P2Y$_{12}$ receptor antagonists: a rapidly expanding group of antiplatelet agents

Marco Cattaneo*

Unità di Ematologia e Trombosi, Ospedale San Paolo—Università di Milano, Via di Rudini 8, 20142 Milano, Italy

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This editorial refers to 'Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y$_{12}$ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin' by S. Husted et al., on page 1038

Adenosine-5'-diphosphate (ADP) plays a key role in platelet function, because, although ADP itself is a weak platelet agonist, when secreted from the platelet dense granules where it is stored, it amplifies the platelet responses induced by other platelet agonists. The transduction of the ADP signal involves both a transient rise in free cytoplasmic calcium mediated by the G$_q$-coupled P2Y$_1$ receptor, and inhibition of adenyl cyclase mediated by the G$_i$-coupled P2Y$_{12}$ receptor. Concomitant activation of both the G$_q$ and G$_i$ pathways by ADP is necessary to elicit normal ADP-induced platelet aggregation. Activation of the G$_q$ pathway through P2Y$_1$ leads to platelet shape change and rapidly reversible aggregation, whereas the activation of the G$_i$ pathway through P2Y$_{12}$ elicits a slow progressive and sustained platelet aggregation not preceded by shape change. In addition to its role in ADP-induced platelet aggregation, P2Y$_{12}$ mediates the potentiation of platelet secretion induced by strong agonists and the stabilization of thrombin-induced platelet aggregates. P2Y$_{12}$ has a more selective tissue distribution than P2Y$_1$, making it an attractive molecular target for therapeutic intervention. Indeed, P2Y$_{12}$ is the target of efficacious antithrombotic agents like ticlopidine and clopidogrel, which are already used in clinical practice either alone or in combination with other antithrombotic drugs.

Ticlopidine and clopidogrel are structurally related compounds, belonging to the thienopyridine family of ADP receptor antagonists; they are pro-drugs that are inactive in vitro and need to be metabolized in vivo by the hepatic cytochrome P-450 1A enzymatic pathway to active metabolites, which have very short half-lives. They irreversibly and specifically inhibit the function of the platelet P2Y$_{12}$ receptor, reproducing the platelet function abnormalities that are observed in patients who are congenitally deficient in P2Y$_{12}$ and in P2Y$_{12}$ knock-out mice. The ability of thienopyridines to inhibit platelet aggregation induced by several platelet agonists (such as thromboxane A$_2$, collagen, and low concentrations of thrombin) is accounted for by the suppression of the amplifying effect on platelet aggregation of ADP secreted from platelet dense granules. Treatment with these thienopyridines renders the thrombin-induced platelet aggregates more susceptible to deaggregation and inhibits shear-induced platelet aggregation.

The use of ticlopidine and clopidogrel in the clinical setting, despite their proven antithrombotic activity, has some drawbacks. (i) The need for their metabolism to active metabolites accounts for their delayed antiplatelet effects: a maximum plateau of inhibition of ADP-induced platelet aggregation is observed 4–5 days after daily oral administration of 500 mg ticlopidine or 75 mg clopidogrel. (ii) As a consequence of the irreversible inhibition of P2Y$_{12}$ function, the inhibitory effect of thienopyridines on circulating platelets lasts for approximately 10 days, which corresponds to the lifespan of a circulating platelet. Although the ability of thienopyridines to inhibit irreversibly P2Y$_{12}$ with their short-lived metabolites has theoretical advantages, it may represent a problem for patients who need to undergo coronary bypass surgery, because treatment with clopidogrel within 4–5 days of the procedure is associated with increased blood loss, reoperation for bleeding, increased transfusion requirements, and prolonged intensive care unit and hospital length of stay. (iii) Finally, there is a substantial inter-individual variability in platelet inhibition by ticlopidine and clopidogrel, which is mostly because of the inter-individual differences to the extent of metabolism of the pro-drug to the active metabolite. Preliminary, small-sized studies demonstrated an association between insufficient platelet function inhibition by clopidogrel and heightened incidence of vascular events. Increasing the dose of clopidogrel might reduce the number of poor responders. However, the safety issues should caution against this policy, as severe toxic effects of the drug such as bone marrow aplasia and microangiopathic thrombocytopenia, which might be dose-dependent, have been described, albeit less frequently that with ticlopidine. The above limitations of ticlopidine...
and clopidogrel have fostered the search for new P2Y12 antagonists.

Prasugrel is a new thienopyridine compound with a much faster onset of action than clopidogrel. In a cross-over study, it has been demonstrated that a 60 mg loading dose prasugrel provided rapid and high-grade, irreversible inhibition of ADP-induced platelet aggregation even in those subjects who responded poorly to a standard loading dose of clopidogrel. The higher potency of prasugrel compared with clopidogrel probably reflects more efficient conversion of the pro-drug to the active metabolite. Prasugrel has proven safe in a Phase II trial and is currently undergoing Phase III evaluation (TRITON TIMI-38 trial) in patients with acute coronary syndromes undergoing PCI. This study will determine whether or not the more rapid and potent platelet inhibition achievable with prasugrel provides superior benefit over the approved dose of clopidogrel in a safe and tolerable fashion.

