Introduction

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LEARNING OBJECTIVES:

1. Indicate the need for antiplatelet drug therapy
2. Provide laboratory assays to classify antiplatelet drug efficacy and safety
3. List the actions, dosages, and indications for the glycoprotein inhibitors

ABBRVIATIONS: ACS-acute coronary syndrome; ADP-adenosine diphosphate; ALR-aspirin low response; CLR-clopidogrel low response; DOAC-direct oral anticoagulant; FDA-US Food and Drug Administration; GP-glycoprotein; GPI-glycoprotein inhibitor; IV-intravenous; PCI-percutaneous intervention; POC-point of care; RGD-arginine-glycine-aspartic acid sequence; TRAP-thrombin receptor activating peptide

INDEX TERMS: Antiplatelet drugs, platelet function testing, glycoprotein inhibitor, acute coronary syndrome, percutaneous intervention, coronary artery bypass graft

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Laboratory professionals who specialize in hemostasis have been preoccupied with the development and implementation of assays for the direct oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban since their release in 2010–14. Practitioners have also maintained and improved methods for monitoring Coumadin, unfractionated heparin, enoxaparin (low molecular weight heparin), and fondaparinux (synthetic pentasaccharide). Meanwhile, although antiplatelet therapy is more prevalent than anticoagulant therapy, laboratorians pay scant attention to monitoring antiplatelet drugs. Their lesser laboratory prominence may reflect our understanding that dose-response characteristics are reproducible, or that platelet function assays require specialized equipment, are highly complex, and require fresh blood and thus must be conducted near the patient.

The commonly employed antiplatelet drugs include aspirin, whose antiplatelet effect is delivered through acetylation of platelet cyclooxygenase, and the thienopyridines clopidogrel, prasugrel, and ticagrelor, which occupy and block platelet membrane ADP receptor site $P2Y_{12}$. Aspirin is often prescribed in combination with a thienopyridine to prevent secondary arterial thrombotic events subsequent to acute myocardial infarction (AMI). The aspirin-thienopyridine combination is termed dual antiplatelet therapy, and is a mainstay in post-infarction treatment. Because aspirin and clopidogrel low response (ALR and CLR) have been documented, several laboratory methods are devised to monitor these drugs' efficacy. These are detailed in the accompanying article, Managing Platelet Therapy. Nearly all methods are point of care (POC) modifications of platelet aggregometry. Prasugrel and ticagrelor escape laboratory monitoring, as they have proven to have predictable dose-response characteristics.

The accompanying article, Platelet Structure and Function, provides an overview of platelet physiology.[1] The reader may use this article to gain understanding of antiplatelet drug physiology.

Glycoprotein Inhibitors

There remains a class of intravenous (IV) antiplatelet therapeutics not cited in the accompanying articles. These drugs occupy the platelet membrane receptor glycoprotein IIb-IIIa (GP IIb-IIIa), the receptor that normally binds the arginine-glycine-aspartic acid (RGD) sequence in fibrinogen and von Willebrand

factor and achieves the final stage of platelet aggregation. These therapeutics are commonly called glycoprotein inhibitors (GPIs) and are used during non-surgical cardiac interventions in response to angina and acute coronary syndrome (ACS) and during percutaneous interventions (PCI, cardiac catheterization and stenting).[2] They are abciximab, eptifibatide, and tirofiban, all of which are employed in combination with aspirin, a thienopyridine, and heparin or enoxaparin.[3] The GPIs are contraindicated in patients with a history of hemorrhage, at risk for or history of hemorrhagic stroke, with renal disease, platelet count less than 100,000/μL, oral anticoagulant therapy within the past 7 days, recent trauma or surgery, aneurism, uncontrolled hypertension, vasculitis, or recent use of IV crystalloids and thrombolytic therapy.[4]

Platelet function before, during, and subsequent to GPI therapy may be measured using ADP-induced aggregometry. GPIs suppress platelet aggregation response by 90% within minutes of their initial administration, whereas platelet function recovery varies by the therapeutic employed. A POC methodology, the Accumetrics VerifyNow IIb-IIIa assay (Accriva Diagnostics, San Diego, CA) is a semi-quantitative whole blood platelet aggregation test that employs thrombin receptor activating peptide (TRAP) to stimulate platelets.[5] The assay provides physicians with an accurate assessment of platelet suppression and return to normal in response to abciximab or eptifibatide. The Accumetrics assay has not been cleared for tirofiban therapy.

