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