Editorial

Blocking platelets more: are we skating on thin ice?

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.[2] 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 manifest as either recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease.[3]

Present: the era of clopidogrel

The evaluation of clopidogrel in vitro is impossible because, like ticlopidine, it requires hepatic metabolisation for its anti-aggregating 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.[4]

The hypothesis of the unifying concept of atherothrombosis may also be wrong for prevention with clopidogrel, which was not better than aspirin in patients with myocardial infarction (as an entry criterion in the study) and much more effective in patients with peripheral arterial disease.[3] When considering myocardial infarction as an end point of the study, however, clopidogrel was very effective—the relative risk reduction for myocardial infarction was triple that for stroke in the whole study population. But again, prevention of myocardial infarction was mainly in the subgroup of patients with peripheral arterial disease and much less in the subgroup of patients with a first myocardial infarction (entry criterion).

Clopidogrel will be available very soon and will replace ticlopidine. Cardiologists will require more convincing data to prescribe it in place of aspirin as they will consider myocardial infarction as a criterion for prescription. Patients with multivascular atherosclerotic disease should benefit from clopidogrel. Prevention of coronary stent thrombosis is another hot issue for clopidogrel as ticlopidine has not yet received official approval for this indication. The preliminary data were obtained in a register with ticlopidine as the sole antiplatelet agent providing a low rate of both stent thrombosis and vascular complications.[5] The now classic treatment combining aspirin and ticlopidine is better than aspirin alone or aspirin and warfarin but we do not know whether it is better than ticlopidine alone. This question should be asked in a future study with clopidogrel in prevention of stent thrombosis; in addition, the potential effect of combined aspirin and clopidogrel on restenosis should be studied as this combination might be safe enough for longer term (six months) treatment, providing a pronounced and prolonged antiplatelet effect.

Considering the safety profile of clopidogrel, another challenge is conceivable but ambitious—primary prevention. Aspirin has shown a 44% reduction of myocardial infarction versus placebo in a low risk group of healthy American male physicians, but with a slight increase of haemorrhagic strokes and gastrointestinal complications, neither of which are expected with clopidogrel use.[6] Primary prevention is widely accepted for a few biological markers of vascular risk (diabetes, hypercholesterolaemia) but such markers of risk do not exist for platelets. Selecting high risk patients on clinical grounds for treatment with clopidogrel could show an overall reduction in mortality, which is crucial to convince health authorities to finance another expensive treatment for primary prevention.

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 definitions). 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 cardi-

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.[10 11] 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.[12]

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.[13] 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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