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Improvement of QT analysis for evaluating the proarrhythmic risk of drug: The importance of spatial and temporal dispersion of repolarisation

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Cardiac arrhythmias, in particular life-threatening Torsades de Pointes (TdP) are serious adverse effects associated with a number of pharmaceuticals belonging to different classes. It is therefore critical to have reliable biomarkers for assessing this risk during pre-clinical testing of new compounds. Prolongation of cardiac action potential and consequently of the QT interval of the ECG is generally considered as indicative of a risk of arrhythmia. Evaluation of drug effects on QT in preclinical studies is therefore requested by ICH guidelines (S7B). However there is now growing evidence that the prolongation of mean QT interval is not an accurate indicator of the risk of arrhythmia and that other parameters of cardiac repolarisation are more predictive. They include instability of action potential duration and increase in transmural heterogeneity of myocardial repolarisation (spatial variability), which can be investigated in specific *in vitro* tests. We have evaluated the ECG correlates of both markers in studies testing the effects of isoproterenol, astemizole and hypokalaemia, which are known to be associated with a proarrhythmic risk. Instability of action potential duration is associated with an increase in the beat-to-beat (temporal) variability of the QT interval that is evaluated by calculating the coefficient of variation of this parameter or by plotting QT from each beat vs. QT of previous beat. Spatial variability of repolarisation correlates with changes in the morphology of the T wave, in particular increase in the interval between the peak and the end of the T wave and notching of this wave.

Biography

Gilles Hanton graduated as Doctor in Veterinary Medicine in 1976 and as Diplomate of the American Board of Toxicology in 1991. He has worked for more than 26 years in the Departments of Toxicology of Searle, Pfizer and Tibotec/Johnson & Johnson. He has a large practice of conducting regulatory and mechanistic toxicity studies and he has acquired a broad experience in the development of new molecules and in safety assessment of pharmaceutical compounds. He has developed an expertise in cardiovascular toxicology and pharmacology and in inhalation toxicology. He is currently working as a Consultant for the Pharmaceutical and Biotechnology Industry.

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