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ABCB1 C3435T and CYP2C19*2 polymorphisms in a Palestinian and Turkish population: A pharmacogenetic perspective to clopidogrel

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ABSTRACT

Clopidogrel is an antiplatelet drug used to prevent recurrent ischemic events after acute coronary syndrome and/or coronary stent implantation. Single nucleotide polymorphisms (SNPs) such as CYP2C19*2 and ABCB1 C3435T have been found to play a role in different individual responses to clopidogrel. Since the prevalence of these SNPs is generally known to differ from one population to another, the aim of this study was to examine their prevalence in both a Palestinian and Turkish population. One hundred unrelated Palestinian subjects and 100 unrelated Turkish subjects were analyzed for CYP2C19*2 and ABCB1 C3435T polymorphisms by the amplification refractory mutation system (ARMS).
Results showed an ABCB1 3435 T allele frequency of 0.46 (95% CI 0.391 to 0.529) in the Palestinian sample and 0.535 (95% CI 0.4664 to 0.6036) in the Turkish sample. CYP2C19*2 allele frequency was 0.095 (95% CI 0.0558 to 0.134) in the Palestinian sample and 0.135 (95% CI 0.088 to 0.182) in the Turkish sample.
Our results provide information about the prevalence of the polymorphisms related to clopidogrel response in both the Palestinian and Turkish populations, in order to improve the safety and efficacy of clopidogrel through use of genetically guided, individualized treatment. The prevalence of these clinically significant alleles shed light on the importance of testing them before prescribing clopidogrel.

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Introduction

Genetic polymorphisms are known to have pronounced clinical significance in determining inter-patient variability towards drug response. It is the dominant influencing factor for individual and inter-ethnic variations in drug responses (Evans and Johnson, 2001). Clopidogrel is one such drug whose pharmacokinetic and pharmacodynamic efficiency can be predicted based on an individual's or population's genetic makeup (Angiolillo et al., 2007a; Brandt et al., 2007; Hulot et al., 2006). Clopidogrel administration along with aspirin is the guide line-approved standard of care in acute coronary syndromes and following stent implantation (Antman et al., 2008; Chen et al., 2005; Yusuf et al., 2001). Pharmacodynamic responses to clopidogrel vary greatly among patients (Gurbel et al., 2003); patients with lesser degrees of platelet inhibition are more likely to experience recurrent ischemic events (Hochholzer et al., 2006).

The *ABCB1* (ATP-binding cassette, subfamily B, member1) gene encodes the intestinal efflux transporter P-glycoprotein (P-gp), which modulates the absorption of clopidogrel (Gros et al., 1986; Taubert et al., 2006). Amongst several SNPs within this gene, the ABCB1 C3435T (rs1045642) has been shown to hinder the absorption of clopidogrel (Taubert et al., 2006). Individuals with TT homozygotes for the C3435T variant have lower levels of the active drug metabolite and may have higher rates of adverse clinical outcomes (Taubert et al., 2006; Simon et al., 2009).

Clopidogrel requires biotransformation to its active metabolite through two cytochrome P450-dependent steps (Reese et al., 2012). In particular, the isoenzyme CYP2C19 is involved in both steps contributing to an estimated 45% and 21% of the first and second steps respectively (Kazui et al., 2010). The most common SNP designated CYP2C19*2 (c.G681A) (rs4244285) leads to a splicing defect that functionally affects the enzyme. There are more than 25 known polymorphic groups (Trenk et al., 2008). The CYP2C19*1 allele is the normal (wild-type) copy that has full enzymatic activity. The CYP2C19*2 and CYP2C19*3 alleles are the most common variants resulting in complete loss of enzymatic activity. Carriers of CYP2C19*2 and CYP2C19*3 alleles have reduced metabolism of clopidogrel and demonstrate diminished clopidogrel-induced platelet inhibition (Collet et al., 2009). Previous pharmacogenetic studies have shown the prevalence of *CYP2C19* alleles to vary between different populations (Sameer et al., 2009; Hamdy et al., 2002). In March 2010, the FDA added a boxed warning to the product label of clopidogrel, alerting the clinicians on the risk of reduced clopidogrel efficacy in CYP2C19 poor-metabolizers (annon, 2010).

As several studies indicate, a higher clopidogrel dose could potentially provide a more intense antiplatelet effect in patients with a genetic predisposition to a diminished response to standard dose therapy by providing a greater substrate for biotransformation into the active metabolite (Angiolillo et al., 2004; Angiolillo et al., 2007b; Gurbel et al., 2005; Mega et al., 2011).

The aim of the study is to investigate the frequency of ABCB1 C3435T and CYP2C19*2 polymorphisms involved in clopidogrel pharmacokinetics in Palestinian and Turkish sample populations, in order to contribute to the use of appropriate strategies for clopidogrel therapy in these populations.

Materials and methods

Study population

Two study groups were investigated in this study. Group one included 100 unrelated Palestinian subjects (24–84 years old) geographically originating from the West Bank and Jerusalem. The work on these samples took place in Makassed Islamic Charitable Hospital in Jerusalem. The second group included 100 unrelated Turkish subjects (20–66 years old) and was genotyped in Yeditepe University in Istanbul. Informed consent was obtained from the 200 subjects. The study was approved by the Research and Ethical Committee both at Makassed Hospital and Yeditepe University. Three ml of whole blood in EDTA tubes was collected from each subject.