Pharmacotherapy in cardiovascular diseases and vascular interventions

Karlheinz Peter, Christoph Bode
Department of Cardiology and Angiology, Internal Medicine III, Albert Ludwigs University, Freiburg, Germany

The current theme issue of *Thrombosis and Haemostasis* focuses on antiplatelet, anticoagulative and antithrombotic pharmacotherapy in patients with atherothrombotic diseases and especially those undergoing vascular interventions. This topic is of central importance to the majority of patients treated in most clinical disciplines, but especially in the areas of cardiology, neurology and angiography. Based on an international symposium *Update in Thrombolysis 2003: Arteriosclerosis, Thrombosis and Cardiovascular Biology*, the first collection of review and original articles are assembled in this issue of the Journal and a second part will be published in an upcoming 2005 issue.

Anti-platelet pharmacotherapy

Aspirin® (acetyl salicylic acid) is the prototypic anti-platelet agent, and the benefit/cost ratio of this drug is unsurpassed. Based on the benefits obtained in secondary prevention of the clinical manifestations of atherosclerotic disease, aspirin has saved innumerable lives and is certainly one of the most successful drugs ever developed. As for many drugs in the field of antithrombotic pharmacotherapy, however, there are controversial opinions regarding the indication (e.g. primary prevention), the dose (differing recommendations between 75 and 325 mg daily), the best way of delivery (pure, buffered or newer but less evaluated enteric-coated), and the presence and clinical relevance of “aspirin resistance”. Especially with the latter, there is a large controversy regarding the mechanisms and the potential need to screen patients for “aspirin non-responders” (1). The review by Maree and Fitzgerald (2) provides a concise and informative overview on all these topics associated with aspirin therapy. Furthermore, the authors describe the major target of aspirin, cyclooxygenase (Cox) I, and its mechanism of action. In light of the withdrawal of Rofecoxib (VIOXX®) from the market (3), the comparison of the mechanism between Cox I and Cox II and the sequela of the Cox II inhibition are of special interest.

Another important oral anti-platelet drug without doubt is the thienopyridine clopidogrel. This agent specifically inhibits one of three ADP receptors on platelets, the P2Y12 receptor (4). This drug has a unique history, since it was introduced in the clinic before the target receptor was identified. In contrast to its predecessor, the thienopyridine ticlopidine, clopidogrel has not revealed fatal haematopoetic side effects, and is now used either as an alternative for or in combination with aspirin. Especially for coronary interventions such as stenting, the rates of acute or subacute thromboses have been significantly reduced by the combination of aspirin and clopidogrel (5, 6). As with aspirin, however, several pharmacological issues are not fully elucidated; and several studies, including the reports by Grossmann et al. (7) and Ahnadi et al. (8), have shown large variations in platelet response following the standard dose of 75 mg daily, particularly with overweight patients. Another issue is the starting dose of clopidogrel: In patients with acute coronary syndromes, who need urgent interventions, the ADP blockade is needed as soon as possible. Therefore, a loading dose of 300 mg is now generally accepted among clinicians, whereas twice as much seems to be increasingly used in many cardiology units. In addition, there are patients who do not demonstrate sufficient platelet inhibition upon treatment with the standard daily dose of clopidogrel, likely due to “clopidogrel resistance” (5, 6). However, the pathomechanism and the clinical relevance of this phenomenon have yet to be defined (9). Recent data suggest variations in absorption as an underlying mechanism rather than variations in the metabolism of clopidogrel (10). In particular, since the prodrug clopidogrel is transferred to its active component by the cytochrome P450 3A4, a potential interference with statins is contro-
versally discussed (5, 6). Due to a potential high number of “clopidogrel-resistant” cases, the identification of these patients and the application of an alternative dose or treatment strategy may have a major impact on secondary and potentially also on primary prevention (11). These clinically important but unresolved issues are addressed by Grossmann et al. (7) and Ahnadi et al. (8).

