementary analgesia requirement was not different between groups. Two mild cutaneous adverse reactions were reported in the active group.

Another study by the same first author compared 2.5% niflumic acid gel with placebo, 3 times daily for 7 days, in a randomised, double-blind trial in 60 patients with acute ankle sprain.^[41] Assessments were made at 4 and 8 days with reference to VAS pain scales, physician assessment in terms of pain at rest, pain on passive movement, pain on palpation, pain on passive isometric contraction and degree of functional disability, ankle swelling, and physician and patient global assessment. VAS scores were statistically different, favouring niflumic acid, at day 8 but not at day 4. At day 8 significant benefits for niflumic acid were demonstrated

for pain on palpation and functional disability, with trends for the other physician-measured parameters except swelling, for which there was no difference. Physician global assessment favouring niflumic acid was significant at day 4 but not at day 8; patient global assessment showed significant benefit at both times.

Campbell and Dunn^[42] examined diaries returned by patients presenting to an emergency department with acute ankle sprains, and treated with either topical ibuprofen 5% or topical placebo. Diaries were returned after 1 week by 51 of 100 patients invited to participate, and by a further 25% after 2 weeks. Outcomes were visual analogue scores regarding pain at rest, standing and walking, indices regarding walking ability and use of rescue medications. Combined VAS scores showed a significant benefit for ibuprofen at days 2 and 3 only. No other outcomes at week 1 or week 2 demonstrated a benefit.

In a trial designed to study the effect of ketorolac gel versus placebo gel and etofenamate gel on ankle sprain in a randomised, double-blind trial involving 37 patients over 14 days, after 7 and 14 days all patients had relief of rest pain.^[43] However, after 4 days the improvement in pain was significantly higher for ketorolac than for etofenamate or for placebo. Pain on movement was also significantly improved in patients receiving ketorolac compared with both other groups on days 4 and 8. Overall night pain was reduced in the ketorolac group compared with placebo. Ankle volume, presumably reflecting swelling, was measured using a water displacement method. Ankle volume decreases in both active groups were significantly different compared with placebo at 14 days, but were similar between the active groups.

Upper Limb Soft Tissue Complaints

Schapira et al.^[44] assessed the response of 32 patients with lateral epicondylitis to topical diclofenac of unspecified strength or placebo. They found a statistically significant association of diclofenac use with decreased pain on forced dorsiflexion, using regression analysis, after 14 days of 4-times-daily application. Conventional statistical compar-

isons of differences between placebo and diclofenac were not reported.

Flurbiprofen 40mg patches were compared with placebo (both mentholated) over 14 days in 80 patients with scapulohumeral periarthritis in a randomised, double-blind study.^[45] Pain, shoulder movements, interference with activity and with sleep, patient acceptability and overall assessment were measured. No significant difference was demonstrated between groups at the end of the trial, although trends favouring flurbiprofen in improvement in pain and function were noted, particularly during the first days of the study.

Ginsberg and Famaey^[46] compared 4% indomethacin spray with placebo in a double-blind, crossover study in 30 patients, 28 with shoulder periarthritis and 2 with epicondylitis. Indomethacin was superior in terms of pain and movement indices at 14-day assessment.

Heterogeneous Complaints

Dreiser et al.^[47] performed a second randomised, double-blind study with niflumic acid, examining the effect of 2.5% gel 3 times daily versus placebo over 7 days on 59 patients with recent onset upper or lower limb tendinitis. Niflumic acid demonstrated superiority in terms of VAS pain scores, functional improvement, and both physician and patient global assessment.

Flurbiprofen and placebo patches were compared in 104 patients with a variety of soft tissue complaints in a randomised, double-blind trial.^[48] The authors reported a statistically significant improvement at 14 days for physician overall assessment for flurbiprofen patients, but at the same time did not find significant differences for patient overall assessment, physician pain assessment, physician tenderness assessment, overall change in condition, night pain, day pain, sleep or paracetamol (acetaminophen) consumption. Reduction of pain at day 7 in the active group was of borderline significance. Patients receiving active treatment were less likely to require corticosteroid injections following the completion of the trial.

