EDITORIAL
DOI 10.4070 / kcj.2010.40.7.306

Print ISSN 1738-5520 / On-line ISSN 1738-5555

Cardiovascular Safety of Celecoxib on Top of Dual Antiplatelet Therapy

Bum-Kee Hong, MD

Department of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Refer to the page 321-327

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase that catalyzes the conversion of arachidonic acid into a variety of prostaglandins, thromboxanes and leukotrienes. NSAIDs are widely used for the treatment of various arthritides and pain syndromes.[1] The anti-inflammatory and pain-relieving properties of NSAIDs are the result of prostaglandin synthesis inhibition mediated by cyclooxygenase-2 (COX-2) at the site of tissue injury, while the gastrointestinal tract complications are due to prostaglandin synthesis inhibition mediated by cyclooxygenase-1 (COX-1) in the gastrointestinal mucosa. The recognition of these 2 isoforms of COX led to the hypothesis that selective COX-2 inhibition would achieve the therapeutic benefits of non-selective NSAIDs without gastrointestinal toxicity. Celecoxib and rofecoxib were the first of these new agents that would treat pain without gastrointestinal toxicity. Large clinical trials confirmed that COX-2 inhibitors are associated with less gastrointestinal toxicity than non-selective NSAIDs. COX-2 inhibitors have since become an enormous financial success.[2-5]

However, within months of rofecoxib's approval in May 1999, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial reported a 5-fold increase in thromboembolic cardiovascular events, primarily acute myocardial infarction, despite a 50% reduction in serious gastrointestinal outcomes among patients treated with 50 mg/d of rofecoxib, compared to 1,000 mg/d of naproxen.[2] In 2004, Merck withdrew rofecoxib from the market after its Adenomatous Polyp Prevention on Vioxx (APPROVe) trial showed a 2-fold increase in cardiovascular risk associated with treatment of rofecoxib 25 mg/d, compared to placebo. The Adenoma Prevention with Celecoxib (APC) trial comparing celecoxib with placebo reported a similar risk, especially at 400 mg/d or more. However, in Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), celecoxib (400 mg/d) did not increase cardiovascular risk compared to naproxen.[6]

The cardiovasular effect of COX-2 inhibition is complicated and is not yet fully understood. While non-selective NSAIDs including aspirin inhibit the formation of platelet-derived thromboxane and endothelial prostacyclin, COX-2 inhibitors preferentially suppress vasodilator and platelet inhibitory prostaglandins without blocking vasoconstrictive and platelet-activating prostaglandins, which could result in a prothrombotic state. In addition, the role of COX-2 inhibitors in accelerated atherogenesis may be modulated by renovascular hypertension, inhibition of vascular inflammation, improvement of endothelial function and changes in artherosclerotic plaque stability.[7-9] The safety aspects related to drug-eluting stent (DES) has been continuously addressed and dual antiplatelet therapy with aspirin and clopidogrel is recommended at least for one year following DES implantation. Moreover, many patients implanted with DES are elderly and often suffered from chronic arthritis. These patients are candidates for combined anti-inflammatory agent and dual antiplatelet therapy. Particularly, selective COX-2 inhibitors may be preferred in these patients, considering the implications of life-long aspirin maintenance therapy.

In the current review, Lee et al.[10] assessed whether celecoxib therapy would negate the antiplatelet effects of aspirin and clipidogrel in healthy, young-aged volunteers using light transmittance aggregometry and arachidonic acid metabolite assay.

Correspondence: Bum-Kee Hong, MD, Department of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, 612 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea
Tel: 82-2-2019-3311, Fax: 82-2-3463-3463
E-mail: bkhong@yuhs.ac

Volunteers were divided into 5 groups (n=8 per group) by treatment regimen that included aspirin (100 mg/d), clopidogrel (75 mg/d) and celecoxib (400 mg/d): aspirin; celecoxib; asprin+celecoxib; aspirin+clopidogrel; and aspirin+clopidogrel+celecoxib. Celecoxib alone did not affect platelet aggregation, and celecoxib combined with aspirin+clopidogrel did not affect inhibition of platelet aggregation induced by adenosine diphosphase as well as collagen, suggesting that celecoxib would be administered safely to patients in whom dual antiplatelet therapy is needed. Previous studies showed that celecoxib did not affect aspirin's inhibitory action of platelet aggregation in patients with concurrent osteoarthritis and ischemic heart disease, as well as in healthy volunteers. These outcomes support that of this review.[11)12)] However, the outcomes of previous trials and that of this review can cause public confusion. Is celecoxib different from rofecoxib in terms of cardiovascular risk profile? The answer is 'partly yes' as well as 'partly no'. The cardiovascular effects of COX-2 inhibitors may differ due to distinct molecular structures with different levels of COX-1 or COX-2 selectivity, suggesting that cardiotoxicity is limited to certain drugs within the class, rather than due to a broad class effect. Kimmel et al.[13)] found no evidence of COX-2 inhibitor class effect for cardiovascular toxicity, but demonstrated that rofecoxib use was associated with a statistically significant 2.72 increased odds of myocardial infarction, when compared to celecoxib use. On the other hand, the released data of the APC trial, stopped on the advice of the data safety monitoring board, showed that patients using celecoxib over long-term (average duration 3 years) at high dosages (400 mg/d or more) had a 2.5 to 3.4 fold increased risk for fatal and non-fatal cardiovascular events, compared to those receiving placebo.[14)]

