

The Painful Lesson of Analgesic Drugs: Never Underestimate the Complexity of Biological Systems

Filippo Crea and Simona Giubilato

Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

*"All Things, to each other linked are,
That, you can not stir a flower
Without troubling a star"*

Galileo Galilei

Over the past decades, advances in vascular biology and in the understanding of atherothrombosis have led to consider the endothelium not as a simple barrier between circulating blood and vascular cells but rather as larger endocrine human organ. The healthy endothelium, by the release of several vasoactive substances, such as nitric oxide, prostacyclin, bradykinin, endothelin, thromboxane A₂ (TXA₂) and angiotensin II, is responsible for maintaining the vascular homeostasis in a complex balance between vasodilation and vasoconstriction, anti-thrombosis and pro-thrombosis, anti-inflammation and pro-inflammation, growth inhibition and growth promotion.

Several studies have shown that all cardiovascular risk factors, traditional and non traditional, affect these important endothelial properties thus inducing "endothelial dysfunction."

Usually this term is solely used to indicate an impairment of endothelium-dependent vasodilatation, which is only one of the multiple endothelial functions, probably because it is the easiest to assess by non-invasive methods. Therefore, in order to avoid an over simplification that does not take into account the complexity of this biological system, the term "endothelial dysfunctions" would be more correct.

Extensive studies have convincingly demonstrated that "endothelial dysfunctions," assessed by different techniques, are a marker of the early subclinical stage

of atherosclerosis and perhaps an useful predictor of subsequent cardiovascular events. These findings, together with the evidence that these alterations are, at least partially reversible, have highlighted how the endothelium may represent a new and promising therapeutic target for the prevention and the treatment of atherosclerotic cardiovascular diseases.¹ Interestingly, drugs, such as statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, known to improve cardiovascular outcome, have shown beneficial effects on endothelial functions.

In this issue of *Revista Española de Cardiología*, Flórez et al² present an interesting study addressing the effect of celecoxib, a selective COX-2 inhibitor, on endothelium-dependent vasodilatation, assessed by brachial artery flow-mediated dilation (FMD), and also on biochemical markers of inflammation in patients with peripheral artery disease (PAD). In particular, the treatment of these patients with celecoxib for 1 week was associated with a significant increase of FMD and reduction of high sensitivity C-reactive protein (hs-CRP), endothelin and LDL cholesterol levels. The data of Flórez et al's study,² in keeping with similar findings shown in a previous study by Chenevard et al³ in the setting of coronary artery disease, arise the hypothesis that the selective inhibition of COX-2 isoform may become, in the future, a novel treatment of endothelial damage. Of note, as recently confirmed by the data of the Reduction of Atherothrombosis for Continued Health (REACH) Registry,⁴ patients with peripheral arterial disease (PAD) represent an intriguing patient population because of the high risk of cardiovascular events, which is not fully accounted for by traditional risk factors. Most importantly, in these patients, high levels of hs-CRP and low FMD are independent predictors of cardiovascular outcome.

Furthermore, recent studies on animal models have demonstrated that COX-2 inhibition is associated with a reduction in infarct size and an improvement of myocardial remodelling. Considering that ischemia induces up-regulation of COX-2 expression in cardiomyocytes, that COX-2 is an important source of pro-apoptotic mediators, including oxygen radicals,

SEE ARTICLE ON PAGES 851-7

Correspondence: Filippo Crea, MD, FACC, FESC, Department of Cardiology, Largo A. Gemelli 8, 00169 Rome, Italy
E-mail: filippo.crea@rm.unicatt.it

and that apoptosis is a key mechanism of post-ischemic cardiomyopathy, the more favourable post-ischemic pattern obtained through COX-2 inhibition could be explained by a significant reduction of myocardial apoptosis in peri-infarct regions.^{5,6} Taken together, these clinical and experimental findings suggest that COX-2 is involved in pro-inflammatory and pro-oxidant pathways which exert detrimental effects on both endothelium and myocardial tissue. Accordingly, COX-2 blockade should have beneficial effects on the cardiovascular system.

Is this statement true? The answer is a plain no! A positive answer should generate a misleading message: why?

Prostaglandin G/H synthase enzyme, commonly known as cyclooxygenase (COX), is the rate-limiting step in the synthesis of prostaglandins, a large class of short-life lipid mediators involved in several physiological and pathological processes. There are 2 isoforms of this enzyme: COX-1 is a constitutive enzyme with housekeeping functions in most cells and tissues, including endothelium, platelets, stomach, and kidney, while COX-2 is an inducible enzyme selectively expressed in inflammatory cells in response to inflammatory cytokines and growth factors. The notion of a sharp separation between COX-1 and COX-2 functional roles represented the scientific foundation for the development of a new class of drugs, the COX-2 selective inhibitors. Indeed, these drugs were designed to have the same anti-inflammatory and analgesic effects of nonsteroidal anti-inflammatory drugs (NSAIDs), mediated by COX-2 blockade, but without their gastrointestinal (GI) side effects mediated by COX-1 blockade.

