



quantities into the systemic circulation; bioavailability and maximal plasma NSAID concentration after topical application are generally less than 5 and 15%, respectively, compared with equivalent oral administration. Product formulation may have a dramatic impact, not only on absorption rates but also on penetration depth.

Compared with oral administration, topical application leads to relatively high NSAID concentrations in the dermis. Concentrations achieved in the muscle tissue below the site of application are variable, but are at least equivalent to that obtained with oral administration. NSAIDs applied topically do reach the synovial fluid, but the extent and mechanism (topical penetration versus distribution via the systemic circulation) remain to be determined. In addition, marked interindividual variability was noted in all studies; percutaneous absorption may be strongly influenced by individual skin properties.

In general, interpretation of clinical studies measuring efficacy of topical NSAIDs in rheumatic disease states is difficult because of a remarkably high placebo response rate, use of rescue paracetamol (acetaminophen), and significant variability in percutaneous absorption and response rates between patients.

Overall efficacy rates attributable to topical NSAIDs in patients with rheumatic disorders ranged from 18 to 92% of treated patients. Topically applied NSAIDs have a superior safety profile to oral formulations. Adverse effects secondary to topical NSAID application occur in approximately 10 to 15% of

patients and are primarily cutaneous in nature (rash and pruritus at site of application). GI adverse drug reactions are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs. Available clinical studies suggest, but do not document, equivalent efficacy of topical over oral NSAIDs in rheumatic diseases.

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**Background**

Rationale for the Use of Topical Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The concept of transdermal application of nonsteroidal anti-inflammatory drugs (NSAIDs) is not new. Phenylbutazone cream was utilised over 30 years ago to treat superficial thrombophlebitis.[1] The renewed interest in topical delivery of NSAIDs for patients with rheumatic diseases stems from the potential advantages of transdermal administration.

In theory, an NSAID applied topically could achieve therapeutic concentrations in the tissues subjacent to the site of application while maintaining low serum concentrations. This could provide numerous potential benefits to patients, including avoidance of gastrointestinal (GI) tract and first-pass metabolism, as well as reduced risk of serious adverse events related to elevated serum NSAID concentrations. Avoidance of the GI tract should mitigate the common direct toxicities of nausea, vomiting, dyspepsia and diarrhoea which occur secondary to

high local concentrations of NSAID in the alimentary tract.

NSAID-mediated toxicity is often dose related. Thus, reduction in serum concentrations should also lessen the risk of potentially serious systemic adverse effects secondary to NSAID-induced prostaglandin inhibition: acute renal insufficiency, nephrotic syndrome, NSAID gastropathy, prolonged bleeding time, and fluid retention. Finally, topical application should mitigate the risk of drug-drug interactions, such as NSAID-mediated protein binding displacement of warfarin.

In 1980, benzydamine was the first topical NSAID to be licensed in the UK.[2] Since that time, several other topical NSAIDs have been licensed in Europe, Japan and South Africa for the treatment of rheumatic diseases, and some of these transcutaneous formulations are currently available without a prescription.[1,2]

The use of topical NSAIDs for acute musculoskeletal conditions has been reviewed extensively;[3,4] this review will therefore focus exclusively on the efficacy and safety of topical NSAIDs in chronic rheumatic diseases, including osteoarthritis, bursitis, tendinitis and epicondylitis. Unfortunately, no clinical trials have assessed the effectiveness of topically applied NSAIDs in rheumatoid arthritis, even though it has a prevalence rate of 1% in the adult population and oral NSAIDs are a mainstay of therapy.[5]

Overview of Rheumatic Diseases

The appellation 'rheumatic disease' is an umbrella term encompassing a remarkably broad range of disorders characterised by varying degrees of inflammation, tissue damage and loss of function.[6] The inflammatory process is a normal response to tissue insult. However, in chronic disease states such as rheumatic disorders inflammation itself can fuel progressive disease manifestations.[7] This review will focus primarily on investigations in patients with osteoarthritis (OA) and regional rheumatic pain syndromes such as bursitis, tendinitis, tenosynovitis and epicondylitis.

