

Sven Mensing
Dr. sc. hum.

Quantification of Repolarization Effects Induced by Moxifloxacin in Preclinical and Clinical Studies

Geboren am 06. September 1979 in Hannover

Diplom der Fachrichtung Biomathematik am 17. Juni 2005 an der Universität Greifswald

Promotionsfach: Medizinische Informatik

Doktorvater: Prof. Dr.-Ing. Hartmut Dickhaus

The consumer safety of new chemical entities (NCE) needs to be evaluated by multiple studies. One important factor for the approval of a new drug substance is the assessment of potential adverse cardiovascular (CV) effects. The possible induction of Torsade de Pointes arrhythmia is one of the major concerns during the drug development process. Thus many methods for the assessment of CV safety have been proposed.

This thesis gives a compact literature review of methods for preclinical and clinical CV risk assessment. The methods are applied to datasets from preclinical and clinical studies on moxifloxacin, which is commonly used as a standard reference drug. The preclinical study performed for this project originates from cardiac tissues stimulated according to a periodic stimulation protocol. The clinical data focuses on ECG recordings from a phase I trial grouped into three different ECG recording classes.

In addition to the application of published methods, three novel methods have been developed and used to assess CV risk for NCEs. The first method is an Algorithm for Pre-/Clinical Analysis of Repolarization Trajectories (APART) allowing the analysis of the dynamics in action potentials of isolated cardiac tissues subjected to periodic pacing cycles. The second method is an iterative clustering algorithm that detects representative beats in the ECG. Furthermore, a novel method has been developed to assess T-loop morphology in the vectorcardiogram.

The concentration-dependent effect of moxifloxacin upon isolated cardiac tissues has been demonstrated in this thesis using standard repolarization duration analysis. With the use of APART, tissue differences in the repolarization dynamics during periodic stimulation protocol could be shown: the Purkinje fiber reacts distinctly different relative to the papillary muscle.

In the clinical study, the evaluation of ECGs showed the expected prolongation of repolarization (QT/QTc) related to the moxifloxacin treatment. A comparison of three ECG recording classes did not reveal any significant differences. The use of 24h Holter recordings allowed the application of heart rate binning methods, detailed individual heart rate correction and assessment of QT-RR hysteresis. Vectorcardiographic morphology measures of the repolarization did not reveal significant changes in the T-loop caused by moxifloxacin. The clustering algorithm for the detection of presentable beats showed good results (area under ROC of about 0.95) when applied to reference datasets. Thus this method might help in the analysis of datasets, where detailed assessment of waveforms is not possible (e.g. no available raw data, speed of analysis).

This thesis was supported by Abbott GmbH & Co. KG, Ludwigshafen (Germany).