Role of Anti-Inflammatory Drugs in the Treatment of Acute Coronary Syndromes. From Athero-Inflammation to Athero-Thrombosis

Raúl Altman and Alejandra Scazziota

Coronary thrombosis is the most important cause of morbidity and mortality and the most severe manifestation of atherosclerosis. Knowledge of the pathophysiology of atheroma formation and the causes of atheroma accidents have allowed the development of new therapeutic measures for reducing thrombotic events after a coronary episode. Treating the thrombosis after plaque rupture is useful, but a late measure once coronary flow is disturbed. Therefore, treatment at an earlier stage, which we call athero-inflammation, a central event in atheroma progression leading to atherothrombosis, seems wise.

There is evidence of an inflammatory component in the pathogenesis of atheroma rupture in acute coronary events. Earlier studies of anti-inflammatory medication have not demonstrated a reduction in thrombotic complications after an acute coronary episode. However, there are pathophysiological arguments and clinical findings that suggest that it would be advisable to include anti-inflammatory medications, especially those that inhibit preferentially COX-2, in the therapeutic arsenal for this pathology.

We postulated that blocking athero-inflammation could prevent thrombosis. A pilot study was carried out in 120 patients with acute coronary syndrome without ST-segment elevation in which 60 patients were treated with meloxicam, a preferential COX-2 inhibitor. All patients received heparin and aspirin. During the stay in the coronary care unit, as well as after 90 days, meloxicam lowered composite outcomes (myocardial infarction, death and revascularization procedures) compared with the control group. These results and available pathophysiological and clinical evidence support the hypothesis of potential benefits of non-steroidal anti-inflammatory drugs with preferential inhibitory activity on COX-2 in patients with acute coronary syndromes. More trials are needed to confirm their preventive effect.


Papel de los antiinflamatorios en el tratamiento de los síndromes coronarios agudo, de la ateroinflamación a la aterotrombosis

La trombosis coronaria es la causa más frecuente de morbimortalidad y la manifestación más grave de la aterosclerosis. El conocimiento de la fisiopatología de la formación del ateroma y de las causas del accidente de placa han permitido nuevas medidas terapéuticas para disminuir los acontecimientos trombóticos que siguen a un episodio coronario. Tratar la trombosis que sigue a la rotura de una placa es una terapéutica útil pero se aplica tardíamente, ya constituidas las alteraciones del flujo coronario. Por ello el tratamiento en una etapa más temprana, la que llamamos ateroinflamación, eje central en la progresión del ateroma y que lleva a la aterotrombosis, aparece como más racional.

Hay evidencias importantes acerca del componente inflamatorio en la patogenia de la rotura del ateroma en los acontecimientos coronarios agudos. Aun cuando en estudios previos donde se utilizaron antiinflamatorios no pudo demostrarse una disminución de las complicaciones trombóticas tras un episodio coronario agudo, existen pautas fisiopatológicas y hechos clínicos que hacen pensar en la inclusión de los antiinflamatorios, especialmente aquellos con inhibición preferencial de la COX-2, en el arsenal terapéutico contra esta enfermedad.

Postulamos que la disminución de la ateroinflamación lleva a la reducción de los acontecimientos aterotrombóticos. En un estudio piloto de nuestro grupo, donde se incluyó a 120 pacientes con síndrome coronario agudo sin elevación del segmento ST, 60 fueron tratados con meloxicam, un inhibitor preferencial de la COX-2. Todos estuvieron medicados también con heparina y aspirina. El meloxicam redujo los acontecimientos coronarios (infarto de miocardio + maniobras de revascularización miocárdica + muerte) tanto durante el período hospitalario como a los 90 días de seguimiento.

Con estos resultados y con los fundamentos fisiopatológicos y las bases clínicas disponibles, sostenemos la necesidad de seguir investigando, en los síndromes coronarios agudos, las posibilidades terapéuticas de los diversos antiinflamatorios no esteroideos (AINE) con inhibición preferencial de la COX-2.


Full Spanish text available at www.revespcardiol.org

Correspondence: Dr. R. Altman. Centro de Trombosis de Buenos Aires. Viamonte, 2008. 1056 Buenos Aires. Argentina. E-mail: draaltman@arnet.com.ar
INTRODUCTION. ATHEROTHROMBOSIS AND AHEROINFLAMMATION

Coronary thrombosis is the most frequent cause of morbidity and mortality and the most severe manifestation of atherosclerosis. In addition, although death due to coronary disease has decreased in frequency in the last 20 years in the U.S. and Europe, it has increased in other regions. Knowledge of the pathophysiology of atheroma formation, as well as of the causes of plaque instability and rupture that lead to thrombosis, has grown, thus making it possible to implement new therapeutic measures to curtail the thrombotic events that follow an acute coronary episode.