Few years after selective COX-2 inhibitors were approved for clinical use because clinical randomized trials confirmed that their analgesic effects were associated with less GI side effects, an unexpected safety issue stirred the scientific community and gained popularity among lay person. Indeed, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, which was designed to compare analgesic efficacy and GI adverse effects of the COX-2 inhibitor rofecoxib with those of the nonselective NSAID, naproxen, in 8076 patients with rheumatoid arthritis who were not taking aspirin, showed a 2-fold reduction in the incidence of serious GI adverse events but also a 5-fold increase in the incidence of myocardial infarction in patients allocated to rofecoxib arm.⁷ Some researchers at that time proposed that these findings did not reflect a pro-thrombotic effect of rofecoxib but rather an anti-thrombotic effect of naproxen, mediated by a potential "aspirin-like" COX-1 inhibition.

However, a confirmation of the increased risk of cardiovascular events associated with the use

of rofecoxib came from the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial.⁸ This study, designed to assess the effect of COX-2 inhibition on benign colon adenomas, showed a 1.7-fold increase in the risk of myocardial infarction and cerebrovascular events in patients treated with rofecoxib compared with patients treated with placebo. As a result of these findings, in September 2004, MERCK voluntarily withdrew rofecoxib from the market. These data were followed by the results of the Coronary Artery Bypass Graft Surgery II (CABG-II) trial and the Adenoma Prevention with Celecoxib (APC) Study, that reported a statistically significant increase in cardiovascular events in patients treated respectively with valdecoxib (and its prodrug parecoxib) and with celecoxib compared with placebo.^{9,10}

Furthermore, subsequent studies, such as the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) trial, and meta-analyses showed that traditional NSAIDs increased the risk of cardiovascular events and that this increase was similar to that of COX-2 inhibitors.¹¹⁻¹³

Accordingly, the Food and Drug Administration (FDA) requested that all patient package inserts of NSAIDs showed a block box highlighting the potential risk of cardiovascular events. In addition, FDA asked Pfizer to withdraw valdecoxib and contraindicated the use of COX-2 inhibitors in the setting of CABG surgery. The European Medicines Agency was even stricter than FDA and contraindicated the use of COX-2 inhibitors in patients with ischemic heart disease or stroke and recommended to prescribe these drugs with caution for patients at risk for cardiovascular disease.

How to reconcile the beneficial effects of COX-2 inhibitors on endothelial function and inflammatory markers published by Flórez et al in this issue of the Journal² and the increased risk of cardiovascular events consistently observed in clinical studies?

Several studies have suggested that the interplay between COX-2 derived prostaglandins in the arterial wall and COX-1 dependent TXA₂ production in platelets have a central role in determining thrombus formation at the site of atherosclerotic plaque.¹⁴ In particular, the endothelial expression of COX-2 induced by physiological (shear stress) or pathological (inflammatory cytokines and growth factors) conditions may represent an important pathway in the modulation of the pro-thrombotic effects of TXA₂.

Indeed, mice genetically deficient for prostacyclin receptor (IP) have an increased response to exogenous thrombogenic stimuli and interestingly this response is completely abolished by concomitant deletion or selective inhibition of the TXA₂ receptor (TP). Additionally, patients with severe atherosclerosis

have a higher excretion of both prostacyclin and TXA₂ metabolites.

Given the evidence that in the endothelium prostacyclin formation is to a large extent COX-2 dependent, it can be argued that selective COX-2 inhibition increases cardiovascular risk by removing the negative feedback regulation of prostacyclin on TXA₂. This important beneficial effect of COX-2 was initially overlooked, thus opening the way to the use of selective COX-2 inhibitors, because it was felt that endothelial production of prostacyclin was mainly COX-1 dependent and was not affected by aspirin which, instead, fully inhibits COX-1 dependent TXA₂ production in platelets. Moreover, since COX-2 plays a crucial role in the induction of myocardial preconditioning, a second mechanism which may account for the increased risk of myocardial infarction associated with the use of these drugs is the potential negative effect of COX-2 inhibition on this protective phenomenon. Thirdly, several studies have shown that prostaglandins have important effects on renal mechanisms of blood pressure regulation. IP deletion like COX-2 inhibition are associated with reduced sodium excretion and thus with increased fluid retention. This mechanism may explain the increase of blood pressure levels associated to the use of both COX-2 inhibitors and NSAIDs.¹⁵