McLatchie et al.^[49] compared felbinac gel with placebo in a randomised, double-blind trial in 384

patients with acute soft tissue injuries and showed superiority of felbinac in most parameters measured. The difference was most evident at day 4 and decreased in significance at day 7.

Topical 0.5% piroxicam gel and placebo were compared in a 7 to 21 day randomised, double-blind trial in 200 patients with acute soft tissue injuries (Achilles or supraspinatus tendinitis, and ankle and acromioclavicular sprains).^[50] The author reported a superiority of piroxicam for pain, tenderness and increased freedom of movement. There was more rapid improvement in the piroxicam group, but no increase in adverse events. Analysis by subgroup of diagnosis showed the improvement in pain difference to persist only in the tendinitis group and not in the strain group.

Thorling et al.^[51] studied 120 patients with acute soft tissue injuries to compare naproxen 10% with placebo in a randomised, double-blind trial. The dosage was variable according to the need perceived by the patients. Statistically significant differences were shown in favour of naproxen for pain, tenderness, swelling, limitation of use and patient overall assessment, but not for blinded physician estimation of response or efficacy. Later, Airaksinen et al.^[52] studied 56 patients with a variety of acute soft tissue injuries in a randomised, double-blind trial to compare ketoprofen 2.5% gel twice daily for 7 days with placebo. Contrary to the results reported by Thorling et al.,^[51] in the Airaksinen et al.^[52] study comparison of pain at rest, pain threshold and function data between ketoprofen and control groups showed no significant differences, although trends for more improvement with active agent were apparent. Placebo patients were more likely to report no improvement, but did not use more rescue paracetamol.

Indomethacin 1% spray was tested against indomethacin capsules and placebo in 70 athletes with subacute or acute soft tissue injuries in a randomised, double-blind study design.^[53] All patients received spray and capsules, either or both of which might have been placebo. There were no significant differences between groups at the end of 14 days, although topical indomethacin patients re-

ported significantly greater improvement in patient global assessment and pain at 1 week, compared with placebo.

Grahame et al.^[54] performed a meta-analysis of 4 trials evaluating topical flurbiprofen against placebo in 507 patients with soft tissue rheumatism. A statistically significant difference was demonstrated for improvement in clinical condition but not for improvement in pain.

A quantitative review of trials of topical NSAIDs against placebo, in the form of a meta-analysis, assessed adequately designed trials examining pain as the major outcome. This work suggested that for acute soft tissues condition, the use of an active agent conveyed a treatment benefit of 1.7 (95% CI 1.5-1.9) in reduction of pain by at least 50%. The authors calculated that the number needed to treat, that is, the number of patients who would need to be given treatment for one to improve who would not have done so with placebo, was 3.9 (95% CI 3.4-4.4). For chronic conditions, assessed together as joint and soft tissue complaints, a benefit of 2.0 (1.5-2.7) was calculated, with the number needed to treat being 3.1 (2.7-3.8). Unfortunately, chronic joint problems and chronic soft tissue problems were not assessed separately.^[55]

In summary, there is a large body of evidence to support efficacy of topical NSAIDs in a variety of soft tissue complaints although improvement was consistently noted in patients treated with placebo as well. Topical agents may therefore hasten resolution of symptoms without affecting long term outcome.

2.1.2 Trials Against Oral Formulations

The randomised double-blind study by Akermark and Forsskahl^[53], as discussed above, did not show differences between topical indomethacin and oral indomethacin at 7 or 14 days in 70 athletes with overuse injuries.