OA is one of the most common rheumatic disorders. This chronic, painful disease state is estimated to affect 15.8 million adults in the United States alone,[8] and is the principal source of pain and disability in the elderly.[9] OA is characterised by degeneration and loss of articular cartilage, manifesting as joint pain, stiffness and limitation of movement.[8] Regional rheumatic pain syndromes are classified as painful, inflammatory processes occurring in muscles, tendons, joints, cartilage, ligaments, fascia, bone and nerve tissues.[10]

First-line treatment of localised rheumatic pain and joint stiffness generally consists of oral paracetamol (acetaminophen) and/or topical counterirritants, such as capsaicin.[7,8,10,11] NSAIDs are effective,[8] but are generally considered second-line therapy because of their adverse effect profile.[12,13] As mentioned earlier, adverse effects secondary to NSAID use include GI tract, renal, cutaneous, CNS,

hepatic and haematopoietic system toxicities.[7]

#### Mechanism of Action of NSAIDs

The primary mechanism of action of NSAIDs is reversible inhibition of the cyclo-oxygenase (COX) enzyme responsible for synthesis of prostaglandins, which are mediators of the inflammatory process.[14] The relative potency of COX inhibition by various NSAIDs in vitro tends to be proportional to their anti-inflammatory potency in vivo.[15] The mode of COX inhibition by NSAIDs is complex and varies considerably between agents in this class.[16]

#### Objective Criteria for Topical Administration

In order to confirm the validity of the postulate that topical NSAID administration is superior to the oral route, the following basic criteria should be met:[2]

- \* therapeutic concentrations of NSAID must be achieved in the target tissues
- \* efficacy must be demonstrated in well-designed clinical trials
- \* the risk for serious adverse events secondary to topical NSAID therapy must be less than that of oral treatment,
- \* topical administration of NSAIDs must be cost effective.

This review will attempt to address all of these criteria as they apply to the treatment of rheumatic diseases.

#### Absorption and Distribution of Topically Administered NSAIDs

### Basic Principles

The skin acts as an efficient barrier to the passage of materials into and out of the body.[17] The keratinised stratum corneum is the outer, horny layer which consists primarily of multilaminar hydrophobic and hydrophilic channels composed of nonpolar fatty acid chains and polar head groups.[18,19] Thus, the ideal drug candidate for transdermal delivery would have a low molecular weight, be highly potent, and have both hydrophobic and hydrophilic properties.[17] In addition, the best delivery system would release the drug to the skin at a rate lower than the maximum rate of skin transport. This would control for variability in skin permeability between individuals and ensure a constant release rate.[17,20]

In several in vitro studies, a linear relationship has been established between the initial topical NSAID concentration and the release rate from the vehicle, suggesting a diffusion-controlled model.[20,21] Vehicle pH and penetration enhancers such as polyethylene glycol, limonene, emulsion preparations or iontophoresis can also have dramatic effects on NSAID release rates, increasing penetration rates by up to 75-fold.[21-26]

### In Vivo Animal Studies

In order to treat patients rationally with topically applied NSAIDs, the issue of 'local enhanced topical delivery' of NSAIDs must be addressed. This concept postulates that local accumulation of drug in target tissues occurs by direct diffusion to a greater degree than could have resulted by prior absorption and

redistribution through the cutaneous vasculature.[2] This issue has been addressed directly by McNeill et al.,[27] who administered equivalent 50[micro]g doses of titrated piroxicam either intravenously or topically to the right shoulder of male rats. In the muscle tissue subjacent to the topical Piroxicam application, 2 distinct piroxicam peaks were noted at 4 and 12 hours after application. The contralateral muscle tissue from the nondosed shoulder produced a single peak at 12 hours. The authors' interpretation of this data was that the first peak could only be accounted for by topical piroxicam delivery; the second peak was attributed to redistribution from the general blood supply. The concentrations of piroxicam achieved in the acromiotrapezius muscle subjacent to the treated shoulder at 2 hours after topical application exceeded that found in the same muscle of rats given equivalent intravenous piroxicam by 14-fold.

This work was confirmed by Mikulak et al.[28] These authors reported that topical application of indomethacin produced maximal tissue concentrations in the subjacent deltoid muscle, joint capsule and rotator cuff 2 to 10 times greater than that achieved with equivalent oral dosing.

