

Safety Advantages of Topical versus Oral Nonsteroidal Antiinflammatory Drugs

To the Editor:

Makris, *et al* are to be congratulated for highlighting potential safety advantages of topical nonsteroidal antiinflammatory drugs (NSAID) versus oral NSAID¹. However, one of the 2 topical NSAID available in the United States is not well represented in their review. Only one of 19 trials that were cited evaluated diclofenac sodium 1% gel (DSG), and 5 of 19 evaluated diclofenac sodium in dimethyl sulfoxide solution (D-DMSO). Two major trials of DSG in knee osteoarthritis (OA) were published after the authors' search period^{2,3}, and additional subanalyses in at-risk populations have been presented^{4,5}.

Barthel, *et al*³ evaluated DSG in 492 patients with knee OA. Patients treated with DSG or placebo vehicle experienced gastrointestinal (GI) adverse events (5.9% vs 5.0%, respectively) with similar frequency. However, only 2 GI adverse events (nausea, dyspepsia) were considered to be treatment-related. Similarly, Baraf, *et al*² compared DSG with vehicle in 420 patients with knee OA. GI events occurred in 5.3% of the DSG group and 4.2% of the vehicle group, but only one GI adverse event (diarrhea) in the vehicle group was considered treatment-related. No cardiovascular or other serious adverse events were considered to be treatment-related in either trial. In the trial of DSG in patients with hand OA⁶ cited by Makris, *et al*, 7.6% of patients treated with DSG experienced a GI adverse event, but only 1% experienced a GI adverse event related to treatment. No bleeding events were reported in any trial of DSG.

It appears likely that the 4% to 5% GI adverse event rates reported with vehicle in these trials reflect the all-cause frequency of GI events that would be expected over a 2- to 3-month period, irrespective of treatment. The 5% to 8% rates reported with DSG represent at most a slight increase in mild GI adverse events. The substantially increased occurrence of GI and other systemic adverse events reported with oral NSAID relative to placebo in clinical trials is clearly attributable to differences in tolerability between active and placebo treatment.

Good tolerability with DSG has also been demonstrated in older patients and those with comorbidities (diabetes, hypertension, and cardiovascular disease). Makris, *et al* cite a pooled analysis of three 12-week trials of DSG in patients with knee OA in which there was no significant difference in tolerability between younger (< 65 years) and older (≥ 65 years) patients. In separate analyses of the same population^{4,5}, DSG in the total population and in patients aged ≥ 65 years was not associated with an increased rate of overall adverse events, cardiovascular adverse events, or renal adverse events in patients with hypertension, diabetes, or cardiovascular disease, regardless of age. No patient with cardiovascular disease experienced a cardiovascular or renal adverse event. One patient with diabetes experienced a renal adverse event. An 80-year-old woman with diabetes and hypertension experienced a deep vein thrombosis with pulmonary embolism, considered to be possibly treatment-related. The event was mild in severity and was managed successfully with heparin and warfarin. No other serious treatment-related adverse events were reported.

Makris, *et al* correctly observed that application site reactions are the main tolerability concern with topical NSAID, whereas GI bleeding is a significant tolerability concern with oral NSAID. It should be noted, however, that topical agents differ with respect to skin reactions. The 39.3% rate of application site reactions reported by Baer, *et al*⁷ was from a trial of D-DMSO and is only slightly higher than rates in other populations treated with this agent^{8,9,10}. In 3 published trials of DSG^{2,3,6}, 4.5% to 5.1% of patients experienced application site reactions, mostly mild and self-limiting, that did not lead to treatment discontinuation. More frequent application site reactions with D-DMSO relative to DSG are probably due to differences between the vehicles used to deliver diclofenac topically. As Makris, *et al* note, DMSO has also been associated with halitosis and taste perversion.

Finally, Makris and colleagues cite evidence that topical NSAID have similar or slightly less effectiveness than oral NSAID, making safety rather than efficacy the primary motivation for prescribing them. However, the most recent Osteoarthritis Research Society International guidelines for the treatment of knee and hip OA¹¹ list the effect size for pain reduction with oral NSAID as 0.29 and cite a superior effect size of 0.44 for topical NSAID. In summary, it is clear that topical NSAID provide a safe and effective alternative to oral NSAID in patients with OA pain in superficial joints such as the knee or hand.

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