

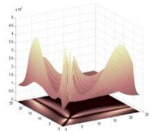
Prediction of Torsades de Pointes – Amisulpride Case Series



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Introduction

- TdP is a potentially fatal ventricular arrhythmia associated with drug-induced QT prolongation¹.
- 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

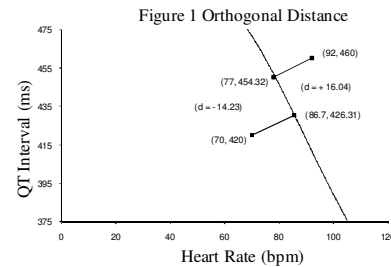
- To determine if the magnitude of QT prolongation is a better predictor of TdP than dose alone in a series of amisulpride poisonings.

Methods

- 457 ECGs arose from 86 patients who took an amisulpride overdose (median dose 6g, range 0.4-120g)².
- The longest median QT interval³ 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]⁴.
 - QT value corrected for heart rate using Fridericia's formula [QTcF]⁵.
 - Shortest distance of the QT-HR pair from the QT-nomogram⁶ – 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:
$$d = [(x_2 - x_1)^2 + (f(x_2) - y_1)^2]^{1/2}.$$
 - 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.

Figure 2 Orthogonal Distance and TdP

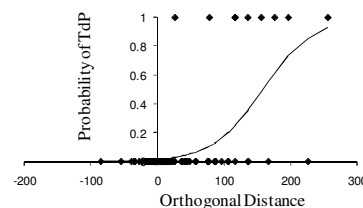
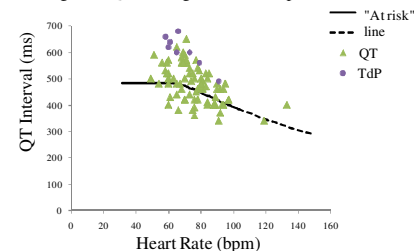


Figure 3 QT Nomogram - Amisulpride Overdoses



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

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4. Bazett HC Heart 1920;7:353-70.
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