Prediction of Torsades de Pointes – Amisulpride Case Series

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Introduction

- TdP is a potentially fatal ventricular arrhythmia associated with drug-induced QT prolongation\textsuperscript{1}.
- Prior reports have looked at a wide spectrum of different drugs which has confounded the causal relationship of the magnitude of QT interval prolongation with the inherent cardiotoxicity of the drug.
- This amisulpride case series has eliminated the confounding drug effect and allowed the magnitude of QT prolongation to be assessed as a predictor of TdP.

Objective

- To determine if the magnitude of QT prolongation is a better predictor of TdP than dose alone in a series of amisulpride poisonings.

Methods

- 457 ECGs arose from 86 patients who took an amisulpride overdose (median dose 6g, range 0.4-120g)\textsuperscript{2}.
- The longest median QT interval\textsuperscript{3} was analysed, or that which occurred within one hour prior to TdP.
- The QT interval metrics used were the:
  - Absolute QT value.
  - QT value corrected for heart rate by Bazett’s formula [QTcB]\textsuperscript{4}.
  - QT value corrected for heart rate using Fridericia’s formula [QTcF]\textsuperscript{5}.
  - Shortest distance of the QT-HR pair from the QT- nomogram\textsuperscript{6} – orthogonal distance [OD].
- Logistic regression was performed using NONMEM (version 6).
- Dose (positive control) & RR-interval (negative control) were included.

Orthogonal Distance as a Risk Factor

- Calculating OD from the QT interval nomogram:
  - $x_1, y_1$ represent the observed HR and QT values.
  - $x_2, y_2$ represents the orthogonal point of HR and QT on the ‘at risk’ line of the QT-nomogram.
  - $y_2$ can be represented as a function of HR; $y_2 = f(x_2)$.
  - The distance of a HR and QT pair can be calculated: $d = [(x_1-x_2)^2 + (f(x_2) - y_1)^2]^{1/2}$.
  - The orthogonal point is estimated by finding the value of $x_2$ that minimises $d$ (see figure 1).

Results

- TdP occurred in 8 (9.3\%) of patients, the dose of amisulpride in these patients ranged from 4-80g.
- Both dose and RR interval improved the prediction of TdP over and above simply the presence of a prolonged QT interval.
- All four QT metrics the absolute QT, QTcB, QTcF and OD were superior to both dose and RR interval – but the different QT measures were indistinguishable from each other.
- Figure 2 shows orthogonal distance and the probability of TdP.
- Figure 3 shows each maximum QT interval plotted on the QT-nomogram, with the cases of TdP.

Conclusions

- All measures of the magnitude of QT prolongation, QT, QTcB, QTcF and OD, were better predictors of TdP compared with dose or the presence of an abnormal QT-HR pair.
- The different QT metrics were indistinguishable from each other in their ability to predict TdP.

References