Thrombosis can totally or partially occlude the vascular lumen and condition either acute myocardial infarction, with or without changes in the ST segment, or acute coronary events without a detectable myocardial lesion. The mechanism of the formation of a thrombus on an atherosclerotic plaque is complex and the pathophysiological phenomena involved may be related to atheroma rupture (Figure 1): superficial erosion of the intima, or hemorheological phenomena that take place on the distal face of the atheroma in response to blood flow. Thrombi form in all these circumstances, with the relative participation of platelets and fibrin differing in accordance with the pathophysiological mechanisms involved, and usually resulting in the formation of a mixed thrombus. Based on this mechanism of arterial occlusion, in which thrombosis appears as a complication of atheroma, the atherothrombosis concept was created and therapy has been oriented toward detaining the mechanisms of extrinsic and intrinsic coagulation and inhibiting platelet activation. However, it is clear that thrombosis is the final event in a mechanism that for years has remained on the sidelines, inflammation. The treatment of coronary thrombosis, while useful and necessary, takes place somewhat late because the process could have caused important disturbances (sometimes almost mortal) in the cardiovascular system. Thus, athero-inflammation is the central axis around which uncomplicated atheroma progresses to athero-thrombosis. It is reasonable, therefore, to seek to understand the mechanisms that precede plaque rupture in order to find an alternative therapy that can be applied before thrombotic arterial occlusion occurs.

INFLAMMATION AND ACUTE CORONARY EVENTS

The idea that inflammation is related to acute ischemic myocardial conditions dates from more than 60 years ago. There is major evidence of an inflammatory component in the pathogenesis of atheroma rupture in acute coronary events. Inflammation is more important in the acute rupture of the atherosclerotic plaque than in complete coronary thrombotic occlusion secondary to a stable plaque. In addition, inflammation is less evident in occlusive conditions dependent on superficial erosion of the endothelium, without atheroma rupture. The proliferation of smooth muscle cells (accelerated progression pattern) is less frequent (30%) in patients with stable angina than in those with unstable angina (64%-100%).

The inflamed vascular wall influences pathogenesis and conditions the evolution of patients with unstable angina, determining plaque instability and endothelial cell dysfunction. The inflammatory cells secrete proteolytic enzymes that tend to degrade the fibrous plaque. The fibrinolytic substances, together with the system of metalloproteinases (collagenases, stromalysins, and gelatinases), degrade the extracellular matrix and contribute to plaque rupture. The pathophysiological basis of these disturbances is regulated by pro-inflammatory mediators. These observations provide evidence of the importance of inflammation in the episodes that occur in the evolution of patients with unstable angina.

After rupture, the components of the lipid nucleus are exposed to the circulating blood, lipids, microcalcifications, and cellular detritus that includes activated macrophages and smooth muscle cells. This material is highly thrombogenic and, together with the exposure of tissue factor, conditions local thrombin formation, platelet activation, and fibrin formation. Inflammation followed by rupture at the shoulder of the atheroma, and subsequent thrombosis, determine the progression of the atherosclerotic plaque.

However, even when one of the lesions is clinically active and originates symptoms of acute coronary...
syndrome, it is a local manifestation of a multifocal systemic process\textsuperscript{21,23} in which inflammatory components participate.

Under these conditions, infections, especially by \textit{Chlamydia pneumoniae}, can become established in the atheromatous plaque as a result of its affinity for the endothelial cell. \textit{C. pneumoniae} is transported from the respiratory tree by macrophages arising from monocytes in the peripheral blood. A latent infection exists that becomes active during inflammation. These possibilities have been considered, but have not been clarified by studies (Figure 2). The use of antibiotics in the prevention of ischemic complications in patients with acute and chronic coronary disease has not yielded homogeneous results or made it possible to confirm the importance of infection in coronary diseases.\textsuperscript{24-27} Even though a direct correlation between \textit{C. pneumoniae} infection and inflammation has not been corroborated,\textsuperscript{28,29} the macrolides used in these studies have anti-inflammatory effects in addition to their antibacterial action. Perhaps the different results obtained in various investigations derive from differences in anti-inflammatory properties.\textsuperscript{27,28}

In addition to the inflammatory mechanisms mentioned, some components of the coagulation system, like thrombin, can favor inflammation.\textsuperscript{30} The expression of the tissue factor in endothelial cells and monocytes is regulated in part by proinflammatory cytokines like interleukin 1 and tumor necrosis factor (TNF).\textsuperscript{31} Therefore, there are several synergic mechanisms that determine and sustain inflammation\textsuperscript{31} (Figure 3).

