The electro-mechanical window in anaesthetized guinea-pigs: a new marker for TdP risk screening

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Introduction

QT prolongation is commonly used as a surrogate marker for the pro-arrhythmic activity of non-cardiovascular drugs. However, it is increasingly recognized that QT prolongation alone is not a reliable marker for identifying the risk of Torsade de Pointes (TdP) in clinical or preclinical settings. Over the years several potentially more reliable risk markers have been proposed (e.g. transmembrane dispersion, QT instability, QT dispersion, triangulation of the AP). Recently, a negative electro-mechanical (E-M) window has been proposed as additional risk marker for TdP in a canine QT11 model by van der Linden et al. The current work was aimed at explore the E-M window in anaesthetized guinea-pigs as potential screening marker for TdP risk in humans.

Methods

The E-M window, defined as the temporal dispersion of the duration of the electrical and mechanical systole (E-M window = Q1/4dp/dt - QT), was automatically measured (EMMA software) in anaesthetized and instrumented guinea-pigs. First the influence of changes in body temperature (rectal probe) and changes in heart rate on the E-M window were assessed. Secondly, the effects of various clinical reference drugs on the E-M window (and on the QTcB interval) were evaluated.

1. Effect of changes in body temperature on the E-M window

Cooling (heating pad switched off) of anaesthetized guinea-pigs from 38°C to 34°C induced a decrease of the heart rate and resulted in an increase of the QTcB interval (14.6 ms per 1°C). The E-M window remained fairly constant despite the temperature decline, and even slightly increased below 35.5°C. Graphs show mean and s.e.mean of 3 different experiments.

2. Effect of changes in heart rate on the E-M window

Salbutamol and diltiazem respectively drastically increased and decreased the heart rate. In contrast to the QTcB interval, the E-M window was minimally affected by drug induced changes in heart rate. Graphs show mean and s.e.mean; n=5 (salbutamol); n=4 (diltiazem).

3. Validation with clinical reference drugs: the E-M window versus the QTcB interval

Clinical reference drugs with documented TdP liability (quinidine, diltiazem, haloperidol, terfenadine, dexamfetamine and thioridazine) consistently inverted the E-M window, whereas compounds with no TdP risk in humans (salbutamol and diltiazem) failed to affect the E-M window. Interestingly, drugs with documented clinical QT prolongation, but with lower risk for TdP (ciprofloxacin, moxifloxacin and amiodarone) did not decrease the E-M window. The highest dose of amiodarone even increased the E-M window and prevented the induction of a negative E-M window by diltiazem. Graphs show mean and s.e.mean; n=3 (haloperidol); n=4 (quinidine, dexamfetamine, terfenadine, vehicle, diltiazem, amiodarone, moxifloxacin and ciprofloxacin); n=5 (thioridazine, salbutamol).

Conclusions

- Automated measurements of the electro-mechanical (E-M) window in anaesthetized guinea-pigs are feasible and reproducible.
- The E-M window is a robust marker, minimally affected by changes in heart rate or body temperature.
- Negative E-M windows were consistently observed with drugs with high TdP risk, but not with drugs with no or low TdP risk.

These results suggest the electro-mechanical (E-M) window in anaesthetized guinea-pigs is a predictive risk marker for TdP in man.