While 2 unpublished trials^[56,57] of felbinac versus ibuprofen in acute neck sprain and mild to moderate osteoarthritis of the knee are reported to have shown equivalence of these preparations, Tsuyama et al.^[58] compared topical felbinac with

oral fenbufen in 275 patients with osteoarthritis of the knee using a double-dummy, double-blind format, over 2 weeks. No differences were found in overall improvement after 1 or 2 weeks. Although adverse reaction rates for each drug were similar (11 to 12%), the authors felt almost all adverse reactions in the topical group were unrelated to the drug. They concluded that the topical formulation was as effective as, and better tolerated than, an oral NSAID for osteoarthritis of the knee, although their conclusions may be considered subjective in some respects.

Diebschlag et al.,^[43] found differences between ketorolac gel and etofenamate gel in terms of pain but not in terms of ankle swelling reduction in acute ankle sprains.

Vanderstraeten and Schuermans^[59] compared etofenamate gel with oral naproxen in a randomised trial (with unknown blinding) in 60 patients with acute sports-related soft tissue injuries. The authors found no significant differences in terms of pain or physician assessment between the 2 groups.

2.1.3 Trials Against Corticosteroids

A matched, double-blinded study reported in abstract form compared intra-articular triamcinolone with topical felbinac for acute rotator cuff tendinitis.^[60] The authors reported improvements in all parameters measured compared with baseline for both groups. Triamcinolone injection provided a greater benefit than felbinac in terms of resolution of painful arc, pain score and patient assessment, but no difference between groups was measured for pain on resisted movements, range of active abduction and thermographic index.

Duteil et al.^[61] performed a study assessing the effect of several topical NSAIDs, topical corticosteroids and topical placebo on methyl-nicotinate-induced skin inflammation in 16 healthy male volunteers. The outcome measure was degree of skin inflammation as measured by increase in skin blood flow using laser-Doppler probes. Topical NSAIDs, and in particular diclofenac and indomethacin, were better at inhibiting skin inflammation than corticosteroids, which were better than placebo.

2.1.4 Trials Against Rubefacients

There are few, if any, data regarding the comparative efficacy of topical NSAIDs against topical rubefacients.^[62,63]

2.1.5 Trials Against Other Topical Agents

A randomised, observer-blinded study of diclofenac gel versus felbinac gel in 384 patients (predominantly men) with acute soft tissue injuries assessed rest pain, pain on pressure, bruising, degree of recovery, use of rescue analgesia and daily pain concentrations over 7 days.^[64] Trends for superiority of diclofenac existed for all measures except end-point bruising, but statistical significance was only reached for rest pain and bruising at day 3, and pain on pressure at day 7.

An open, crossover study of flurbiprofen 40mg patch twice daily against piroxicam gel 0.9g 4 times daily was performed in 137 patients with shoulder and elbow soft tissue complaints.^[65] Each agent was given for 4 days, followed by 6 days of the treatment preferred by the patient. The authors reported superiority of flurbiprofen in terms of pain, tenderness and overall condition as assessed by patient and physician. Significantly more patients (69 versus 31%) chose to continue flurbiprofen compared with piroxicam. Adverse reactions were similar (9 versus 7%, respectively).

Zerbi et al.^[66] compared ketoprofen foam, ketoprofen gel and placebo foam in a single-blind trial in 154 acute soft-tissue injuries. Both active formulations were superior to placebo in terms of pain and mobility at 1 week. There were no significant differences between the active agents, although the trend was in favour of gel compared with foam for all measurements.

2.2 Arthropathies

2.2.1 Trials Against Placebo

There have been, to date, few trials comparing topical NSAIDs with placebo for arthritis rather than soft tissue conditions.

Radermacher et al.^[27] performed a double-blind, randomised, placebo-controlled trial comparing diclofenac gel with placebo gel for patients with an inflammatory arthropathy of both knees, using a

different agent on each knee. The principal purpose of the study was to examine relative synovial fluid and plasma concentrations (discussed in section 1.3.2) but as a secondary exercise, knee flexion and knee circumference were measured. There was no significant difference between knees for improvements in clinical parameters, although the trend appeared to be for the placebo knee to be more improved.