Singh and Roberts [29] investigated the relative epidermal permeabilities of salicylate, indomethacin, naproxen, diclofenac and piroxicam solutions in anaesthetised rat dermis. These authors concluded that 'local direct penetration was evident for all NSAIDs up to a depth of about 3 to 4mm below the applied site, with distribution to

deeper tissues being mainly though the systemic blood supply'. While this information seems to contradict the studies by Mikulak et al.[28] and McNeill et al.[27] with respect to deeper tissue penetration, it is important to note that the drugs utilised in the study designed by Singh and Roberts [29] were in aqueous solution, while Mikulak et al.[28] utilised a lipophilic penetration enhancer and McNeill et al.[27] used a carbopol gel base. Thus, product formulation may have a dramatic impact, not only upon absorption rates, but also on penetration depth.

### **Ex Vivo Studies on Human Skin Tissue**

Ex vivo studies utilising cadaver skin tissue to investigate transdermal penetration of NSAIDs have determined that occlusion of the skin surface can enhance drug penetration by up to 2-fold.[30] In a study of 7 different NSAIDs, Cordero et al.[31] determined that the flux across human cadaver skin was related primarily to the lipophilic character of the drug. Roy and Manoukian [32] demonstrated that the flux of ketorolac through skin tissue in vitro decreased exponentially as the solution pH was raised from 3.5 to 7.0. This is consistent with the findings of Cordero et al.,[31] given that this pH shift would increase the unionised percentage of ketorolac by several orders of magnitude, making it more lipophilic.

In essence, ex vivo studies suggest that occlusion can enhance NSAID skin penetration, lipophilicity is an important characteristic, and the pH of the vehicle is extremely important. However, these data

must be interpreted with caution, as cadaver skin obviously has no functional blood supply and is therefore an incomplete model for true skin penetration.

### **Human In Vivo Studies**

Many investigators have attempted to quantitate maximum plasma concentrations (C<sub>max</sub>) and the time required to reach this blood level (t<sub>max</sub>) after transdermal administration of NSAIDs in healthy humans.[32-40] These reports have been summarised in table II for both single dose and multiple dose studies, along with a calculation comparing the reported mean C<sub>max</sub> values to expected plasma concentrations after equivalent oral administration. These data indicate that systemic absorption after topical administration produces peak plasma values less than 10% of that obtained after oral administration (range 0.2 to 8.0%). Another important point gleaned from table II is the significant inter- and intra-individual variability, which is consistent with that seen in the ex vivo data.[31] This variability has been attributed to individual skin differences between study participants, including hydration status,[41] permeability characteristics [31,38] and individual differences in subcutaneous vasculature.[41]

Shah et al.[40] compared serum ketoprofen concentrations after equivalent gel applications to the forearm, back or knee in a crossover design. These authors found that anatomical site of application had little effect on systemic absorption. The study by Seth [34] comparing

equivalent doses of ibuprofen applied to equivalent skin surface areas emphasises the importance of the vehicle on percutaneous drug absorption. This author demonstrated a 5-fold enhancement of maximal serum concentration by changing the drug formulation from an ointment base to a gel base. Overall, given that different NSAIDs, vehicles, methods of occlusion and/or permeability enhancers were utilised in every study described in table II, it is difficult to draw any conclusions regarding superior permeability of any one NSAID formulation.

As demonstrated by the available in vivo studies (see table II), topical NSAIDs penetrate slowly and in small quantities into the general circulation. Marked interindividual variability was noted in all studies. Reported maximal plasma concentrations of NSAIDs applied topically are generally less than 15% of the concentration which would be expected from equivalent oral administration. The reported maximal serum concentrations after topical administration are uniformly below the accepted therapeutic drug concentrations for NSAIDs, which is advantageous when viewed from the vantage point of systemic toxicity. The time required to achieve C<sub>max</sub> is approximately 10 times longer than that of equivalent oral administration, ranging from 2.2 to 23 hours. Bioavailability studies suggest that NSAIDs administered topically achieve only 3 to 5% of the total systemic absorption when compared with oral administration.[33,42,43] Anatomical site of application does not appear to influence plasma concentrations,[40] but the formulation can enhance

systemic absorption by as much as 5-fold.[34] Steady state is achieved fairly rapidly after  $t_{max}$  (generally within 2 to 5 days of initiation of repeated topical application),[41,42] and plasma concentrations after repeated administration have been reported to rise to 2.5 times the  $C_{max}$  after a single application.[42]

