others; (3) the exceptional safety reported for this triple combination (11% drop-outs on the triple combination vs. 22% on MTX) needs to be corroborated; and (4) the high drop-out rate resulted in a study whose size was small enough to make one wish for a corroborating study.
Despite these shortcomings, this study certainly has solidified a change in treatment philosophy which has been advocated by others [notably Wilske and Healey (2)] in the past.

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Topical non-steroidal anti-inflammatory drugs are effective in acute and chronic pain conditions

Authors: R.A. Moore *et al.*
Title: Quantitative review of topically applied non-steroidal anti-inflammatory drugs.
Source: *British Medical Journal* 1998; 316: 333-8.

Aim: Topical NSAIDs represent an alternative to oral non-steroidal anti-inflammatory drugs (NSAIDs), which may often cause severe adverse gastrointestinal effects. In a systematic review Moore *et al.* examined whether topical NSAIDs are safe and effective, and if various topical preparations show different degrees of efficacy in the treatment of acute and chronic pain conditions.
Methods: A search of the Medline (1966 to September 1996), Embase (1981 to September 1996), and Oxford Pain Relief (1950 to 1994) databases was carried out to identify randomised controlled trials comparing topical NSAIDs with either placebo, another NSAID or an oral NSAID. In addition, pharmaceutical companies in the UK were invited to report the results from their files of randomised controlled trials of NSAIDs. Only trials considering pain as a clinical outcome in acute (soft tissue trauma, strains, and sprains) or chronic conditions (osteoarthritis and tendinitis) were chosen. Treatment success was considered to be a ≥ 50% reduction in pain, and local and systemic adverse effects had to have been analysed at one week from the study start for acute conditions and at 2 weeks for chronic conditions. The quality of each of the studies under consideration was assessed on a scale from 1 to 5. A scattergram was used to analyse the distribution of success rates with NSAID against the success rate with placebo. A random effect model was used to calculate the relative risk or benefit (95% confidence interval) of treatment, based on pain data from placebo-controlled studies, and the data on efficacy was used to calculate "the number needed to treat" (i.e., to obtain a successful outcome compared with placebo) (95% CI).
Results: 86 reports (10,160 patients) fulfilling the inclusion criteria were found. These were divided into two groups (acute and chronic pain) which were then subdivided into groups based on the study design (placebo or active controlled).
For acute pain conditions, placebo had a relative benefit of 1.7 (1.5 - 1.9), and the number needed to treat was 3.9 (3.4 - 4.4). Pooling the data for each drug that had been studied in three or more trials showed ketoprofen, felbinac, ibuprofen and piroxicam to be significantly superior to placebo (the number needed to treat being 2.6, 3.0, 3.5, and 4.2, respectively), while benzydamine and indomethacin did not differ significantly from placebo.
For chronic pain, placebo had a relative benefit of 2.0 (1.5 - 2.7); the number needed to treat was 3.1 (2.7 - 3.8). It is interesting to note that trials with less than 40 pts. overestimated the effectiveness of topical NSAIDs (by 33%) in patients with acute conditions but not in those with chronic conditions.
Five studies (3 of acute and 2 of chronic pain conditions) comparing topical with oral NSAID preparations did not show a significantly greater benefit with oral NSAID. No relationship between the quality of the trial and the treatment effect was found. Local and systemic adverse effects and dropout rates were very low and similar to placebo in both groups.
Conclusions: Topical NSAIDs are effective and safe for acute and chronic conditions. For the treatment of rheumatic pain, topical NSAIDS can be considered a satisfactory alternative to oral and intramuscular NSAIDs. The partial substitution of oral with topical NSAIDs, particularly in cases of chronic pain, could significantly reduce gastrointestinal side effects without sacrificing the anti-inflammatory benefits of NSAIDs.

Comment

Primum non nocere *(first do no harm) is a wise motto in medicine. Although there is no doubt regarding the necessity and efficacy of NSAIDs in chronic rheumatic diseases, the price paid for this treatment can be quite high. Therefore, alternatives are very welcome. One interesting possibility is the use of topically applied non-steroidal anti-inflammatory drugs.*
Moore et al. evaluated, according to by now widely used meta-analysis methods, the available evidence regarding the use of topical NSAIDs. Their data are quite convincing; they found that topical NSAIDs are effective in reducing pain in acute and chronic rheumatic conditions. Interestingly, we have no idea about the exact mechanisms involved in this pain relief. How much is due to the pharmacological effects of the topical NSAID and how much to psychological effects ? Nevertheless, the effects are positive and safe; it is therefore a pity that these topical NSAIDs are not available in all European countries, and that in those cases where they are available, they are not always covered by the national health care system. It would be interesting to see the results of cost-effectiveness studies on the (adjuvant) use of topical NSAIDs in acute and chronic rheumatic pain.

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