Dreiser et al.^[67] performed a randomised, double-blind trial comparing diclofenac plaster with placebo plaster in 155 patients with osteoarthritis of the knee, over 15 days. Diclofenac was superior to placebo in terms of visual analogue pain scales, patient and physician global assessment, night awakenings and need for rescue analgesia. Tolerability between groups was similar.

Kageyama^[68] assessed 0.5% piroxicam gel used 3 to 4 times daily compared with placebo in 246 patients with osteoarthritis of the knee in a multicentre, randomised, double-blind study. Although the data were reported only in abstract form, piroxicam appeared to be superior in terms of patient and physician overall assessment. Of the 28% of patients with bilateral involvement, the untreated knee improved less overall than the treated knee for both active agent (31 versus 80%) and placebo (26% versus 66%) groups.

Roth^[69] examined regular use of 3% diclofenac/2.5% hyaluronic acid (sodium hyaluronate) gel versus placebo gel in 59 osteoarthritis patients on long term oral NSAIDs. Treatment was randomly allocated but the degree of blinding was not clear. Change in patient pain assessment from baseline to 2 weeks tended to favour diclofenac and approached statistical significance ($p = 0.057$). No difference was demonstrated in physician assessment. Pruritis and rash were reported in up to 25% (placebo) and 12% (active) of patients. The authors concluded that topical NSAIDs may be a useful alternative to increasing oral NSAID use in patients with osteoarthritis who might be using these drugs on a long term basis.

Shackel et al.^[70] performed a randomised, double-blind trial comparing copper-salicylate gel

and placebo gel, both containing methanol, camphor and eucalyptus oil and applied twice daily for 4 weeks, in 116 patients with osteoarthritis of the hip or knee. The gel was applied to the distal forearm in all patients, as the authors wished to assess its systemic effect on distant joints. A large number of withdrawals (20% overall) were predominantly due to adverse cutaneous reactions in the active group. No significant difference was found in pain scores, physician and patient global assessment or use of rescue paracetamol. The authors concluded that use of copper-salicylate gel was not of major benefit in osteoarthritis of the hip and knee when used in this manner but acknowledged that topical use close to the site of pain might have produced a different result.

Trolamine (trolamine salicylate) cream was compared with placebo in a randomised, double-blind, crossover trial in 26 patients with osteoarthritis of the knee, using each agent for 1 week.^[71] The authors found no difference in terms of pain, overall assessment of physician or patient, joint tenderness or movement, but did find a statistically significant benefit in terms of swelling for placebo. No English language studies specifically related to the use of topical NSAIDs in osteoarthritis of the hands were found.

In summary, the data in arthropathies are much less convincing than in soft tissue complaints. Some studies support efficacy in osteoarthritis of the knee but this has not been demonstrated consistently.

2.2.2 Trials Against Oral Agents

Sandelin et al.^[72] compared 1% eltenac gel with placebo and with oral diclofenac in 290 patients with osteoarthritis of the knee in a randomised, double-blind, multicentre trial. Main end-points were visual analogue pain score and Lequesne's index (a composite index measuring pain and function) at 2, 3 and 4 weeks. There was no difference between the 3 groups in these indices in the overall assessment. Subgroup analysis did show both eltenac and diclofenac to be superior to placebo in patients with pain scores above the median. Response in this group appeared to be similar for

oral and topical agents, suggesting a role for the topical agent as an alternative therapy to systemic NSAIDs in this group.

2.2.3 Trials Against Other Topical Agents

Giacovazzo^[73] compared felbinac gel against diclofenac gel in 40 elderly patients with osteoarthritis of the lumbar spine, cervical spine, knees and osteoarthritis. Allocation was random but it is not clear whether patients or the assessor were blinded. No placebo group was included. Results were assessed using a single VAS for pain. Diminution of pain of the order of 70% compared with baseline was reported after 1 week of therapy. The author claimed that there were no significant differences between groups, although the significance level quoted was ' $p < 0.085$ ', and insufficient detail was provided to re-analyse the data.