### Penetration Studies

The concept of local enhanced topical delivery of NSAIDs requires proof not only that the drug reaches the systemic circulation, but that it reaches higher and therapeutically effective concentrations in the tissues localised below the site of application. Verification of local enhanced topical delivery is essential, given the proposed rationale behind the use of topical NSAIDs - that enhanced, localised concentrations minimise systemic toxicity while maintaining efficacy.

Muller et al.[38] attempted to address the issue of depth of diclofenac penetration in vivo. In this study, 12 healthy volunteers were given topical diclofenac foam (diclofenac 80mg over 200cm<sup>2</sup> applied to the shaved surface of the thigh with occlusion) twice daily for 8 days. Immediately prior to the last topical dose, 2 microdialysis probes were inserted to a tissue depth of 11.7 +/- 0.4mm without local anaesthesia into the medial vastus muscle at least 4cm lateral from the margin of the application site. Concentration versus time profiles were obtained for plasma and interstitial fluid of skeletal muscle. Significant interindividual variability was noted. The mean  $C_{max}$  in plasma was

18.75 +/- 4.97 [micro]g/L, and corresponding interstitial concentrations in skeletal muscle were 219.68 +/- 66.36 [micro]g/L (12-fold higher than the plasma level).

A similar study was conducted by Tegeder et al.[44] These investigators administered ibuprofen 800mg either orally or topically over 323cm<sup>2</sup> to the thighs of 11 healthy volunteers in a 2-way crossover design, then monitored serum and tissue concentrations by microdialysis probes inserted into the thigh to a depth of 4 to 5mm (dermis) and 25 to 30mm (muscle). Topical administration led to 22.5-fold greater concentrations of ibuprofen in the dermis than those obtained after oral administration (p value not reported). Ibuprofen concentrations achieved in the muscle after topical administration were almost identical to those obtained after oral administration. There was significant interindividual variability (for example, muscle ibuprofen concentrations after topical administration exceeded those from oral administration by over 2 orders of magnitude in 1 volunteer). In approximately 50% of the volunteers, ibuprofen concentrations in the muscle tissue after topical administration were increased over concentrations after oral administration. The authors attributed this variability to differences in the microvasculature at the site of drug administration.

Keeping in mind that the interstitial drug concentration in the muscle tissue measured by Muller et al.[38] was 11mm deep and 4cm lateral to the application site, these results directly contradict the in vivo

animal study by Singh and Roberts,[29] which postulated that distribution to tissues deeper than 3 to 4mm below the applied site were accounted for by the systemic blood supply. The authors note that the microdialysis method employed measured only the pharmacologically active unbound drug fraction; total tissue drug concentrations were probably higher. The study by Tegeder et al.[44] suggests that, for approximately 50% of patients, local enhanced topical delivery of NSAIDs accounts for tissue concentrations of drug that are above that which can be obtained by equivalent oral administration up to 25 to 30mm subjacent to the site of application.

In an elegant, nonblind study design, Dominkus et al.[45] compared topical administration of ibuprofen 375mg in a gel formulation applied 3 times daily for 3 days to oral administration of ibuprofen 600mg given twice daily for 3 days in 17 patients with degenerative knee disorders. Ibuprofen administration occurred in the time period immediately preceding knee surgery. Twelve patients received the topical preparation (1125 mg/day for 3 days) and 5 received the oral formulation (1200 mg/day for 3 days). Samples of blood, synovial fluid, muscle, fasciae and subcutaneous tissue were obtained during the operation, 15 hours after the last administration of ibuprofen. Mean plasma concentrations of ibuprofen were 1.0 +/- 0.5 mg/L in patients receiving the topical preparation, and 1.6 +/- 1.3 mg/L in patients receiving oral ibuprofen (p = 0.17). Given that the half-life of ibuprofen

is 1.78 to 2.5 hours,[46] at least 6 half-lives elapsed between the last topical or oral dose and the time the serum and tissue samples were removed for analysis, making it very difficult, if not impossible, to compare the blood concentrations. However, it is interesting to note that similar ibuprofen concentrations were achieved in the 2 treatment groups in the synovial fluid, fasciae and muscle tissues. The subcutis was the only tissue in which the ibuprofen concentration derived from topical application exceeded that obtained after oral administration (5.4 +/- 3.3 vs 1.3 +/- 0.3 [micro]g/g; p = 0.03).