The most powerful strategy to inhibit platelet aggregation is provided by the blockade of the glycoprotein (GP) IIb/IIIa, the fibrinogen receptor, which belongs to the adhesion receptor family of integrins, thus termed αIIbβ3-integrin. It is the most abundant membrane receptor on platelets with about 50,000 molecules per platelet. The αIIbβ3-integrin possesses at least two different conformations, a low affinity and a high affinity state in respect to the binding of its major ligand fibrinogen (12). All currently clinically used GP IIb/IIIa-blockers exert their receptor-inhibiting property by binding to the default, the low-affinity state of the receptor that is present on non-stimulated platelets. Therefore, large amounts of GP IIb/IIIa-blockers are needed to sufficiently inhibit platelet aggregation in patients, whereby all platelets irrespective of their activation state are blocked (13). The latter fact may be responsible for bleeding problems associated with GP IIb/IIIa inhibition. The intravenous use of GP IIb/IIIa-blockers provides major benefits in patients undergoing coronary interventions. Lehrke et al. (14) describe a very interesting study that is a typical example for the finding that the higher the risk of the individual patient (e.g. defined by a positive troponin T, high age etc.) the higher the benefit achieved by GP IIb/IIIa-blockage.

Orally available, low molecular weight GP IIb/IIIa-blockers have badly failed in large scale clinical trials, at least in part due to their properties as ligand-mimetics, thereby causing outside-in signalling and subsequent platelet activation (15). These problems together with limitations in efficacy and side effects of the intravenously used GP IIb/IIIa-blockers have prompted lively discussion on potential alternatives in the strategy for the blockade of GP IIb/IIIa. Here, allosteric or activation-specific blockade of integrins, which are not expected to cause outside-in signalling effects, may be worth while testing as an alternative anti-GP IIb/IIIa strategy (16, 17).

Anticoagulant pharmacotherapy
Anticoagulation is one of the most frequently used medical treatments either as prophylaxis, conservative or invasive treatment in thromboembolic patients. Unfractionated heparin, which has been in use for several decades, is inexpensive but generally needs monitoring and has several adverse effects based on its binding promiscuity (18). Nevertheless, especially with vascular interventions unfractionated heparin is still widely used. With increased benefit/cost ratio, however, fractionated heparins (such as enoxaparin) are increasingly replacing the unfractionated counterpart. Furthermore, new anticoagulant strategies using different protease inhibitors are being developed and studies are already underway in patients. One of the most promising therapeutic applications is the direct inhibition of factor Xa. Becker et al. (19) provide a fascinating overview on the development and evaluation of a novel direct factor Xa inhibitor. Thrombin as a target molecule to be inhibited has been revived by the development and successful clinical evaluation of direct thrombin inhibitors such as bivalirudin and (xi)melagatran (20, 21). Furthermore, as exemplified in the study by Peng et al. (22) alternative strategies that target the “protease-activating receptors (PAR) of certain coagulation proteases are being developed. Whereas for many years pharmacotherapeutic approaches in the blood coagulation field did not experience major changes, in the near future we will have a large variety of different anticoagulative drugs available. In addition, the combination of various anticoagulative strategies as discussed by Becker, Alexander, Li et al. (23) may provide further clinical benefits. Of special interest are combinations between new anticoagulative and antiplatelet drugs. One interesting example of such a combination is given by Iwatsuki et al. (24).

Antithrombotic pharmacotherapy
Thrombolysis of acute vessel occlusions has been improved by the development of recombinant plasminogen activators. However, the conjunctive pharmacotherapy with clot lysis is also of major importance. Welsntlyh and Armstrong (25) present a detailed and timely review on this issue. The relative benefits of fibrinolysis and acute vascular interventions are eagerly debated. Also, clinical trials addressing the issue of angioplasty following fibrinolysis (termed “facilitated percutaneous coronary interventions”) in combination with various anti-platelet strategies are still ongoing.

Finally, the issue of how pharmacotherapy can be predicted and followed by individual risk stratification based on various markers will be addressed. The article by Alehagen et al. (26) investigates the serum marker D-dimer, whereas the article by Mannila et al. (27) describes genetic markers and environmental factors in this respect. For atherosclerosis, several serum markers such as high sensitivity C-reactive protein and CD40L seem to be useful for risk stratification (28, 29). To define the risk on an individual basis, the combination of several risk markers, including genetic predisposition, need to be included into the evaluation. The final goal of this stratifying approach will be to provide an individualized pharmacotherapy chosen from a repertoire of various anticoagulative and antiplatelet drugs achieving optimal benefits for the given patient.
References