Abciximab (Rheopro®, Eli Lilly, Indianapolis, IN), cleared in 1997, is a synthetic peptide that mimics the Fab portion of an immunoglobulin molecule developed to possess GP IIb-IIIa affinity.[6] Abciximab's primary indication is PCI.[7] The dosage is an 0.25 mg/kg IV bolus administered 10–60 minutes before the start of PCI, followed by continuous infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 hours. Therapy may be continued for up to 72 hours. Abciximab, like all GPIs, is contraindicated in patients with a bleeding history, risk of hemorrhagic stroke or kidney disease. Abciximab has a 10-minute plasma half-life but remains bound to platelets for an average of 48 hours, whereupon platelet function returns to normal.

Eptifibatide (Integrilin®, Millennium Pharmaceuticals, Cambridge, MA), cleared in 1998, is a cyclic peptide derived from the venom of the southeastern pygmy rattlesnake, *Sistrurus miliarius barbouri*. It is an RGD mimetic that reversibly binds the glycoprotein IIb-IIIa receptor, and is indicated for ACS or PCI. For ACS, a 180 μg/kg IV bolus is administered immediately after diagnosis, followed by continuous infusion of 2 μg/kg/min. Similarly in PCI, a 180 μg/kg IV bolus immediately before the procedure is followed by continuous infusion of 2 μg/kg/min and a second bolus of 180 μg/kg given 10 minutes after the first bolus. Infusion is continued for a minimum of 12 hours, until discharge, or for a maximum of 24 hours. Eptifibatide has a plasma half-life of 2.5 hours and infusion is discontinued prior to coronary artery bypass graft surgery when necessary. When therapy is discontinued, platelets achieve greater than 50% aggregation on average after 4 hours. Eptifibatide efficacy may be monitored using standard aggregometry or by the Accumetrics VerifyNow IIb-IIIa assay.

Tirofiban (Aggrastat®, Medicure, Winnepeg, Manitoba), FDA-cleared in 1998, is a modified version of a small molecule in the venom of the saw-scaled viper, *Echis carinatus*. Tirofiban is indicated for the reduction of thrombotic cardiovascular events in ACS.[8] The dosage regimen, updated in 2013, begins with 25 μg/kg for 3 minutes followed by 0.15 μg/kg/min for up to 18 hours. Aggregation returns to normal 4–8 hours after therapy is discontinued.

The GPIs reduce the risk of secondary arterial thrombotic events during and subsequent to ACS therapy or PCI, but confer an approximately 1% incidence of major bleeds.[9,10] Though laboratory parameters are well established and patients have been shown to respond differentially to standard doses, interventional cardiologists and anesthesiologists seldom order GPI assays and seldom adjust GPI doses. Consequently, we devote little space to the issue of GPI monitoring, awaiting the time when outcomes studies illustrate that laboratory testing with subsequent dose adjustments enhances efficacy and safety. Conversely, surgeons, physicians, and operating room personnel are likely to order assays for unfractionated heparin such as the activated clotting time or activated partial thromboplastin time. They also order frequent platelet counts, as GPIs may induce thrombocytopenia through a haptenic immunologic response.[11]

Antiplatelet therapy is the mainstream approach for prophylaxis and treatment of arterial thrombosis, and presents unique challenges for laboratory measurement in a developing world of antithrombotic therapy.

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