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Can Topical and Oral NSAIDs Be Combined for Pain Relief?

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Question

Are two nonsteroidal anti-inflammatory drugs better than one when it comes to treating pain?

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Patients with moderate to severe musculoskeletal pain may experience suboptimal relief despite the use of a nonsteroidal anti-inflammatory drug (NSAID). Patients seeking additional pain relief may inquire about the use of topical NSAID therapy in addition to oral NSAID therapy.

Currently, no guidelines exist on the use of combination oral and topical NSAID therapy. Regulatory bodies such as the US Food and Drug Administration (FDA) and the European Medicines Agency recommend the use of NSAIDs at the lowest dose necessary.[1,2] In 2015, the FDA strengthened a previous warning for the increased risk for myocardial infarction and stroke with the use of NSAIDs.[3] Thus, the need for adequate pain relief must be carefully weighed against the potential risks of combination oral and topical NSAID therapy.

NSAIDs inhibit COX enzymes involved in prostaglandin synthesis to reduce inflammation. COX-1 inhibition by nonselective NSAIDs increases the risk for gastrointestinal bleeding and ulceration. NSAIDs with specific affinity for the COX-2 enzyme, such as celecoxib, have been developed to reduce the risk for gastrointestinal adverse events. NSAIDs also may increase the risk for cardiovascular events, possibly secondary to the imbalance of COX-2 blockade, which produces vasodilatory prostacyclin, and COX-1, which produces vasoconstricting and platelet-aggregating thromboxane.[2,4]

The increased risk for cardiovascular events and cardiovascular-related death with the use of oral NSAIDs has been demonstrated in several studies.[5-8] Specifically, oral diclofenac, ibuprofen, and celecoxib have been associated with high cardiovascular risk, while naproxen has been associated with the lowest risk for adverse cardiovascular events. From a gastrointestinal perspective, agents such as ketorolac and piroxicam demonstrate a high risk for gastrointestinal bleeding and perforation, while celecoxib, aceclofenac, and ibuprofen are associated with fewer gastrointestinal adverse events at equivalent doses.

All topical NSAIDs carry the same black box warnings found on oral formulations for cardiovascular and gastrointestinal risk. However, risks may vary with the specific agent and formulation.[9] To date, diclofenac is the only NSAID available in the United States for topical use. Although topical diclofenac agents are designed to act locally at the site of application, consideration of the degree of systemic exposure and clinical manifestations is important. The pharmacokinetic data suggest that the use of topical NSAIDs results in minimal systemic exposure and therefore causes fewer cardiovascular and gastrointestinal adverse events than oral NSAIDs.[9-12] Compared with oral diclofenac, topical diclofenac gel 1% (Voltaren®), topical diclofenac solution 1.5% (Pennsaid®), and topical diclofenac patch 1.3% (Flector®) are all associated with lower peak plasma concentrations and fewer systemic adverse events.[9,10,12]

In the single study available evaluating the combination of oral plus topical NSAIDs, the combination of oral diclofenac and topical diclofenac solution 1.5% was compared with oral and topical diclofenac monotherapy. Topical diclofenac as monotherapy was associated with the fewest adverse events. Combination therapy was associated with a greater incidence of rectal hemorrhage, although an evaluation of gastrointestinal safety is difficult because patients in the study were allowed to take proton pump inhibitors. No differences in cardiovascular risk between the treatment arms in this 12-week study were observed.[11,12] In terms of efficacy, oral or topical diclofenac monotherapy was similar to combination therapy in all pain and physical function endpoints.

In addition to the limited evidence surrounding increased efficacy with the use of combination NSAID therapy, one must also consider the ceiling effect with NSAIDs. In one study comparing analgesia with 400 mg, 600 mg, and 800 mg doses of ibuprofen, there was no significant difference in pain relief among these doses. Although higher doses have been shown to further reduce inflammation, this does not equate to additional pain reduction.[13,14] In a systematic review, oral diclofenac 50 mg was associated with greater analgesia in postoperative pain than diclofenac 25 mg; however, diclofenac 100 mg did not show improved efficacy over diclofenac 50 mg, suggesting a ceiling effect at 50 mg.[15,16]

Despite the published pharmacokinetic data that suggest decreased systemic absorption of topical NSAIDs, studies demonstrating the additive analgesic effect of combination oral and topical NSAID therapy have not been published. In the single study available, combination oral and topical diclofenac was no better than either formulation as monotherapy, and it increased the risk for bleeding.[12] Additionally, the ceiling analgesic effect associated with NSAIDs further suggests that combination topical and oral NSAID therapy may not offer additional pain relief. Given the potential for increased risk, and without data to show improved efficacy with combination therapy, concomitant use of oral and topical NSAIDs should not be routinely recommended, especially in patients already at greater cardiovascular or gastrointestinal risk.

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