Arendt-Nielsen et al.^[74] compared ibuprofen cream against placebo on the hands of 11 patients with rheumatoid arthritis. Active cream was applied 3 times daily to a single 'test' joint (metacarpophalangeal joint [MCP] or proximal interphalangeal joint [PIP]) of the left hand and placebo cream to the right. Pain outcomes were measured using an electronic pressure algometer and by a VAS scale following a series of standardised hand movements. A significant benefit was found at 7 days with the active gel for pressure pain tolerance threshold but not for pressure pain detection threshold or visual analogue pain scales. The standardised system of application of active cream or ointment raises some questions about the blinding of the observers.

Doogan reports (in brief letter form) equivalence of ibuprofen gel and piroxicam gel in 235 patients with osteoarthritis of the knee.^[28]

Sandelin and colleagues' work, mentioned above, found similar improvement with topical eltenac and oral diclofenac in a subgroup of osteoarthritis patients with worse baseline pain scores.^[72]

Doogan et al.^[28] compared piroxicam gel and oral ibuprofen in 235 osteoarthritis patients in a double-blinded manner, and found no significant difference in overall rating of effectiveness.

3. Adverse Reactions

Potential adverse reactions can be divided into cutaneous reactions and systemic reactions. The former tend to be mild, and the more pressing issue is whether systemic reactions are reduced by limiting plasma concentrations. Relationships probably exist between plasma concentrations of salicylate and ototoxicity^[5,6,8] and upper gastrointestinal bleeding^[7,8] but in general, data establishing a correlation of plasma concentrations with adverse reactions tend to be sparse.

3.1 Cutaneous

Cutaneous adverse reactions occur in 1 to 2% of patients^[54,75] with erythema, pruritis, irritation, sensation of heat or burning and contact dermatitis being most commonly reported.^[44,76] Pigatto et al.^[76] studied 102 patients with topical NSAID allergic contact dermatitis. 86 patients were sensitised to a single agent, 13 were sensitised to more than 1 agent and 3 patients were sensitised to previously administered systemic NSAIDs. Ketoprofen was the most common culprit in the series, although 15 different NSAIDs had been implicated. A number of patients were sensitised to the nonactive components of the formulation. Aryl-propionic derivatives (including ketoprofen, naproxen, ibuprofen and flurbiprofen) may be more likely to cause (photo)contact dermatitis than other classes of NSAIDs.^[76]

The relative incidence of cutaneous interactions between different formulations is not well established. However, there is some work to suggest that foam preparations are less irritating than gel, possibly because of their lower alcohol content.^[76] The high number of reports of irritation with placebo gels suggests that much of the problem may be with the vehicle rather than the NSAID component of the formulation.

3.2 General

Asthma,^[77] acute renal impairment and dyspepsia have all been reported.^[38,78] Renal impairment may be early, abrupt, severe and irreversible,

and may be more likely in patients who have previously demonstrated renal intolerance to oral formulations.^[78] Similarly, bronchospasm may be more likely in patients who have experienced this effect with oral preparations.^[79] We are unaware of any reports of ototoxicity in association with topical NSAIDs, with the relationship between ototoxicity and plasma concentrations of drug (at least for salicylate) somewhat better defined than for other adverse reactions.^[5,6] The much lower concentrations achieved with topical administration are theoretically likely to reduce the risk of interaction with other medications such as warfarin.