In some clinical situations, inhibition of platelet aggregation by fast-acting and reversible antagonists with a short half-life might be preferable to irreversible inhibitors. Cangrelor is a selective and reversible direct inhibitor of P2Y12. In a study that directly compared the effects of clopidogrel and cangrelor administration in patients with ischaemic heart disease, cangrelor infusion at 2 and 4 μg/mL/min resulted in near-complete inhibition of platelet aggregation measured at 4 min after the addition of 10 μM ADP, whereas 4 to 7 days clopidogrel treatment resulted in only approximately 60% inhibition. The short half-life of the molecule (2.6 min) results in a rapid reversal of its platelet inhibitory effect. Addition of cangrelor in vitro to blood from the cangrelor-treated patients resulted in near complete inhibition of P2Y12-dependent platelet function. It must be noted, however, that cangrelor can only be given intravenously, which limits its use in the clinical practice.

Husted et al. report on the effects of the oral administration to patients with atherosclerosis of AZD6140, the first oral reversible P2Y12 antagonist that fills the last gap in P2Y12 pharmacopeia. AZD6140 belongs to the same family as cangrelor of stable ATP analogues with high affinity for P2Y12. Efforts to find compounds for oral administration led to the discovery of ARC109318X, the first selective and stable, non-phosphate, competitive P2Y12 antagonist; further refinement to increase the oral bio-availability led to the synthesis of AZD6140. The compound does not need metabolic activation to exert its inhibitory effect; however, it is metabolized to an active metabolite, which is thought to contribute to its antiplatelet effects after oral administration. In a model of cyclic flow reductions in the femoral artery of anaesthetized male beagles, AZD6140 displayed a good separation between the antithrombotic effect and the prolongation of the tongue bleeding time that was intermediate between that of cangrelor and clopidogrel. In preliminary studies on healthy volunteers, the compound displayed linear pharmacokinetics, induced a strong and rapid inhibition of platelet aggregation which decreased substantially over the 24 h post-dose, and was well tolerated.

The study by Husted et al. randomized in a double-blind fashion 200 stable atherosclerotic outpatients, who were on treatment with aspirin 75–100 mg once daily, to AZD6140 (50 mg BID, 100 mg BID, 200 mg BID, or 400 mg once daily) or clopidogrel 75 mg once daily for 28 days. The study showed that AZD6140 at doses above 50 mg BID more effectively inhibited platelet aggregation and with less variability than clopidogrel. In addition, the inhibition of platelet aggregation by AZD6140 was very rapid (2 h post-dose, 96 ± 6.1% for 400 mg once daily) compared with that of clopidogrel. The prolongation of the bleeding times was greater in AZD6140-treated patients compared with clopidogrel-treated patients, although no obvious dose-response relationship was observed. The incidence of bleeding events tended to be higher in patients treated with the three higher doses of AZD6140, compared with that observed in patients treated with 50 mg BID or clopidogrel. One major bleeding event was observed in a patient on treatment with 400 mg QD AZD6140. Perhaps of more concern than the higher incidence of bleeding complications, which can be predicted for treatments that very effectively inhibit platelet function, was the unexpected, relatively high frequency of dyspnoea, which appeared to increase with increasing doses of AZD6140 (10% with 50 mg or 100 mg BID, 16% with 200 mg BID, and 20% with 400 mg QD). Further studies are necessary to assess the real frequency and clinical relevance of this side effect of the compound. AZD6140 is undergoing Phase III evaluation that will address the issues of its efficacy and safety.

In conclusion, the pharmacopeia of drugs inhibiting the platelet P2Y12 receptor for ADP is rapidly expanding. In addition to ticlopidine and clopidogrel, well-known compounds of proven antithrombotic efficacy, a new thienopyridine, prasugrel that is characterized by higher potency and faster onset of action, is currently under clinical evaluation. Two direct and reversible P2Y12 antagonists, cangrelor, which can only be given intravenously, and AZD6140, which can be given orally, have rapid onset and reversal of platelet inhibition, which make them attractive alternatives to thienopyridines, especially when rapid inhibition of platelet aggregation or its quick reversal are required. Therefore, in the near future, physicians will have a panel of different P2Y12 inhibitors to choose from, which will enable them to tailor the most appropriate antithrombotic therapy to the individual patient and risk situation.

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References

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A rare complication after pacemaker implantation: unusually shaped lead coil

Michele Correale*, Riccardo Ieva, Luigi Ziccardi, and Matteo Di Biase
Department of Cardiology, University of Foggia, viale L Pinto, 1. 71100 Foggia, Italy

*Corresponding author. E-mail address: opsfco@tin.it

A 77-year-old man with history of dementia and stereotyped movement was referred to Division of Cardiology for a bradycardia–tachycardia syndrome. A ventricular pacing lead was introduced via subclavian venous puncture and was connected to the pulse generator that was implanted in a subcutaneous pocket fashioned over the pectoralis mayor. Inadequate capture and muscle contraction were observed within the first 3 months after the implantation. Chest X-ray and fluoroscopy revealed a lead dislodgement with a ‘chain-like’ form (Figure). The surgical revision showed the absence of fibrous tissue, and therefore, the generator had been able to be rounded so many turns, with dislodgement of the pacing lead. The patient was subjected to a new implantation of pacemaker lead via cephalic venous puncture.

A fluoroscopic examination revealed a lead retraction and dislodgement, with a ‘chain-like’ form (black arrow), because the generator was able to be rounded so many turns. A new lead submitted via cephalic venous puncture (white arrow).