Pharmacist-led CYP2C19 genotyping in patients on clopidogrel therapy following percutaneous coronary intervention

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Background

CYP2C19, a cytochrome P450 enzyme encoded by a highly polymorphic gene, is involved in the metabolism of clinically important drugs such as clopidogrel. The 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 genotype and clopidogrel therapy[1], classify CYP2C19 genotypes into 4 groups according to metaboliser status in relation to clopidogrel: 'Extensive metabolisers', carrying only normal function alleles (EMs *1/*1), 'ultra-rapid metabolisers', carrying at least one gain-of-function (GoF) allele (UMs *1/*17, *17/*17), 'intermediate metabolisers', carrying one loss-of-function (LoF) allele (IMs *1/*2, *2/*17), and 'poor metabolisers', carrying two LoF alleles (PMs *2/*2).

Objective

To implement a laboratory-based, pharmacist-led process to genotype patients who were prescribed clopidogrel therapy post-percutaneous coronary intervention (PCI) for the CYP2C19 LoF (*2) and GoF (*17) variant alleles.

Method

- University Research Ethics Committee approval was granted.
- After obtaining informed written consent from each of 252 patients undergoing PCI, 5 mL of peripheral blood were collected into a purple-top EDTA tube and stored between 2-8°C. Patients were recruited by non-probability sampling.
- Genomic DNA purification was undertaken using the QIAamp DNA Mini Kit with the fully automated QiaCube (Qiagen) and frozen at -20°C. CYP2C19 SNP genotyping for variant alleles *2 (rs4244285) and *17 (rs12248560) was undertaken using TaqMan® Universal Master Mix and TaqMan® SNP drug metabolism assays (Life Technologies) on the 7500 Real-Time PCR system (Applied Biosystems).
- CYP2C19 SNP distribution and total allele frequencies were calculated.

Setting

Mater Dei Hospital (Cardiac Catheterisation Suite, Cardiology Department and Molecular Diagnostics Unit, Pathology Department)

Results

Patient demographics (N = 252)

Mean age of the patients was 65 years (range 29-89 years), 74.6% were male and 99.2% were Caucasian.

CYP2C19 SNP genotype and allele frequency distribution

- The majority of patients (74.2%) were non-carriers of the CYP2C19 LoF *2 allele (51.2% EMs and 23.0% UMs).
- 25.8% of patients were carriers of one *2 allele (IMs) and no patients were carriers of two *2 alleles (PMs) (Table 1).
- Total frequencies of allele *2 and *17 were 13% and 15% respectively.

Table 1: CYP2C19 SNP genotype distribution (N=252)

CYP2C19 genotype (metaboliser status)	Number of patients	Percentage ± 95% CI
*1/*1 (EMs)	129	51.2 ± 6.2
*1/*17 (UMs)	56	22.2 ± 5.1
*17/*17 (UMs)	2	0.8 ± 1.1
*1/*2 (IMs)	49	19.4 ± 4.9*
*2/*17 (IMs)	16	6.4 ± 3.0*

Review of clopidogrel use warranted (26%)

Conclusions and implications to practice

These findings may have important clinical implications for clopidogrel use in Malta since according to the CPIC genotype-guided therapeutic recommendations[1], carriers of one or two LoF *2 alleles (26%) should be switched to an alternative antiplatelet agent, provided there is no contra-indication. For non-carriers of the *2 allele, the guidelines recommend standard dosing of clopidogrel. Pharmacist-guided optimisation of antiplatelet therapy, directed by CYP2C19 SNP genotyping, may limit occurrence of adverse cardiac events, stent thrombosis and stent restenosis post-PCI.

Reference

1. Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther* 2013; 94 (3): 317-23.

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