Many studies involving NSAIDs exclude patients at higher risk of adverse effects, e.g. the elderly and those with a history of peptic ulcer disease. However, a postmarketing surveillance study of felbinac involving 23 590 patients showed an incidence of adverse events of 1.5%, mostly cutaneous, with an incidence of gastrointestinal effects of 0.1% (all nonserious). These figures are similar to those reported in controlled trials.^[79,80]

A review of integrated trial data of 2086 patients exposed to flurbiprofen patches reported 6% adverse reactions, predominantly nonserious dermal reactions.^[81] This work states that postmarketing surveillance data in Japan show a similar incidence in nontrial patients. A Spanish study based on spontaneous reporting of adverse reactions to topical NSAIDs in 98 patients^[2] noted one gastrointestinal haemorrhage in a patient also using an oral formulation. Two patients reported dyspnoea. 95% of adverse reactions were local.

The incidence of adverse reactions related to previous sensitisation with oral agents, or vice versa, is not known.

3.3 Gastrointestinal

One of the most appealing prospects of the reduction of plasma concentrations by the use of topical NSAIDs is the possibility of reducing often life-threatening adverse gastrointestinal events, compared with the incidence found with systemic formulations.

Wynne and Rawlins^[7] performed a case-control study comparing plasma piroxicam concentrations in patients who had, and had not, experienced gastrointestinal haemorrhages. They found a significantly higher plasma concentration (8.27 versus 5.06 µg/L, respectively) in bleeding patients, giving support to the concept that plasma concentrations may be important in determining risk of gastrointestinal haemorrhage. A case control study^[82] of patients admitted to hospital for gastrointestinal haemorrhage or perforation using hospital and community controls did not demonstrate an increased risk for gastrointestinal haemorrhage in patients using topical NSAIDs when adjustments were made for concomitant use of oral anti-inflammatories and antiulcer drugs. However, there have been a number of reports of adverse gastrointestinal events with topical indomethacin,^[53] diclofenac,^[82] ibuprofen,^[81,82] flurbiprofen,^[81] ketoprofen,^[82] piroxicam^[2,50] and felbinac^[82] occurring in frequencies of 2 to 9%. Nausea, abdominal pain and heartburn are the most commonly reported adverse gastrointestinal events.

4. Availability and Economics

4.1 Available Formulations

Available formulations of topical NSAIDs are shown in table II. Formulations consist of both hydrophilic and lipophilic phases to facilitate transport across the epidermis.^[83]

4.2 Economic Issues

There are a number of methods of cost comparison between topical and oral NSAIDs. Studies comparing direct cost tend to highlight the high initial cost of the topical formulations. They may incorporate the costs of managing adverse effects into the overall costs of each formulation. In the US, the cost of treating the gastrointestinal adverse effects of NSAIDs has been estimated at 30% of the total cost of treating arthritis,^[84] although this figure has been put as high as 95% in the UK.^[85]

Peacock and Rapier^[85] performed a cost-effectiveness analysis in the UK comparing topical fel-

Table II. Available formulations of topical nonsteroidal anti-inflammatory drugs (NSAIDs)

Ointment	Indomethacin
Cream	Diclofenac, ibuprofen, benzydamine, salicylic acid
Spray	Indomethacin
Patch/plaster	Flurbiprofen, diclofenac
Gel	Piroxicam, diclofenac, felbinac, ketoprofen, indomethacin, ibuprofen, salicylic acid, eltenac
Drops	Ketorolac, flurbiprofen, suprofen, diclofenac
Foam	Ketoprofen, felbinac

binac, oral ibuprofen and an oral diclofenac-misoprostol combination, taking into consideration direct drug costs, 'shadow costs' of treating peptic ulcer and total costs. The study assumed equal efficacy and an incidence of 0.1% of nonserious gastrointestinal problems requiring only ambulatory care for felbinac.^[79] The authors concluded that the total costs using felbinac were 40% of the total costs of diclofenac-misoprostol, and 12 to 18% of the costs of ibuprofen. At this stage, other studies comparing topical versus oral NSAIDs in this manner are not available, possibly because large, long term studies of adverse reactions to topical NSAIDs are still awaited.

