

Clopidogrel (Plavix®) Monitoring

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INTRODUCTION:

Coronary heart disease is the leading cause of death in the United States today. To combat the rise in mortality new treatment therapies are targeting the modification of platelet function. New and existing platelet function tests are increasingly being used for monitoring the efficacy of the antiplatelet drugs used in these conditions. Monitoring an individual's response to antiplatelet therapy allows dosage optimization and cessation to help control and minimize the risk of either thrombosis or bleeding.

BACKGROUND:

Clopidogrel is a thienopyridine, of which active metabolites are known as platelet ADP-receptor blockers. Specifically, it irreversibly blocks the platelet ADP P2Y₁₂ receptor (responsible for ADP-induced aggregations¹ but not the second ADP receptor P2Y₁). P2Y₁ contributes to change of platelet shape and triggers the initial wave of aggregation. Platelet inhibition by clopidogrel is both dose- and time-dependent. Patients are usually given a loading dose of 300-600 mg and then maintained on 75 mg/day. Several large randomized clinical trials have demonstrated the superiority of clopidogrel in patients with established vascular disease and in coronary stenting procedures.²⁻⁴ However, inter-individual variability in platelet response to clopidogrel has been observed⁵, and 5-10% of patients still experience acute or subacute thrombosis after coronary stent placement.^{6,7} The possible mechanisms that may account for the inadequate response to clopidogrel include: poor compliance to the treatment, variable absorption of the pro-drug, variable clearance of active metabolite, and potential drug-drug interactions.⁶ It has been estimated that "resistance to clopidogrel" is seen in 4 to 30% of patients.

Despite the common use of clopidogrel in patients with vascular disease, monitoring of platelet inhibition is still not conventional in clinical practice. Many tests of platelet function are now available for clinical use in monitoring the efficacy of antiplatelet drugs. Methodological variability within each technique, however, makes comparison of results difficult, thus contributing to the uncertain role of platelet function

testing in the clinical setting. This article will discuss aggregometry and a point of care device, VerifyNow® and their potential roles in clinical management.

LIGHT TRANSMISSION AGGREGOMETRY:

Light transmittance aggregometry (LTA) or turbidimetric aggregometry is considered to be the "gold standard" for determining the effects of antiplatelet therapy on platelet function. This traditional assay is not only difficult to perform but is expensive, time consuming and requires relatively large volumes of fresh blood. These requirements limit the use of aggregometry to specialized laboratories.

LTA measures platelet aggregation in response to given agonists particularly ADP to test clopidogrel or P2Y₁₂ inhibitors response. ADP, as an agonist, stimulates both P2Y₁₂ and P2Y₁ platelet receptors. LTA using 5, 10 or 20 µM ADP can be used to assess adequate response of patients based upon measuring the change in (delta) aggregation at baseline and post-drug.⁸ Non-responders can be defined with a delta aggregation of <10%.

ADP-induced aggregation studies are not very practical to test on a large number of clinical samples. In addition, the heterogeneity observed with LTA suggests that utilization of the ADP agonist alone may not be specific enough to measure the effect of clopidogrel and other P2Y₁₂ agonists.⁹ Despite the complexity of LTA, Matezky et al. found evidence that ADP-induced aggregations predicted adverse outcomes.¹⁰

VerifyNow®:

The VerifyNow® instrument is a POC (point of care) turbidimetric optical detection system that was developed to monitor antiplatelet agents. It was designed to overcome the complexities of LTA. The assay uses prostaglandin (PG) E1 in addition to ADP to increase intracellular cyclic adenosine monophosphate (cAMP), thereby enhancing the sensitivity and specificity of the test for ADP-induced activation of platelets via P2Y₁₂.¹¹ PGE1 should suppress the activation of platelets by P2Y₁. Fibrinogen-coated particles are used in the VerifyNow® cartridge to bind to available platelet

receptors. Activated platelets bind to the exposed fibrinogen particles and result in agglutination in proportion to the number of available platelet receptors. The VerifyNow®-P2Y₁₂ results are expressed in P2Y₁₂ reaction units (PRU).

Two results are reported for each VerifyNow®-P2Y₁₂ assay: P2Y₁₂ reaction units (PRU) report the amount of ADP-mediated aggregation specific to the P2Y₁₂ receptor, and are calculated as a function of the rate and extent of platelet aggregation in the ADP channel; and percent inhibition (%) is the percent change from baseline aggregation, and is calculated from the PRU result and the BASE result, which is a dependent measurement based on the rate and extent of platelet aggregation in the TRAP (thrombin receptor activating peptide) channel. It is recommended that pre and post drug loading be evaluated since baseline and drug response values vary amongst individuals and changes in inhibition are best compared to individual baseline values. In general, % inhibition less than 20 can be attributed to normal background and indicate little antiplatelet effect.

The VERITAS study has demonstrated that the VerifyNow®-P2Y₁₂ assay is sensitive for measuring platelet inhibition with clopidogrel.¹² However, this study was not designed to define the cut-off point for clopidogrel non-responsiveness and further studies are needed to address this important issue for patient management.

CONCLUSIONS:

Because of the widespread use of the PFA-100 closure time (Dade Behring, Miami, FL), it is important to note that this device is considered unsuitable for monitoring antiplatelet function and does not distinctively reflect the effect of clopidogrel on platelets.¹³

The VerifyNow®-P2Y₁₂ assay is a promising method suitable for determining platelet response to clopidogrel in lieu of platelet aggregation studies.

Carefully controlled, large randomized trials are required to correlate the assessment of platelet function with clinical outcomes to define clopidogrel resistance. The RESISTOR (Research Evaluation to Study Individuals who Show Thromboxane or P2Y₁₂ Resistance) trial is currently underway and may determine if the level of P2Y₁₂ inhibition correlates with clinical outcome and if changing therapy in resistant patients will result in improved outcomes.

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