The Platelet VASP Test: a clinically practical test of clopidogrel responsiveness

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SUMMARY

- Clopidogrel is an oral antiplatelet agent that acts as a specific irreversible antagonist at the platelet P2Y12 ADP receptor.
- Interindividual response to clopidogrel has been well described.
- The PLT-VASP test provides a specific assessment of the inhibition at the P2Y12 ADP receptor.
- A full citrate tube is required for this test. The sample is stored at room temperature and the test needs to be performed within 48 hours of collection.
- The optimal time to perform the test is 7 days after commencing maintenance therapy (or 6 hours after giving a loading dose)
- A Platelet Reactivity Index is obtained (PRI)
- Quite consistently in the current literature, a PRI of >50% is emerging as predictive of stent thrombosis and major adverse coronary events. This cut-off has a very high negative predictive value but a low positive Predictive value.

Clopidogrel is an oral antiplatelet agent of the thienopyridine group. It acts as a specific irreversible antagonist at the platelet P2Y12 ADP receptor. It is extensively metabolised by the hepatic cytochrome P450 enzymes.

It is used to prevent adverse cardiovascular events before, during and after percutaneous coronary intervention (PCI) and in the setting of recent stroke, recent myocardial infarction, unstable angina and established peripheral vascular disease.

Interindividual response to clopidogrel has, however, been well described. It is estimated that clopidogrel fails to elicit an adequate response in 4-30% of patients (depending on the method and criteria used).

Several mechanisms are thought to be involved in this variable response including variability in intestinal absorption, variability in hepatic conversion to an active metabolite, drug interactions and receptor polymorphisms.

Light transmission aggregometry (LTA) has traditionally been considered the reference assay for assessing platelet reactivity, but has some limitations (requires immediate analysis in a specialised laboratory, lacks standardisation).

The Platelet VASP test (PLT-VASP) is a new flow cytometry test that can assess the effect of the platelet P2Y12 antagonists (clopidogrel, ticlopidine, prasugrel).

This test is highly specific and has significant logistical advantages:
- Analysis only needs to be performed within 48 hours from collection.
- The samples are stored at room temperature.
- Reproducible.
- Only a single full citrate tube is required.
- Aspirin and other medications such as GPIIb/IIIa antagonists do not interfere with the results.

In general the PLT-VASP test and light transmission aggregometry show good correlation, although not complete agreement. While the PLT-VASP test is specific to the P2Y12 antagonists, light transmission aggregometry will be affected by aspirin or GPIIb/IIIa antagonists. In light transmission aggregometry, multiple ADP pathways are assessed, while with the PLT-VASP test only the ADP pathway relating to the P2Y12 receptor is assessed. The PLT-VASP test is currently the most specific assay for measuring P2Y12 receptor blockade.

A recent study was performed to assess which platelet function test provided the best reflection of the in vivo plasma levels of the active metabolite of clopidogrel (1). The PLT-VASP assay demonstrated the highest correlation.

Care must be taken not to activate platelets during the collection process and the first few mls of blood collected must be discarded.

Based on the pharmacodynamic properties of clopidogrel, the optimal time to perform the test is generally at least 7 days after commencing maintenance therapy, or 6 hours after giving a loading dose.
The sample is analysed on a flow cytometer using a commercial kit.

A Platelet Reactivity Index (PRI) is obtained. This is a (percentage value).

A good response to clopidogrel is associated with a lower percentage value and a poor response (hyporesponsive) is associated with a higher percentage value. Normal individuals (not receiving clopidogrel) usually have a percentage value >69%.

Recent literature has shown a link between values obtained on the PLT-VASP test and clinical outcomes, especially in the setting of percutaneous coronary intervention.

There are studies showing a link between values obtained on the PLT-VASP test and stent thrombosis (2;3;4;5), and also between PLT-VASP values and recurrent ischaemic events (6;7;8).

In general, patients with a PRI < 50% (or at least <69%) appear to be protected. The studies have shown this cut-off to have a very high negative predictive value but low positive predictive value. Currently the PLT-VASP test therefore appears to be more reliable in identifying low risk patients than isolating a small group of high risk patients. It may, however, be very useful in the setting of conditions such as high risk percutaneous coronary intervention, to optimise therapy and prevent complications.

A few small studies have shown that PLT-VASP guided adjustment of clopidogrel loading doses and maintenance therapy improves clinical outcome and is safe (9;10). Larger, definitive prospective studies are needed to confirm these findings.

Another area needing further investigation, is to assess the utility of PLT-VASP for assessing bleeding risk. For further information, please contact the Flow Cytometry Laboratory - (011) 358 0721.

References:
9. Bonello et al: J Am Coll Cardio Apr 8:51(14)1412-4