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Medical Center

Clopidogrel Resistance: Is it useful to do genetic testing?

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What is Clopidogrel Resistance?

Clopidogrel is a pro-drug. It has to be metabolized in the liver into an active metabolite (approximately 15% of the total dose) before it can exert its anti-platelet action. In the liver, the cytochrome 450 system is responsible for activating clopidogrel. There are several genes regulating the function of the cytochrome 450 system, the most important of which is the CYP 2C19 gene. Several polymorphisms of this CYP 2C19 gene have been detected.

In particular, the CYP 2C19*2 and CYP 2C 19*3 variant alleles have been found to be associated with the loss of function of the cytochrome 450 system. An individual can be either homozygous or heterozygous for the loss of function alleles. Carriers of the loss of function alleles will experience poor metabolism of the clopidogrel pro-drug leading to lower active metabolite levels in the blood.

Why is it important?

Recently, some studies have identified certain genetic polymorphisms of the CYP 2C19 gene to be the most important predictor of low metabolism of the clopidogrel pro-drug. Carriers of a low metabolizer allele of CYP 2C19 had a 53% increase in risk for death from cardiovascular causes, myocardial infarction or stroke and 3 times higher risk for stent thrombosis. Polymorphisms of the CYP 2C19 gene can be seen in up to 55% of East Asians, and could potentially result in adverse events in our local population.

Who will benefit from Screening for the Gene Mutations?

a) To identify individuals who are resistant to clopidogrel and who require long term clopidogrel therapy (eg post myocardial infarction or stroke) and switch them to an alternative anti-platelet drug;
b) To identify individuals who are partially resistant to clopidogrel who could then be given a higher dose of clopidogrel;
c) For patients on dual anti-platelet therapy post-PCI, it may help reduce the risk of stent thrombosis which may be fatal;

RECENT BLACK BOX WARNING AND RECOMMENDATION BY FDA IN THE UNITED STATES

On March 12, 2010, the Federal Drug Administration of the US required a box warning for Clopidogrel (Plavix, BMS and Sanofi Partnership) to caution that poor metabolizers of the drug may not receive full protection from heart attacks, stroke and cardiovascular deaths.

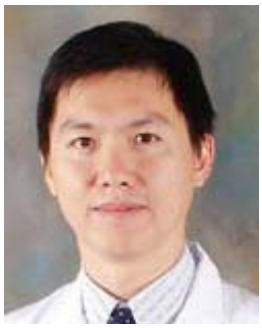
The box warning also stated that tests are available to determine the genetic profile of a key liver enzyme (CYP 2C19) and predict whether a patient will ineffectively convert Clopidogrel to its active form. It advised clinicians to consider other anti-platelet medications or alternative dosing strategies for Clopidogrel in patients who are poor metabolizers.

What is the take home message?

1) For patients who are already on Clopidogrel (Plavix), it is important to determine if they are carriers of the low metabolizer alleles. This will enable you to switch them to a different anti-platelet agent.
2) For patients who are already on dual anti-platelet therapy including Clopidogrel, the information will help you determine if increasing the dose of clopidogrel is feasible or whether to continue with the strategy of the duaanti-plateletet therapy.
3) For patients who are not yet on clopidogrel and who need anti-platelet therapy, an alternative agent could be considered.

What is involved in the Gene Test?

1) You will have to draw a blood sample of 3 milliliters into an EDTA tube (same as the tube you use for full blood count).
2) Call Ms Serene Toh of Cardiogenics Pte Ltd at 63972004 to collect the specimen and the result will be sent to you in 3 working days.
3) The average cost of each gene test is SGD$500.



Dr. Kenneth Ng is a consultant cardiologist at Novena Heart Center, Singapore. He is trained in the field of cardiac imaging, heart failure and heart transplant medicine. He did his undergraduate training at the National University of Singapore (1992) and completed his advanced specialist training in cardiology in Singapore (2001). He underwent sub-specialty training in Echocardiography, Heart Failure and Heart Transplantation Medicine (Cleveland Clinic Foundation, USA).

He was the former director of the heart failure program of the National Healthcare Group (2003-2007). He ran a very successful heart failure service at the Tan Tock Seng Hospital. He has regularly published research articles on heart failure in peer reviewed international cardiology journals. He is widely recognized as an expert in the field of heart failure in the ASEAN region and has regularly been invited to give talks on heart failure at both local and regional conferences as well as the American Congress of Cardiology Annual Scientific Meeting. He has also established surgical and mechanical assist device therapy programs for heart failure in Tan Tock Seng Hospital. He is a board certified cardiologist in Adult Comprehensive Echocardiography issued by the National Board of Education in the USA.

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