In a recent randomised, parallel investigation, Rolf et al.[47] compared ketoprofen concentrations in plasma, synovial fluid and intra-articular tissues in 100 patients undergoing knee arthroscopy. Forty patients received a single topical plaster containing ketoprofen 30mg, 30 received multiple 30mg plaster applications over 5 days and 30 received ketoprofen 50mg orally. Ketoprofen concentrations were measured in plasma, synovial fluid, synovial tissue, meniscus and cartilage at time points up to 14 hours after drug administration. Interestingly, while synovial fluid ketoprofen concentrations averaged 70 to 80% of the plasma concentrations after topical application, the meniscus and cartilage concentrations were elevated 20- to 30-fold over those in plasma in the same patients. Median ketoprofen concentrations achieved in meniscus and cartilage tissues after topical administration (single or multiple application) were 4.1- to 6.8-fold higher

than those achieved after oral administration.

Dominkus et al.[45] reported that tissue and synovial fluid ibuprofen concentrations achieved after topical application exceeded the in vitro IC50 (concentration of ibuprofen required to inhibit 50% of enzyme activity) for prostaglandin synthetase [48] even 6 half-lives after last administration of drug. IC50 values for ibuprofen inhibition of COX-1 and COX-2 have been determined in vitro to be 0.8 to 3.8 mg/L and 0.0006 to 0.0012 mg/L.[16] COX-2 is the isoform primarily associated with inflammation;[16] thus, ibuprofen applied topically appears to exceed the threshold quantity required for anti-inflammatory activity. However, Gierse et al.[16] have recommended caution when interpreting the COX IC50 data, because of the complex and distinct mechanisms of enzyme inhibition of each COX isoform by NSAIDs (including competitive, covalent and time-dependent variable binding mechanisms). These authors state that 'comparison of inhibitory activity on COX-1 and COX-2 using IC50 ratios [are of] questionable validity'. [16] Judicious interpretation of IC50 data is reasonable, then, particularly when considering that COX-2 is an inducible enzyme which increases in concentration during the inflammatory response.[8]

As noted with ibuprofen,[48] topically-applied diclofenac hydroxyethylpyrrolidine (DHEP) has also been detected in the synovial fluid of patients with monolateral knee joint effusion by Gallacchi and Marcolongo.[49] These authors treated 8 patients with OA of the knee with plasters containing 180mg DHEP

twice daily for 4.5 days. Four hours after the last application, synovial fluid from the treated knee joint was collected. Plasma diclofenac concentrations were also assessed at 1, 4 and 8 hours after the last topical application. The mean concentration of diclofenac detected in the synovial fluid was 30% of that found in the plasma at the same 4-hour time point (1.02 +/- 0.38 vs 3.62 +/- 1.05 [micro]g/L; p

It has been postulated that the major site of action for NSAIDs in the treatment of arthralgias is probably within the synovial compartment.[50] These studies prove that topically applied NSAIDs can indeed reach the synovial fluid. Orally administered NSAIDs generally result in synovial drug concentrations approximately 60 to 80% of the mean plasma concentration;[47,50] this difference in concentration has been attributed to lower albumin levels in synovial fluid compared with plasma.[15] It is interesting to note that in the study conducted by Dominkus et al.,[45] the mean NSAID concentration in the synovial fluid actually exceeded that found in the plasma, although statistical tests were not applied to this data. Given the relatively slow transfer rate of NSAIDs into and out of the synovial compartment,[15] the sustained synovial NSAID levels observed,[49] and the fact that the levels in the study conducted by Dominkus et al.[45] were taken 15 hours after the last topical administration, it is not possible to state conclusively that topically applied NSAIDs are capable of concentrating in the synovium. However, Rolf et al.[47] provide persuasive evidence that ketoprofen applied

topically can concentrate in the intra-articular tissues, and that less vascularised tissues (cartilage and meniscus) may actually act as a drug reservoir.

