UPDATE

Myocardial Revascularization (V)

Advances in Adjunctive Pharmacological Therapy for Percutaneous Coronary Interventions

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All percutaneous interventions disrupt atherosclerotic plaque and denude the endothelium. These processes stimulate both platelet aggregation and the coagulation cascade. Therefore, pharmacological treatment during percutaneous intervention is based on the use of antithrombotic agents. In addition to aspirin, whose benefit has been clearly demonstrated in all forms of ischemic heart disease, clopidogrel, given before and after cardiac catheterization, also reduces the rate of thrombosis after stent placement. Moreover, the introduction of glycoprotein IIb/IIIa inhibitors has improved the results of percutaneous revascularization, especially in high-risk patients. On the other hand, anticoagulants are essential for preventing the acute thrombotic complications that result from the invasive nature of the procedure. Low-molecular-weight heparins, direct thrombin inhibitors (e.g., hirudin and its derivatives), and recently developed pentasaccharides, which inhibit factor X, provide new alternatives to classical unfractionated heparin. These novel compounds lead to fewer hemorrhagic complications than unfractionated heparin and do not require such extensive monitoring. Finally, new antiproliferative agents, such as oral rapamycin, have been introduced to reduce the rate of coronary restenosis during follow-up.

Key words: *Percutaneous coronary intervention. Pharmacological therapy. Antithrombotics. Anticoagulants.*

Avances en el tratamiento farmacológico coadyuvante en la intervención coronaria

El intervencionismo percutáneo genera una rotura de la placa aterosclerótica y una denudación del endotelio que estimulan la agregación plaquetaria y la coagulación. Por ello, los agentes antitrombóticos son la base del tratamiento farmacológico coadyuvante al cateterismo intervencionista. Además de la aspirina, fármaco de beneficio indiscutible en la cardiopatía isquémica, el clopidogrel, administrado antes y después del cateterismo, ha demostrado su utilidad en la reducción de las tasas de trombosis tras la implantación de *stent*. A su vez, la introducción de los inhibidores de la glucoproteína IIb/IIIa ha mejorado los resultados de la revascularización percutánea, especialmente en los pacientes de mayor riesgo. Por su parte, los fármacos anticoagulantes son indispensables para evitar las complicaciones trombóticas agudas derivadas de las características invasivas del procedimiento. Las heparinas de bajo peso molecular, los inhibidores directos de la trombina (hirudina y derivados) y los inhibidores directos del factor X son las nuevas alternativas a la heparina no fraccionada clásica, que han demostrado reducir las complicaciones hemorrágicas sin requerir una monitorización tan exhaustiva.

Finalmente, con objeto de reducir la reestenosis coronaria a medio plazo, se han ensayado fármacos con actividad antiproliferativa. Es el caso de la rapamicina oral.

Palabras clave: *Intervencionismo coronario percutáneo. Tratamiento farmacológico. Antitrombóticos. Anticoagulantes.*

INTRODUCTION

All percutaneous revascularization techniques rupture atherosclerotic plaque and denude the vascular endothelium to a greater or lesser extent, leading to this material and subendothelial tissue being exposed to the bloodstream. This stimulates adhesion and platelet aggregation as well as the coagulation

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cascade. Both processes lead to thrombin production (thrombus formation) and ultimately to fibrin production (for thrombus stabilization), which might have repercussions on the coronary lumen. Thus, since the beginning of percutaneous coronary intervention (PCI), multiple strategies have been tried to reduce the acute complications stemming from thrombus formation, mainly based on the administration of drugs with antiaggregation and anticoagulant activity.

Initially, angiographic flow and residual stenosis in the coronary lumen were taken as parameters to evaluate the success of the intervention. However, it was soon observed that, independently of epicardial coronary flow, optimal reperfusion, with prognostic implications, also guaranteed myocardial and microvascular reperfusion. Adequate myocardial perfusion is hindered by microvascular dysfunction mainly due to the ischemia itself, reperfusion injury, and distal embolization of thrombotic and atherosclerotic material during the procedure. Different strategies have been tried to minimize these events occurring during PCI. Regardless of the distal protection devices, the drugs used for this purpose mainly relate to the treatment of acute ST-segment elevation myocardial infarction. As this topic deserves its own space they will not be described in detail here.

Finally, a third problem of concern to the catheterization specialist is restenosis of the coronary artery in the mid- and long-term. In addition to strict control of cardiovascular risk factors and secondary prevention drugs in ischemic heart disease, drug-eluting stents are presented as the main alternative to reduce the incidence of restenosis. From the pharmacological standpoint, promising outcomes have recently been achieved with certain immunosuppressive drugs, the process of restenosis being understood as a general inflammation process.

In the following, the main adjuvant drugs for PCI are presented. First, drugs with antithrombotic action, which are basic to PCI, are described in detail; second, drugs that have recently proven to reduce the incidence of coronary restenosis are briefly described, this being the case of oral sirolimus.

ANTITHROMBOTIC DRUGS (I): ANTIPLATELET AGENTS

Acetylsalicylic Acid

Aspirin or acetylsalicylic acid (ASA) acts by irreversibly inhibiting platelet cyclo-oxygenase-1 that synthesizes thromboxane A_2 (TxA_2) from arachidonic acid. The inhibition of TxA_2 synthesis, one of the main potentiators of platelet aggregation, gives rise to the antiplatelet effect of ASA (Figure 1).

The studies that established the benefit of ASA therapy in the context of PCI date to the end of the 1980s. Compared to placebo, they demonstrated a reduction in acute ischemic events, such as periprocedural thrombosis and acute myocardial infarction (AMI).[1-3] Indefinite ASA therapy continues to be the indisputable indication in patients with ischemic heart disease referred for cardiac catheterization, and its usefulness in secondary prevention (reduction in death rates, reinfarction, or stroke) has been fully demonstrated.

On the other hand, the antiinflammatory role of low-dose (80 mg/day) ASA has been recently described. This action, apart from its antiplatelet effect, helps to partly explain the benefits attributed to the drug in cases of ischemic heart disease and specifically in PCI. In general, it is accepted that a dose of 80-325 mg/day ASA should be administered at least in the 2 h prior to the procedure.[4,5] However, these doses are empirical, without an effective minimum dose having been definitively established. When ASA therapy is combined with other antithrombotic drugs (mainly clopidogrel or acenocoumarol), yet lower doses (75-100 mg/day) are recommended based on a substudy of the CURE study, which demonstrated a higher incidence of major hemorrhages in the groups that received doses of ASA higher than 100 mg/day (maximum incidence in the ASA group receiving >200 mg/day).[6]

Thienopyridines

The thienopyridines (ticlopidine and clopidogrel) act by irreversibly inhibiting the adenosine diphosphate platelet receptor (Figure 1), and thus its antiplatelet effect complements that of ASA. This means that, since their introduction, these drugs have been mainly studied in combination with ASA, in an attempt to obtain a stronger antiplatelet effect, since, with the introduction of the intracoronary stent, the subacute thrombosis rate with single antiplatelet therapy with ASA still reached 3.5%-8.6%.

Like ASA, in addition to their antiplatelet effect, the thienopyridines, specifically clopidogrel, have an antiinflammatory effect because they eliminate certain inflammation markers such as CD62 and CD40L and reduce the increase in C-reactive protein that follows coronary catheterization, which has prognostic value.