Differentiating Multichannel Block on the Guinea Pig ECG: use of T_{peak}-T_{end}, J-T_{peak} and T-wave amplitude

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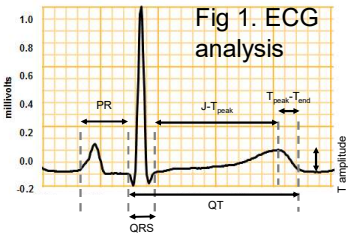
Introduction: A prospective study was performed recently by the FDA to assess whether multichannel blockers could be characterised from the human ECG by analysis of effects on early repolarisation (J-T_{peak}) and late repolarisation (T_{peak}-T_{end}) (Johannesen et al., 2014; Vicente et al., 2015). We tested three of the same ion channel blockers in anaesthetised guinea pigs and, applying a similar ECG analysis, compared our results with those obtained in the human study.

Methods: Female guinea pigs, anaesthetised with pentobarbitone, were instrumented to record six-lead ECG. Animals (n = 4-6) received either vehicle control,

Methods (cont): dofetilide (pure I_{Kr} blocker), ranolazine (I_{Kr} and late I_{Na} blocker) or verapamil (I_{Kr} and $I_{Ca,L}$ blocker) administered as 3 ascending 15-min intravenous infusions. Blood samples were taken to assess drug concentrations after each dose.

ECG parameters (Fig. 1) were analysed from Lead I using DSI Ponemah ECG PRO (5.2). QT and J-T_{peak} were corrected for heart rate changes using Bazett's formula.



Results: Figs 2a-c show the effects of reference compounds on repolarisation parameters in guinea pigs analysed statistically using a linear mixed effect model.

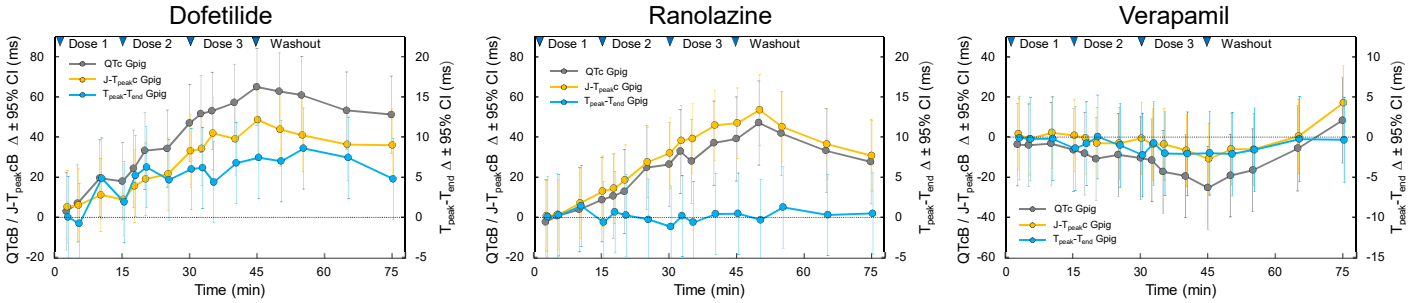


Fig 2a: Dofetilide significantly increased J-T_{peak}cB, T_{peak}-T_{end} and QTcB.

Fig 2b: Ranolazine significantly increased J-T_{peak}cB, and QTcB. No effect on T_{peak}-T_{end}.

Fig 2c: Verapamil significantly decreased QTcB. No effect on J-T_{peak}cB or T_{peak}-T_{end}.

Results: Figs 3a-c show concentration-response plots comparing the effects of the reference compounds in guinea pig with effect in human. In vivo results overlay ion channel inhibition curves. Human and ion channel data is taken from the FDA study data.

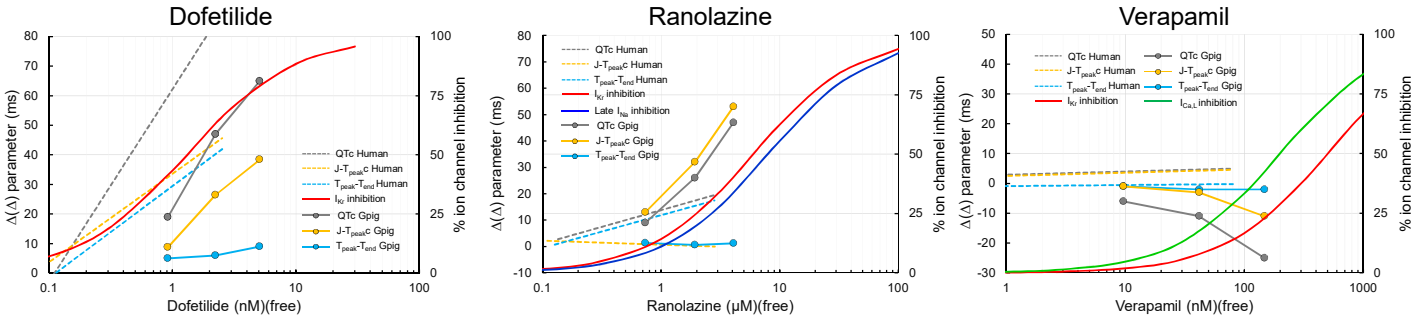


Fig 3a: Dofetilide prolonged early and late repolarisation in both guinea pigs and humans - data concordant.

Fig 3b: Ranolazine prolonged late repolarisation in human but early repolarisation in guinea pigs – data non-concordant.

Fig 3c: Verapamil had no effect on early or late repolarisation in both guinea pigs and human – data concordant.

Results: Both dofetilide and ranolazine increase T-wave flatness in humans (Vicente et al., 2015) and significantly decreased T-wave amplitude in guinea pigs. Verapamil had no effect on T-wave amplitude in humans (Vicente et al, 2015) but significantly increased T-wave amplitude in guinea pigs. Both ranolazine and verapamil prolonged PR interval in the guinea pig, consistent with human data.

Johannesen et al. Clin Pharmacol Ther. 2014 96:549-58.
Vicente et al., J Am Heart Assoc. 2015 4: 1-13

Conclusion: These results suggest that including measurements of early and late repolarisation, in addition to QT interval, may help differentiate pure hERG channel blockers with high risk of TdP from multichannel blockers with lower risk. Some differences in results versus clinical data were noted with ranolazine and . assessment of additional reference drugs may be beneficial.