In summary, local enhanced topical delivery of NSAIDs does occur. However, the maximal depth to which it occurs varies among individuals. Topically applied NSAIDs do reach the synovial fluid compartment and can concentrate in intra-articular tissues. However, without direct, objective measurement of contralateral tissue and synovial fluid drug concentrations in well-designed trials, a determination of the mechanism of NSAID transport - whether it is direct or via the systemic circulation or both - cannot yet be made. While essentially all tissue concentrations of topically applied NSAIDs result in subjacent tissue concentrations which exceed the IC50 for COX-2, this data must be interpreted cautiously based upon variable and complex mechanisms of COX enzyme inhibition.[16]

## **Efficacy**

### Topical NSAIDs versus Placebo and Active Controls

Indeed, the discouraging results reported by Shackel et al.[54] are not unexpected, given that patients with OA of the hip and/or knee were instructed to apply the copper-salicylate gel to their forearms, instead of over the painful joint.

However, of the 5 studies that reported 'no difference' in pain ratings between topical NSAID and placebo treatments,[51-54,57] 2 reported decreases in subjective pain scores by 35 to

60% from baseline which were attributable to placebo alone (p values

The trend of significant pain resolution from baseline noted in the placebo-controlled studies continued in the comparative topical NSAID versus topical NSAID trials summarised in table III. Reported pain scores decreased from 39 [62] to 70%,[63] and the percentage of patients who improved from baseline ranged from 26 [61] to 87%[60] (p

It is also difficult to deduce the optimal topical NSAID formulation. In the sole study which directly compared 2 different formulations of diclofenac, the total daily dosages were dramatically different (360 vs 80mg), preventing any conclusions regarding vehicle superiority from being drawn.[62]

### Topical NSAIDs versus Oral NSAIDs

Objective, clinical evidence for the relative efficacy of topical versus oral NSAIDs in rheumatic disorders is scant.

Methodological issues cloud the results presented here. Of the 4 studies summarised in table IV,[65-68] 1 was nonblind, 3 failed to specify the surface area of application and none utilised a crossover design. A crossover methodology, with the advantage of utilizing patients as their own controls, would have helped minimise the interpatient variability that seems to plague these investigations. Further, all 4 studies chose oral NSAID dosages on the lower end of the recommended dosage range and compared these oral forms to topical preparations which have not demonstrated superiority to vehicle controls.

Documentation of compliance with the study protocol, application technique (the extent of 'rubbing in'), occlusion and skin surface area to be covered are all important variables which need to be standardised in these studies. The methods section of the study reported by Sandelin et al.[67] stated that 'in bilateral cases both knees were treated with same treatment and treatment regimen'. Thus, patients suffering from OA in both knees received twice the dosage (and achieved presumably twice the serum concentration) of patients with monolateral OA. However, the data analysis was not structured to control for this variable. Furthermore, exclusion criteria common to these studies included a history of peptic ulcer disease, GI haemorrhage or renal dysfunction. Thus, the safety and tolerability data may have been skewed in favour of oral NSAIDs.

The issue of allowance and tracking of rescue medication is also very important. The study reported by Dickson [68] is interesting in this respect. This author compared piroxicam gel and ibuprofen tablets in patients suffering from OA of the knee. Patient ratings of efficacy were good to excellent in 64 and 60% of patients given topical piroxicam or oral ibuprofen, respectively. However, paracetamol rescue analgesia was required in 69 and 62% of patients in the topical and oral groups, respectively. This is the only study reviewed that reported such high rescue analgesic use. Many of the efficacy studies allowed rescue paracetamol and, of the studies that tracked rescue drug use,[52,54-56,66] most reported

low incidences of use (under 5%).[56,66]