COX-2 can be a fascinating target for the prevention of restenosis following PCI, because inflammation plays an improtant role in neointimal hyperplasia following vascular injury and COX-2 is a key mediator of inflammation. Previous studies showed that celecoxib inhibits neointimal hyperplasia following vascular injury by blocking Akt signaling, and possibly monocyte chemoattractant protein-1 (MCP-1) expression.[15)16)]

This review would be good news for physicians as well as patients who have been suffered from chronic arthritis, and those require dual antiplatelet therapy following DES implantation. However, there is inconsistency in the cardiovascular safety data from various trials using selective COX-2 inhibitors and non-selective non-aspirin NSAIDs, and the evidence is currently too limited to exclude the possibility of a COX-2 inhibitor class effect. Moreover, difference in cardiovascular safety between placebo and two principal COX-2 inhibitors, rofecoxib and celecoxib, became apparent only after several years of continuous treatment at high doses. Therefore, so far, the choice of anti-inflammatory regimens in patients who need antiplatelet therapy should be made to minimize the overall burden of adverse gastrointestinal and cardiovascular outcomes. Further research is needed to elucidate the safety of long-term COX-2 inhibitor use, in conjunction with non-selective non-aspirin NSAIDs.

REFERENCES

1) Fitzgerald GA, Patrono C. *The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001;345:433-42.*
2) Bombardier C, Laine L, Reicin A, et al. *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343:1520-8.*
3) Silverstein FE, Faich G, Goldstein JL, et al. *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: arandomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284:1247-55.*
4) Schnitzer TJ, Burmester GR, Mysler E, et al. *Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665-74.*
5) Abelson R, Gardiner H. *Pfizer warns of risks from its painkiller. The New York Times 2004:B1.*
6) ADAPT Group. *Cardiovasucalr and cerebrovascular events in the randomized controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). PLoS Clin Trials 2006;1:e33.*
7) Altman R, Luciardi HL, Muntaner J, et al. *Efficacy assessment of meloxicam, a preferential cyclooxygenase-2 inhibitor, in acute coronary syndromes without ST-segment elevation: the Nonsteroidal Anti-Inflammatory Drugs in Unstable Angina Treatment-2 (NUT-2) pilot study. Circulation 2002;106:191-5.*
8) Chenevard R, Hurlimann D, Bechir M, et al. *Selective COX-2 inhibition improves endothelial function in coronary artery disease. Circulation 2003;107:405-9.*
9) Whelton A, White WB, Bello AE, Puma JA, Fort JG. *Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002;90:959-63.*
10) Lee W, Suh JW, Yang HM, et al. *Celecoxib does not attenuate the antiplatelet effects of aspirin and clopidogrel in healthy volunteers. Korean Circ J 2010;40:321-7.*
11) Wilner KD, Rushing M, Walden C, et al. *Celecoxib does not affect the antiplatelet acitivey of aspirin in healthy volunteers. J Clin Pharmacol 2002;42:1027-30.*
12) Renda G, Tacconelli S, Capone ML, et al. *Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther 2006;80-264-74.*
13) Kimmel SE, Berlin JA, Reilly M, et al. *Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med 2005;142:157-64.*
14) Burklow J, Ralbovsky D. *NIH Halts Use of COX-2 Inhibitor in Large Cancer Prevention Trial. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health;2004.*
15) Yang HM, Kim HS, Park KW, et al. *Celecoxib, a cyclooxygenase-2 inhibitor, reduces neointimal hyperplasia through inhibition of Akt signaling. Circulation 2004;110:301-8.*
16) Wang K, Tarakji K, Zhou Z, et al. *Celecoxib, a selective cyclooxygenase-2 inhibitor, decreases monocyte chemoattractant protein-1 expression and neointimal hyperplasia in the rabbit atherosclerotic balloon injury model. J Cardiovasc Pharmacol 2005;45:61-7.*