Although available data suggest the presence of a class effect, the trials mentioned above have shown a different degree of adverse cardiovascular profile for the different COX-2 inhibitors. It is likely that these differences reflect the different selective profile of these drugs and therefore their variable affinity for the 2 COX isoforms. Indeed, the dichotomous distinction between COX-1 and COX-2 selective inhibitors is more theoretical than real and it must be regarded as a continuous variable among all NSAIDs. Thus, traditional NSAIDs, such as diclofenac, nimesulide, and meloxicam, with a degree of COX-2 selectivity similar to that of COX-2 inhibitors, can be associated with a similar degree of cardiovascular risk.

On the other hand, traditional NSAIDs, such as ibuprofen, with a high COX-1 selectivity, can induce an increased cardiovascular risk in patient chronically treated with low dose of aspirin, undermining the cardioprotective effect of this drug. The underlying mechanism seems to be a competitive inhibition at the acetylation site of platelet COX-1. Because aspirin (irreversible inhibition) and ibuprofen (reversible inhibition) bind at similar sites on COX-1, the presence of ibuprofen may interfere with aspirin binding. Once ibuprofen leaves the binding site, COX-1 will not be inhibited because aspirin, that has a very short half-life, will already have been metabolized.

In conclusion, on the basis of the current knowledge on COX-1 and COX-2 biology in patients with chronic pain who need analgesic treatment the lowest effective dose of NSAIDs should be prescribed for the shortest duration. Furthermore, low dose aspirin should be assumed concurrently by patients who are at high risk for atherothrombotic events and non selective NSAIDs, such as ibuprofen, should be avoided in patients under chronic treatment with low dose aspirin because it might interfere with its antiplatelet effects.

The painful history of analgesic drugs has reminded us as in nature, *"all things, to each other linked are,"* as said Galileo, the father of modern science. Researchers must always consider the gap between experimental findings and pathophysiological observations, that reflect the need to simplify the complexity of biological systems, and the results of clinical trials, that conversely reflect the final and often unpredictable consequence of a simple intervention on a complex interplay of actions and reactions. We should humbly remember the words of Paul Erlich, the great pharmacologist who lived at the end of 19th century: *"Drugs are substances which we do not know very well, we use them to treat diseases which we know even less, and we introduce them in organisms which we do not know at all."* Thus the observation by Flórez et al² that in patients with PAD celecoxib is acutely associated to an improvement of FMD and to a reduction of inflammatory marker levels is interesting but these beneficial effects unfortunately do not offset the prothrombotic and other detrimental effects of NSAIDs. Thus, their use should be strongly contraindicated in patients with overt atherosclerotic disease.

REFERENCES

1. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation*. 2004;110 Suppl 3:27-32.
2. Flórez A, de Haro J, Martínez E, Varela C, Bleda S, Acín F. La inhibición selectiva de la ciclooxigenasa-2 mejora la disfunción endotelial y disminuye el estado inflamatorio en pacientes claudicantes. *Rev Esp Cardiol*. 2009;62:851-7.
3. Chenevard R, Hürlimann D, Bèchir M, Enseleit F, Spieker L, Hermann M, et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. *Circulation*. 2003;107:405-9.
4. Steg PG, Bhatt DL, Wilson PW, d'Agostino R Sr, Ohman EM, Röther J, et al. REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197-206.
5. Abbate A, Santini D, Biondi-Zoccai GG, Scarpa S, Vasaturo F, Liuzzo G, et al. Cyclo-oxygenase-2 (COX-2) expression at the site of recent myocardial infarction: friend or foe? *Heart*. 2004;90:440-3.
6. Abbate A, Limana F, Capogrossi MC, Santini D, Biondi-Zoccai GG, Scarpa S, et al. Cyclo-oxygenase-2 (COX-2) inhibition reduces apoptosis in acute myocardial infarction. *Apoptosis*. 2006;11:1061-3.

7. 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.* 2000;343:1520-18.
8. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005;352:1092-102.
9. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoefft A, Parlow JL, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med.* 2005;352:1081-91.
10. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med.* 2006;355:873-84.
11. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet.* 2006;368:1771-81.
12. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ.* 2006;332:1302-8.
13. Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal A. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. *Aliment Pharmacol Ther.* 2007;25:913-24.
14. FitzGerald GA. COX-2 and beyond: Approaches to prostaglandin inhibition in human disease. *Nat Rev Drug Discov.* 2003;2:879-90.
15. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest.* 2006;116:4-15.