Past: the era of aspirin and ticlopidine

Over the past century, the enormous success of aspirin was mainly due to its analgesic and anti-inflammatory properties. However, aspirin has triumphed during the past decade in the prevention and treatment of platelet mediated arterial events. The modern history of aspirin may have started with the ISIS-2 trial and antiplatelet treatment in vascular diseases has rapidly become a monopoly for aspirin as no other drug compares favourably in terms of both risk:benefit and cost-effectiveness analyses.1 Indeed, only one study compared ticlopidine and aspirin head to head showing a borderline superiority for ticlopidine in a high risk population with cerebrovascular disease.7 The other studies conducted with either drug were placebo controlled and demonstrated relative risk reductions for the composite outcome of stroke, myocardial infarction or vascular death of 33% with ticlopidine and 25% with aspirin. This difference of efficacy was used to calculate the sample size of the second major trial comparing two oral antiplatelet drugs, aspirin and clopidogrel (a ticlopidine derivative), to prevent thrombotic complications in patients with atherosclerotic disease.8 The final difference observed in the CAPRIE trial for the risk reduction of stroke, myocardial infarction or vascular death significantly favoured clopidogrel over aspirin. The risk reduction was small but it was close to the difference expected before starting the study (relative risk reduction of 8.7%, p = 0.04). Tolerance of clopidogrel was excellent and at least as good as for aspirin. There were fewer cases of neutropenia, fewer haemorrhages, and less gastrointestinal discomfort but a few more cases of rash and diarrhoea than with aspirin. Furthermore, aspirin sensitive patients were excluded from the study, which might have underestimated the safety profile of clopidogrel. Therefore, clopidogrel is the first oral antiplatelet drug with a better risk:benefit ratio than aspirin in atherothrombosis. However, the CAPRIE study considered that manifestations of atherothrombosis were the same in patients with cerebrovascular, coronary, and peripheral arterial disease, and that a similar prevention strategy could be applied with the same success for all patients. This hypothesis derives from the interpretation of prevention studies with aspirin; however, while the success of aspirin is clear in stroke and myocardial infarction, we lack clinical studies demonstrating its efficacy in peripheral arterial disease.9

Present: the era of clopidogrel

The evaluation of clopidogrel in vitro is impossible because, like ticlopidine, it requires hepatic metabolism for its anti-agregating effect. Clopidogrel interferes with ADP binding sites thereby affecting ADP dependent activation of the glycoprotein IIb/IIIa receptors. Clopidogrel is 100 times more potent than ticlopidine and both drugs affect platelets irreversibly, as does aspirin. The final difference observed in the CAPRIE trial for the risk reduction of stroke, myocardial infarction or vascular death significantly favoured clopidogrel over aspirin. The risk reduction was small but it was close to the difference expected before starting the study (relative risk reduction of 8.7%, p = 0.04). Tolerance of clopidogrel was excellent and at least as good as for aspirin. There were fewer cases of neutropenia, fewer haemorrhages, and less gastrointestinal discomfort but a few more cases of rash and diarrhoea than with aspirin. Furthermore, aspirin sensitive patients were excluded from the study, which might have underestimated the safety profile of clopidogrel. Therefore, clopidogrel is the first oral antiplatelet drug with a better risk:benefit ratio than aspirin in atherothrombosis. However, the CAPRIE study considered that manifestations of atherothrombosis were the same in patients with cerebrovascular, coronary, and peripheral arterial disease, and that a similar prevention strategy could be applied with the same success for all patients. This hypothesis derives from the interpretation of prevention studies with aspirin; however, while the success of aspirin is clear in stroke and myocardial infarction, we lack clinical studies demonstrating its efficacy in peripheral arterial disease.9

Future: oral IIb/IIIa receptor blockers

Parenteral agents blocking platelet glycoprotein IIb/IIIa have been successfully developed, and the monoclonal antibody to this receptor (abciximab) is effective (versus placebo) for preventing acute complications in all types of patients undergoing coronary angioplasty.7,9 A drug can be more effective than a placebo but it can never be safer, and this statement of the obvious has been verified again with abciximab, which induced an excess of major bleedings partly related to an overdose of heparin (3.8% in CAPTURE and 10.6% in EPIC with the same definition). The incidence of thrombocytopenia was increased (5.6% with abciximab versus 1.3% with placebo in CAPTURE) and readministration of abciximab remains theoretically hazardous. The favourable risk:benefit ratio led abciximab to a success, limited mainly by the excessive cost of the drug and the skepticism of interventional cardiological physicians.10
ologists preferring often mechanical rather than pharmacological prevention of acute thrombotic occlusions. However, when analysing the recent data of the CAPTURE and EPILOG trials, the use of stents and abciximab together appears to decrease synergistically the incidence of clinical end points, but also to increase the cost of the procedures.

Two other IIb/IIIa blockers were tested in coronary angioplasty with a very satisfactory safety profile but no clinical benefit at 30 days. Success has come more recently for the parenteral peptidomimetic tirofiban demonstrating a better stabilisation at seven days of severe unstable angina with tri-therapy combining aspirin, heparin, and tirofiban compared to the classic aspirin–heparin combination.

We will soon be very rich in medications for the acute phase of coronary syndromes but will remain quite poor for the chronic phase of prevention, with aspirin still standing alone and clopidogrel having to prove its efficacy in coronary artery disease. New oral antiplatelet agents are needed and they must be more potent than aspirin with far fewer side effects than abciximab because they will be prescribed in ambulatory patients for long term prevention with a cumulative risk of bleeding and other complications. This challenge resembles the CAPRIE hypothesis. Several oral IIb/IIIa blockers are now entering phase III trials; should they be developed with or instead of aspirin? These agents seem more effective and more risky than aspirin; however, the administration of both drugs may not be redundant because aspirin does not only acetylate a serine of the cyclo-oxygenase. Aspirin also acetylates fibrinogen and has many cyclo-oxygenase independent mechanisms including modulation of thrombolysis, effects on membrane proteins, red blood cell–platelet interactions, and other multicellular interactions, which contribute to its preventive effect in patients with coronary disease.

Although globally very safe, aspirin slightly increases the incidence of bleeding including haemorrhagic stroke. All parameters should be examined carefully before discarding aspirin or embarking on powerful antiplatelet combinations. The need for better long term secondary prevention is real in terms of antithrombotic action but the safety requirements are high. What incidence of haemorrhagic stroke, gastrointestinal and other bleeding, and thrombocytopenia will be acceptable with the new treatments? What cost will be acceptable considering the degree of clinical benefit? Time has come for the use of parenteral IIb/IIIa blockers and we are already skating freely with these drugs to prevent complications in the catheterisation laboratory and soon in the intensive care unit. Time is coming for oral blockers of the same class but the ice may be thinner for out of hospital prevention.

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Blocking platelets more: are we skating on thin ice?

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