[Two of the authors respond:]

As Vivian McAlister notes, the study by Hui and associates[1] demonstrated some systemic absorption of diclofenac after topical application. However, the plasma level was only 11.8 (standard deviation [SD] 4.2) ng/mL, approximately 125 times below the level seen after ingestion of a 50-mg tablet of an oral formulation.[2]

This finding is consistent with the site-specific action of topical NSAIDs, which can achieve an analgesic effect much greater than that expected on the basis of observed serum levels.[3] For example, according to Vaile and Davis,[3] "topically applied versus orally administered drug[s] generally show very low relative concentrations [in the plasma] … unlikely to explain efficacy." Similarly, in studies of patients scheduled for knee surgery, tissue levels of topically applied NSAIDs were much greater than blood levels and were similar to tissue levels achieved with oral therapy.[4] After multiple applications of topical diclofenac for up to 84 days,[5] the mean plasma level of the drug was still only 8.95 (SD 9.17) ng/mL.[6] Early experiments in rats[7] demonstrated an effect of oral diclofenac at 0.3 mg/kg — an amount that became the basis for oral dose-ranging trials in humans — yet some 30 years later, there is still no recognized pharmacokinetic correlation between clinical effect and blood levels. Intuitively, however, it is difficult to conceive that an oral dose producing the low systemic levels seen after topical application would have any clinical effect.

A more recently published study[8] demonstrating the clinical equivalence of this topical diclofenac solution and oral diclofenac puts the magnitude of its analgesic effect into perspective. The observed improvement in pain scores with topical diclofenac cannot be accounted for by the miniscule blood levels of diclofenac and could be achieved only by local accumulation of a therapeutic concentration at the pain site.

McAlister also asks about the concomitant use of low-dose ASA. When we eliminated the 43 patients who used ASA (up to 325 mg/day) the *p* values were even more convincing.

Our data do show improvements in pain scores in both control groups (vehicle control and placebo).[9] This placebo effect may very well represent a true response,[10] and we agree that establishing efficacy warrants a traditional superiority trial comparing active drug with placebo.[5,9] In standard medical practice, however, we would be inclined to follow the thinking of Hróbjartsson and Gøtzsche[10] that "outside the setting of clinical trials, there is no justification for the use of placebos."

Arthur A.M. Bookman
Division of Rheumatology
University Health Network, Western Division
University of Toronto
Toronto, Ont.
J.Z. Shainhouse
Dimethaid Health Care Ltd.
Markham, Ont.

References

1. Hui X, Hewitt PG, Poblete N, Maibach HI, Shainhouse JZ, Wester RC. In vivo bioavailability and metabolism of topical diclofenac lotion in human volunteers. *Pharm Res* 1998;15(10):1589-95.
2. Voltaren product monograph. In: *Compendium of pharmaceuticals and specialties*. Ottawa: Canadian Pharmacists Association; 2004. p. 2203-4.
3. Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions. A review of the literature. *Drugs* 1998;56(5):783-99.
4. Rolf C, Engstrom B, Beauchard C, Jacobs LD, Le Libroux A. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology* (Oxford) 1999;38:564-7.
5. Roth SA, Shainhouse JZ. Safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. *Arch Intern Med* 2004;164:2017-23.
6. Pennsaid product monograph. In: *Compendium of pharmaceuticals and specialties*. Ottawa: Canadian Pharmacists Association; 2004. p. 1503-6.
7. Krupp PJ, Menasse-Gdynia R, Sallmann A, Wilhelmi G, Ziel R, Jaques R. Sodium (o-((2,6-dichlorophenyl)-amino)-phenyl)-acetate (GP 45 840), a new non-steroidal anti-inflammatory agent. *Experientia* 1973;29:450-2.
8. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (Pennsaid®) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *J Rheum* 2004;31:2002-12.
9. Bookman AAM, Williams KSA, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *CMAJ* 2004; 171(4):333-8.
10. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;344:1594-602.

Competing interests: Dr. Bookman has received compensastion from Dimethaid Health Care Inc. for his participation in a clinical trial and has received speaker fees on 2 occasions. Dr. Shainhouse is a paid employee of Dimethaid and has been granted stock options in the company.

DOI:10.1503/cmaj.1041679

Correction

The DOI published in a recent news item[1] was mistakenly listed as 10.1503/cmaj.1045319. It should be 10.1503/cmaj.045319.

Reference

1. Sibbald B. Tighten Ontario's methadone program states inquest. *CMAJ* 2005;172(3):319-20.

DOI:10.1503/cmaj.050137

Letters submission process

CMAJ's enhanced eLetters feature is now the portal for all submissions to our letters column. To prepare an eLetter, visit www.cmaj.ca and click "Submit a response to this article" in the box near the top right-hand corner of any *eCMAJ* article. All eLetters will be considered for publication in the print journal.

Letters written in response to an article published in *CMAJ* are more likely to be accepted for print publication if they are submitted within 2 months of the article's publication date. Letters accepted for print publication are edited for length (usually 250 words) and house style.