All studies reviewed here, while not consistently documenting superiority of topical or oral administration, reported clinical improvement attributable to topical NSAIDs ranging from 18 [67] to 92%[66] of treated patients. However, the placebo effect issue looms large, since only 1 study included a topical placebo into its design.[67] In this investigation by Sandelin et al.,[67] oral diclofenac showed superior efficacy to topical placebo as measured by investigators' and patients' evaluation of overall efficacy (p

One of the 4 studies comparing oral with topical NSAID summarised in table IV documented superiority of the topical dosage form. Martens [66] compared local action transcutaneous (LAT) flurbiprofen to oral diclofenac in the treatment of soft tissue rheumatism. In the investigator's opinion, 92% of patients treated with LAT showed clinical improvement, whereas 73% of those receiving oral diclofenac showed improvement (p = 0.03). In addition, the investigator's ratings of severity of pain and severity of tenderness were significantly better in the LAT group (p

A nonblind study by Browning and Johson,[69] in 191 elderly patients with mild to moderate OA, demonstrated that patients taking oral NSAIDs for OA could reduce their oral NSAID dose by a factor of 2 by concomitant use of Piroxicam gel with no reduction in perceived efficacy. Thus, addition of a topical NSAID to an existing oral regimen may allow patients to experience equivalent pain

relief while tapering down the dosage of the oral form (and thus reducing their risk of GI haemorrhage, peptic ulcer disease, etc.)

In summary, the empirical evidence suggests, but does not prove, that NSAIDs administered topically are at least as efficacious as oral NSAIDs in the treatment of rheumatic diseases. Larger, placebo-controlled, double-blind studies which control for the variables discussed in detail in this section are necessary before a conclusion can be reached.

### **Safety**

Systemic COX inhibition by NSAIDs results in a cluster of well recognized adverse effects, particularly affecting the GI tract and kidneys.[7] Some of the adverse effects secondary to oral NSAID use are dose related.[70-72] NSAID use pruritus at the site of application. The mean percentage of patients reporting adverse events after topical placebos was 14.4% (range 0 to 52%). Again, these events were primarily rash and pruritus, suggesting that the vehicle itself may be responsible for a significant proportion of the adverse cutaneous reactions.

The tolerability of topical NSAIDs in the elderly has been reviewed.[72] While the majority of adverse effects are skin disorders, there have been case reports of topical NSAIDs associated with systemic effects such as GI and renal toxicities, abnormal hepatic function, hematopoietic disorders and asthma.[72] However, the incidence of these serious systemic ADRs appears to be very low; none of the studies summarised here reported a serious systemic reaction

approximately doubles the risk of acute renal failure,[72] and a linear dose-response relationship has been established between oral NSAIDs and upper GI bleeding.[73] Thus, targeting therapeutic tissue/synovial fluid concentrations of NSAIDs via the topical route while minimising systemic exposure by lowering serum concentrations makes good sense.

Figueras et al.[74] reviewed 194 adverse drug reaction reports attributed to topical NSAIDs. Of these, 95% were dermatological in nature and the remaining 5% were systemic reactions. This data is consistent with the information presented in tables III and IV. On average, adverse drug reactions (ADRs) occurred in 12% of the patients in these studies (range 0 to 85%), and approximately 75% of ADRs were cutaneous, consisting of a rash and/ or p attributable to topical NSAID use. Without considerable post-marketing surveillance data, it will be difficult to assign a definite association between topical NSAID administration and systemic adverse events, since many events may occur independently, and patients may have been taking an oral NSAID at the time of their illness. A case-control study conducted by Evans et al.[75] demonstrated that once adjustments were made for the confounding effects of concomitant oral NSAID use, topical NSAID administration was not significantly associated with upper GI bleeding and perforation.

