

IDENTIFICATION OF MUTATIONS IN HERG AND KCNE2 GENES ASSOCIATED WITH ARRHYTHMIA IN PATIENTS TREATED WITH MACROLIDES

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The safety and tolerability of pharmaceuticals has always been an important object of studies but the exact incidence of specific adverse effects is often impossible to assess. Several new antibiotics have been withdrawn from the market because of rare or exceptional but life-threatening adverse effects. Macrolides and fluoroquinolones are widely prescribed for treatment of infections and are traditionally known to cause Q-T interval prolongation and are at risk to induce Torsade de Pointes (TdP) that represent one of the most dangerous effects with these drugs. Recently, erythromycin was found to induce TdP, with relative high frequency, even if administered by oral route. A recent trial concludes that short term clarithromycin in patients with stable coronary heart disease may significantly cause higher cardiovascular mortality. Genes who are involved in congenital long-QT (cLQT) syndromes may also be involved in acquired LQT (aLQT), induced by drugs. Studies of genetic risk factors have been performed in the United States and Western Europe, suggesting that genetic mutation of potassium channels involved in cLQT may be common in patients with drug-induced arrhythmias. Some studies have shown prolongation of the QT interval and blockade of the potassium channel encoded by HERG gene. HERG forms voltage-gated K channels that are associated with Mink-related peptide 1 (MIRP1), encoded by KCNE2 gene. Mutations in HERG and KCNE2 genes may be correlated with susceptibility to drug-induced arrhythmia.

Methods: Venous blood samples from 25 unrelated patients and of 40 unrelated subjects, as control, were taken after informed consent. Genomic DNA was isolated using standard procedures and PCR was carried out using specific primers that cover the complete coding regions and intron-exon boundaries. Single-strand conformation polymorphism (SSCP) analysis was performed to identify mutations in the coding regions and anomalous PCR products were sequenced.

Results: Screening for mutations in HERG and KCNE2 genes with SSCP, identified an abnormal SSCP conformer in the KCNE2 gene from DNA of one patient during treatment with erythromycin and another in HERG gene from one patient treated with clarithromycin. Sequenced analysis revealed a mutation, leading to 1-bp deletion (delA, 360) and (C1039T) respectively.

Conclusion: Individual case reports have shown that patients with macrolides-induced arrhythmia may carry sporadic mutations in HERG and KCNE2 genes. These results should be validated by further studies in a large population in order to evaluate the statistical association with polymorphisms and drug-induced arrhythmia.