As a result of chronic inflammation, markers like C-reactive protein (CRP), cytokines (interleukin 6, TNF), adhesion molecules (intercellular adhesion molecule 1, ICAM-1), fibrinogen, and some other coagulation factors may be increased in plasma. Some of them can be of prognostic value for future cardiovascular events.\textsuperscript{32-34} Interleukin 18, which induces the production of gamma interferon by T lymphocytes and has a central role in the inflammation cascade, has been found to be a strong predictor of death due to cardiovascular causes in patients with coronary disease and both stable and unstable angina.\textsuperscript{35} On the other hand, CRP has a direct pro-inflammatory action on vascular endothelium. Indeed, the experimental infusion of recombinant human CRP induces the expression in human endothelial cells of VCAM, ICAM, and E-selectin adhesion molecules.\textsuperscript{36} It thus closes a circle in which the factors of cellular aggression condition the inflammation and the products that they form favor the same inflammatory process.

In acute coronary syndromes, the combination of aspirin and heparin is the standard antithrombotic treatment. When treatment is discontinued, an increment in the markers of thrombosis can be detected (fragment 1+2, fibrinopeptides, thrombin-antithrombin complex), which reappear even after the use of abciximab\textsuperscript{37,38} or decrease with the use of eptifibatide. It is likely that the discordant results obtained with drugs that have similar effects indicate that there is more than one cause of reactivation, and that the intraplaque inflammatory process may impede passivation of the atherosclerotic plaque.

In confirmation of this possibility, Lincoff et al.\textsuperscript{39} have demonstrated that abciximab suppresses the increase in circulating inflammation markers (CRP, interleukin 6, TNF) in patients undergoing percutaneous coronary revascularization. These
authors suggest that some of the long-term beneficial effects could derive from reducing the contribution of these molecules to inflammation.

Clopidogrel, which primarily inhibits platelet aggregation, decreases the expression of P-selectin, thus blocking the interaction between platelets, endothelial cells, and monocytes, and modulating the inflammatory process. Also, the inhibitors of hydroxymethyl glutaryl coenzyme A reductase (statins) reduce the incidence of coronary clinical events and high concentrations of serum inflammatory markers. The effects of the statins have been observed in patients with both high and normal cholesterol concentrations, which indicates that their preventive effect is independent of their lipid-lowering action and probably related to their anti-inflammatory activity. Antidiabetic agents could have a similar action, like the thiazolidinediones, which reduce CRP concentrations, a reduction that is parallel to that of the metalloproteinases, a group of enzymes that favor the rupture of the atheroma plaque. Angiotensin II, in addition to its vasoconstrictive action, can favor intimal inflammation, and certain beneficial clinical effects of the angiotensin-converting enzyme inhibitors may derive from their capacity to inhibit this pro-inflammatory activity.

Likewise, innate immune reactions against bacteria and virus have been postulated as the basis of atherosclerosis. Bacterial lipopolysaccharides, through the toll-like receptors (TLR), which are notably increased in atherosclerotic lesions, stimulate smooth muscle cells and the inflammation of endothelial cells and macrophages. This suggests a mechanism by which bacteria can favor the inflammatory process in atheroma. The recent finding that TLR-4 polymorphism, which decreases the response to Gram-negative microorganisms, is associated with a reduction in the risk of atherosclerosis underlines the participation of TLR in inflammation and atheroma.

Recent studies have detected an increase in the number of patients with coronary disease and death in winter and during influenza epidemics. In these circumstances, an autoimmune reaction may stimulate and prolong the inflammatory process, since infection by the influenza virus promotes macrophage infiltration of the arterial wall. Two studies have confirmed the benefits of influenza vaccine against coronary diseases. Naghavi et al. observed that patients with chronic coronary artery disease who had been vaccinated against flu presented a negative association with the possibility of suffering new myocardial infarction. On the other hand, Gurfinkel et al. found a reduction in the cardiovascular death rate of patients with myocardial infarction, with or without ST-segment elevation, who were vaccinated against the flu. Several mechanisms of endothelial injury influence local inflammatory conditions (Figure 3). The development of lesions in different diseases, like the dyslipidemias, hyperhomocysteinemia, hypertension, diabetes, obesity, metabolic syndrome, and renal dysfunction, is related to inflammation. Immunity could be included among these high risk states and inflammation could be the central mediating factor.

