QT INTERVAL CHANGES AS PREDICTOR OF ARRITMOGENIC EFFECT OF DRUGS

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The electrocardiogram (ECG) is used for the diagnosis of cardiac abnormalities, as well as for monitoring drug treated cardiac patients and other utilities. The prolongation of the QT interval which has the ECG features of ‘torsade de points’ can be induced by non-cardiac drugs. When QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmia, particularly when combined with other risk factors. Thus, much emphasis has been placed on the potential proarrhythmic effects of pharmaceuticals that are associated with QT interval prolongation. The rapidly and slowly activating components of the delayed rectifier potassium current, IKr and IKs, have the most influential role in determining the duration of the action potential and thus the QT interval. ECG abnormalities similar to those seen in patients carrying mutations in the hERG gene can also be produced via direct blockade of hERG/IKr channels by a large group of structurally diverse therapeutic compounds including many antiarrhythmics, antihistamines, antipsychotics and antibiotics. The most common mechanism of drug induced QT interval prolongation is inhibition of the delayed rectifier potassium channel that is responsible for IKr. At least three therapeutic compounds reduce hERG/IKr currents not by direct block but by inhibition of hERG/IKr trafficking to the cell surface: (i) arsenic trioxide and and antimonial compounds, (ii) the antiprotozoical agent pentamidine, and (iii) cardiac glycosides. The antidepressant fluoxetine, represents the first member that directly block hERG and inhibit its trafficking at the same time. Thus, it becomes clear the importance of approaches that investigate the safety of therapeutic drugs to prevent them can induce or enhance a picture of arrhythmias from QT prolongation.

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