Title: Development of a drug-specific Long QT-JT Index for prediction of drug-induced QT Prolongation.

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Drug-induced Long QT Syndrome (LQTS) is a potential side effect of over 120 medications and is responsible for at least six medications being withdrawn by the FDA since 1997. Drug-induced LQTS may predispose patients to a potentially lethal polymorphic ventricular tachycardia namely, torsade de pointes (TdP). Current models for estimation of drug-induced LQTS risk are mostly based on their propensity and potency for block of the rapid component of the delayed rectifier (I_{Kr}/hERG). We assessed the hypothesis that a comprehensive index taking into account a medication’s molecular and metabolic properties would give an accurate depiction of clinical risk. In order to do so, we have developed a quantitative drug index taking into account IC_{50} for block of I_{Kr} (hERG), block of I_{Ks} (KvLQT1), block of I_{Ca} (Cav1.2), block of I_{Na} (Nav1.5), percent protein binding, C_{max} at a test dose, maximum daily dose, inhibition of hERG trafficking (phosphorylation), and a drug-drug interaction coefficient (DDIC) allowing calculation of maximum increase in plasma levels under conditions of drug metabolism inhibition. Using this approach, an index value was calculated for more than 155 drugs. More than 90% of drugs with demonstrated high risk of TdP have a Long QT-JT index value <15 under the above conditions. In validating the Long QT-JT Index, we compared the quantitative value calculated for each medication with its propensity to cause Torsade de Pointes in the literature. Using this approach, the sensitivity of the Long QT-JT Index is 86.8%, and the specificity of the Long QT-JT Index is 68.1%. In conclusion, it will be beneficial to pharmacists, prescribers, and regulatory agencies to have a preemptive, quantitative view of what could occur under maximal risk conditions with drugs associated with the drug-induced LQTS.

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