**NON-STEROID ANTI-INFLAMMATORY AGENTS IN THE TREATMENT OF ACUTE CORONARY SYNDROMES**

The cyclo-oxygenases regulate the formation of thromboxane A2, and prostacyclin and participate in the inflammatory process. There are two cyclo-oxygenase (COX) isoforms derived from separate genes. COX-1 is constitutive of various tissues and is responsible for the conversion of arachidonic acid into the cyclic endoperoxides that give rise to the formation of a strong platelet aggregator and vasoconstrictor, thromboxane A2 , and a strong inhibitor of platelet aggregation and vasodilator, prostacyclin, in addition to other intermediate substances with different types of biological activity. On the other hand, COX-2 is the rapidly inducible enzyme at the site of inflammation. It is expressed by endothelial cells, smooth muscle cells, and macrophages in atherosclerotic lesions, and it is very important in inflammatory process.

Aspirin and other nonsteroid anti-inflammatory drugs (NSAIDs) have a non-selective inhibiting effect on COX-1 and COX-2.

Even when anti-inflammatory drugs were used in previous studies, no decrease in thrombotic complications could be demonstrated after acute coronary episodes, either because of the medication used or the study design of the investigation. However, there are pathophysiological patterns like those described earlier, and clinical findings that suggest the need to include certain anti-inflammatory agents in the therapeutic arsenal of this disease.

Burleigh et al. found that COX-2 favors atherosclerotic lesions in mice deficient in LDL receptors, suggesting that anti-inflammatory agents could be used in the prevention of atherosclerosis. The inhibition of COX-2 can reduce vascular inflammation and, consequently, monocyte infiltration, improve the availability of nitric oxide, reduce the progression of atherosclerosis, and improve plaque stability.

In the Physicians’ Health Study, Ridker et al. found that CRP is a marker predictive of myocardial infarction and that aspirin use is associated to a significant reduction in risk, probably due to its anti-inflammatory activity. In studies of mice, several cytokines that increase during experimental atherogenesis were significantly reduced by treatment with aspirin.
A new generation of NSAIDs that selectively inhibit COX-2 has been described. Among these drugs are celecoxib, meloxicam, and rofecoxib.

In contrast with the anti-inflammatory agents that have a greater COX-1 inhibitory effect, these drugs reduce the formation of prostacyclin by the vascular endothelium without modifying the formation of platelet thromboxane, thus conditioning a thrombotic risk (Figure 4). In the VIGOR study, an increase in thrombotic cardiovascular complications was observed with rofecoxib versus naproxene, a NSAID that has a greater inhibitory effect on COX-1. However, in the CLASS study, in which celecoxib was compared with the NSAIDs ibuprofen and diclofenac, there were no differences in the frequency of thrombotic coronary complications.

Although it is theoretically possible, the analysis of several studies did not confirm that rofecoxib (and perhaps other COX-2 inhibitors) produces a larger number of cardiovascular complications. The results do not seem to depend on the increase in thrombotic complications induced by rofecoxib, but on the protective effect of the antiplatelet activity of naproxene.

The concomitant use of aspirin and heparin is the accepted treatment in acute coronary syndromes. Through the inhibition of platelet thromboxane A2 formation by aspirin, the thrombotic load that might theoretically be determined by specific COX-2 inhibitors would be counteracted.

Meloxicam has a powerful anti-inflammatory activity and low gastric toxicity, more strongly inhibiting prostaglandin synthesis at the site of inflammation than in the gastric mucosa, so that it produces digestive effects less frequently.

We postulated that the decrease in atheroinflammation would lead to a reduction in the frequency of atherothrombotic events. Guided by this concept, we made a pilot study in patients with acute coronary syndrome without elevation of the ST segment that included 120 patients treated with heparin and aspirin, 60 of which were administered, at the time of admission, 15 mg of meloxicam intravenously, followed by 15 mg a day per os, which was maintained for 30 days. During the stay in the coronary unit (mean, 4.4 days), the conjunction of recurrent angina, myocardial infarction, and death was significantly less frequent (P=.007) in the group treated with meloxicam. Significant results were also obtained when the endpoints of myocardial infarction plus myocardial revascularization maneuvers plus death were used (P=.034). These variables remained different at both 30 and 90 days of follow-up. Since it was a pilot study, it will be necessary to carry out a study on a larger scale to corroborate the results obtained by our group.

Atherothrombosis occurs very late in the pathophysiological cascade of events. Atheroinflammation occurs at an earlier stage, when myocardial ischemia has not yet taken place. Therefore, we believe that there is sufficient pathophysiological evidence and a clinical basis for continuing to investigate the therapeutic possibilities of different NSAIDs that preferentially inhibit COX-2 in acute coronary syndromes. Their use in chronic coronary diseases is another possibility to be investigated.

REFERENCES


46. Gurfinkel EP, De la Fuente RL, Mendiz O, Mautner B, for the FLUVACS Study Group. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary

32