In summary, topically applied NSAIDs are safer than orally administered NSAIDs. ADRs can be expected in approximately 10% of patients, the vast majority being localised pruritus and/or rash at the site of

administration that resolves quickly upon discontinuation of the product. Cross-sensitivity between different topical NSAIDs has been established.[76] Skin reactions secondary to oral NSAID use have been reported in 5 to 10% of patients.[77] GI ADRs after topical NSAID use are rare; in comparison, the incidence of serious GI events associated with oral NSAIDs is 15%.[78]

### **Cost Effectiveness**

By the year 2030, people over the age of 65 are expected to constitute 17% of the US population and to account for approximately 40% of total drug expenditures.[79] OA is the most common of the rheumatic diseases, and the overall disease prevalence increases with age: 10 to 20% of people over 65 have clinical OA of the knees and hips, and over half of these have radiographic evidence of OA.[8,80] Currently, over 50% of oral NSAID prescriptions are written for OA.[15] Furthermore, increasing age is associated with an increased likelihood of adverse events after oral NSAID therapy, particularly with respect to peptic ulcer disease. The overall odds ratio for the risk of serious GI toxicity associated with oral NSAID administration is 2.74 [95% CI (confidence interval): 2.54 to 2.97]; the risk assessed in people aged 60 years or greater (compared with those under 60 years taking NSAIDs) has been estimated to be 5.5 (95% CI: 4.6 to 6.6).[81] Thus, the issue of cost effectiveness of oral versus topical administration of NSAIDs is an important consideration.

Topical NSAIDs have been considered a costly alternative to oral formulations.[64,82] However, in the US alone, oral

NSAID-induced GI damage has been reported to account for 42% of hospital admissions of patients with rheumatic diseases and for one-third of the total cost of rheumatic disease treatment.[83] When this 'shadow' cost of treating adverse effects is taken into account, and assuming equal efficacy (which remains to be proven), the cost-benefit analysis shifts decidedly in favour of topical over oral NSAIDs.[64] It remains to be seen if the new COX-2-specific NSAIDs can indeed reduce the GI morbidity and mortality associated with oral NSAID treatment of rheumatic disorders.

### **Conclusions**

Topical NSAIDs have been used to treat a wide variety of conditions: musculoskeletal injuries,[3,4] postoperative pain,[84,85] herpetic neuralgia,[86] periodontitis,[87] aphthous ulcers [88] and actinic keratoses.[89] The anti-inflammatory efficacy of topically applied NSAIDs, even remote from the site of application, has been well established in animal models.[90] Evidence for anti-inflammatory activity from topical NSAIDs in humans is more equivocal, characterised by a considerable placebo effect (5 to 60% in chronic rheumatic diseases [91]) and significant interpatient variability in response.

Local enhanced topical delivery of topically applied NSAIDs does occur in humans, but the tissue depth at which the systemic circulation takes over distribution of the drug is highly variable among individuals. Individual variability in subcutaneous

vasculature may account for the wide range of tissue depths reported after topical administration, as well as inconsistency in patient response to topical NSAIDs.

Few generalisations can be made regarding the best drug or topical dosage form for enhancing cutaneous NSAID penetration and efficacy. Optimisation of vehicle formulation, pH and occlusion have all been documented to enhance penetration.

Transdermal application gives rise to much lower plasma concentrations than oral administration. NSAID concentrations in the synovium subjacent to the site of topical application are at least comparable to those achieved after equivalent oral administration; subcutaneous concentrations after topical administration far exceed that which are normally achieved after oral administration.

Adverse effects secondary to topical NSAID application occur in approximately 10 to 15% of patients, and are primarily cutaneous in nature (rash and pruritus at site of application). GI ADRs are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs.

Positive treatment outcomes reported in patients with chronic rheumatic disorders range from 30 to 95%, with considerable interpatient variability.[91] On average, 1 out of 3 patients using topical NSAIDs will achieve a successful outcome who would not have done so had they used a placebo.[91]

The clinical evidence suggests, but does not prove, that NSAIDs applied

topically are as effective as oral NSAIDs in the treatment of chronic rheumatic diseases. However, the contribution to efficacy by the rather dramatic placebo effect seen in these studies remains to be teased out by larger, well controlled, crossover studies comparing oral administration of clinically effective doses with topical formulations with proven superiority over vehicle controls. The safety profile of topical NSAIDs in terms of cutaneous ADRs is approximately equivalent to that of oral formulations, but topical preparations are clearly superior in terms of GI adverse effects. Given the relatively benign adverse effect profile of topical NSAIDs and the increasing risk of serious NSAID-mediated GI events with age, it seems rational to give patients with rheumatic disorders a trial of topical NSAIDs prior to institution of an oral NSAID if oral paracetamol fails to control their pain.