cardiovascular system.[4] However, the COX-2 enzyme might be exerting detrimental effects elsewhere, because analysis of protein extracts from normal arteries has revealed constitutive COX-1 only, but atheromatous lesions contained both COX-1 and COX-2 protein.[5] Some studies suggest that prostanoids and nitric oxide may have proatherosclerotic effects[6] resulting from the formation of peroxynitrite species in the affected vessels, possibly involving "cross talk" between the COX-2, iNOS and other enzyme systems, which may generate oxidants including dihydrogen trioxide and even ozone from singlet oxygen and water in atheromatous plaques.[7]

Well-planned basic research is essential to show whether COX-2 activity is beneficial or harmful for the cardiovascular system in different sites or in cardiovascular disease and to exploit the benefits of COX-2 inhibitor therapy.

Syed A.H. Zaidi
Department of Pharmacology
University of Oxford
Oxford, UK

References

1. Cotter J, Wooltorton E. New restrictions on celecoxib (Celebrex) use and the withdrawal of valdecoxib (Bextra). *CMAJ* 2005;172(10):1299.
2. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors [review]. *JAMA* 2001;286(8): 954-9. [Summary for patients in: *Can Fam Physician* 2002;48:1449-51.]
3. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000343(21):1520-8, 2 p following 1528.
4. Bolli R, Shinmura K, Tang XL, Kodani E, Xuan YT, Guo Y, et al. Discovery of a new function of cyclooxygenase (COX)-2: COX-2 is a cardioprotective protein that alleviates ischemia/reperfusion injury and mediates the late phase of preconditioning. *Cardiovasc Res* 2002;55(3):506-19.
5. Schonbeck U, Sukhova GK, Graber P, Coulter S, Libby P. Augmented expression of cyclooxygenase-2 in human atherosclerotic lesions. *Am J Pathol* 1999;155(4):1281-91.
6. Baker CS, Hall RJ, Evans TJ, Pomerance A, Maclouf J, Creminon C, et al. Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalizes with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages. *Arterioscler Thromb Vasc Biol* 1999;19(3):646-55.
7. Wentworth P Jr, Nieva J, Takeuchi C, Galve R, Wentworth AD, Dilley RB, et al. Evidence for ozone formation in human atherosclerotic arteries. *Science* 2003;302(5647):1053-6.

Competing interests: None declared.

DOI:10.1503/cmaj.1050143

Jill Cotter and Eric Wooltorton suggest an approach to prescribing COX-2 inhibitors that includes estimating cardiac risk, using the lowest doses for short periods, and discussing the risks and benefits of long-term use. They provide evidence for the cardiovascular risks of celecoxib.[1] Regarding the benefits, it is helpful to review the results of the CLASS trial,[2] which was designed to evaluate the efficacy of celecoxib in reducing clinically significant upper gastrointestinal (GI) adverse events.

CLASS reported the pooled results of 2 trials comparing celecoxib, 400 mg twice a day, with diclofenac, 75 mg twice a day, and ibuprofen, 800 mg three times a day. The study protocol prespecified that the results would be pooled, but an FDA report[3] gave the results separately for diclofenac and ibuprofen, for the full length of the 2 studies, 12 months and 15 months, whereas the published CLASS study reported 6-month data.

The FDA report concludes that the CLASS trial was a robust testing of the safety of celecoxib at doses 2 and 4 times those currently labelled for rheumatoid arthritis and osteoarthritis, respectively; celecoxib does not appear to be more effective for treating the signs and symptoms of osteoarthritis or rheumatoid arthritis than the NSAID comparators; and celecoxib did not show statistically significant superiority to diclofenac at any point in the trial regardless of ASA use or end point (including the primary end point of clinically significant upper GI events, namely, upper GI bleeding, perforation, or gastric outlet obstruction alone or with gastroduodenal ulcers).

With little indication of benefit in symptom control or reduction of adverse events, it is questionable whether there is a need to prescribe celecoxib at all.

Michael J. Allen
Dalhousie University Office of CME
Halifax, NS
Pamela McLean-Veysey
Team Leader, Drug Evaluation Unit
QEII Health Sciences Centre
Halifax, NS
Isobel Fleming
Senior Detailer, Dalhousie Academic Detailing Service
Dalhousie University Office of CME
Halifax, NS

References

1. Cotter J, Wooltorton E. New restrictions on celecoxib (Celebrex) use and the withdrawal of valdecoxib (Bextra). *CMAJ* 2005;172(10):1299.
2. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000;284:1247-55.
3. Food and Drug Administration. *Celebrex capsules (Celecoxib)*. Medical Officer Review. 14-6-2000. Available: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 2005 June 1).

Competing interests: None declared.

DOI:10.1503/cmaj.1050119

The wrong stuff

If Dr. Ursus gets upset and anxious, indeed paranoid, about misdiagnosing the very early manifestations of an extraordinarily rare disorder such as Guillain–Barré syndrome,[1] he won't last long in this job.

Ian McM. Connor
Pediatrician
Sarnia, Ont.

Reference

1. Query. *CMAJ* 2005;172(12):1648.

DOI:10.1503/cmaj.1050147