The degree to which the cost of these preparations is covered by public insurance programmes varies between countries, but in most circumstances the brunt of the cost is borne by the patient. In general terms, topical agents tend to be substantially more expensive for each course of therapy compared with oral agents.

5. Other Uses

A role that has been suggested for topical NSAID formulations, in particular gels, is to replace inert gels commonly used during therapeutic ultrasound, with encouraging initial results.^[86,87] Koay^[88] recently reviewed the extensive literature regarding use of topical NSAIDs in ophthalmology, where roles exist in the reduction of post-operative inflammation, intraoperative miosis and symptoms of allergic conjunctivitis, and for analgesia. Topical NSAIDs have particular appeal in ophthalmic use as an alternative to corticosteroids,

which may raise intraocular pressure, exacerbate some infective conditions and retard healing. Roles for topical NSAIDs are also being investigated for postoperative pain,^[89] prevention of thrombophlebitis in peripheral cannulation,^[17] periodontal disease,^[90,91] herpetic neuralgia^[75], human pain models^[92] and burn injuries.^[93,94]

6. Conclusions

Many NSAIDs are now available in a topical formulation, but few have been accepted as fundable by government health plans. Although controversy persists, there is reasonable evidence that topically applied NSAIDs exert their effect at least to some extent by direct penetration to underlying tissues. Plasma concentrations are consistently a small fraction of those achieved by oral administration, for both single and repeated doses. Tissue concentrations in most cases are consistent with those considered necessary to produce an anti-inflammatory effect.

Most controlled trials have compared topical formulations with topical vehicle as placebo in cases of soft tissue injury, and there is moderate evidence for benefit in many cases. The stronger-than-usual placebo response in this circumstance may have contributed to this general lack of powerful evidence for benefit, and the natural resolution of most soft tissue complaints is also of relevance. There are relatively few trials at this stage supporting efficacy in arthritis, as opposed to soft tissue injury. Controlled trials against oral formulations tend to show clinical equivalence. A single trial against local corticosteroid in soft tissue shoulder conditions showed greater improvement in some parameters for steroid but equivalence in other respects. Trials between different topical NSAIDs are infrequent. No adequate trials were found comparing topical NSAIDs with other local treatments such as strapping, ice or rubefacient agents such as menthol.

A German pharmacoutilisation study has demonstrated that of 526 patients using systemic NSAIDs, 42% were also using a topical agent, and that this pattern was more likely in older patients.^[95] Follow-up did not show a relationship be-

tween topical use and use of systemic agents over the following year. Although the main driving force for the development of topical agents has been the potential avoidance of adverse reactions associated with systemic agents, this work suggests that topical agents may be being used as adjunctive rather than as replacement therapy.

Adverse reactions most commonly involve cutaneous irritation, in 2% of patients. The rate of systemic adverse reactions, in particular gastrointestinal events, is not well defined, but it is clear that reactions such as gastric irritation, asthma and renal impairment, well established complications of oral therapy, still occur with topical agents. The systematic exclusion of patients at higher risk for adverse reactions from clinical trials may mask the true likely incidence in the general population. It seems reasonable, however, to expect that the incidence of such events may be lower in line with the much lower plasma concentrations achieved by topical agents compared with oral formulations.

In summary, evidence for a role for topical NSAIDs in acute and subacute soft tissue injuries is accumulating, but trials over longer periods will help to define the realistic extent of their value. In the absence of much evidence with regard to relative benefit and toxicity within the group, availability and cost issues are likely to form the basis for such decisions. A clear role for topical NSAIDs has yet to be defined for arthropathies, with a paucity of evidence to support local enhanced topical delivery in this circumstance, and a relative lack of data demonstrating clinical benefit. Cutaneous adverse reactions tend to be infrequent and minor. Long term data regarding adverse reactions are still awaited, but it appears likely that the lower plasma concentrations achieved with topical administration are likely to be associated with reductions in serious systemic adverse effects.

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