QT Assessment in Early Clinical Development: Setting the Stage

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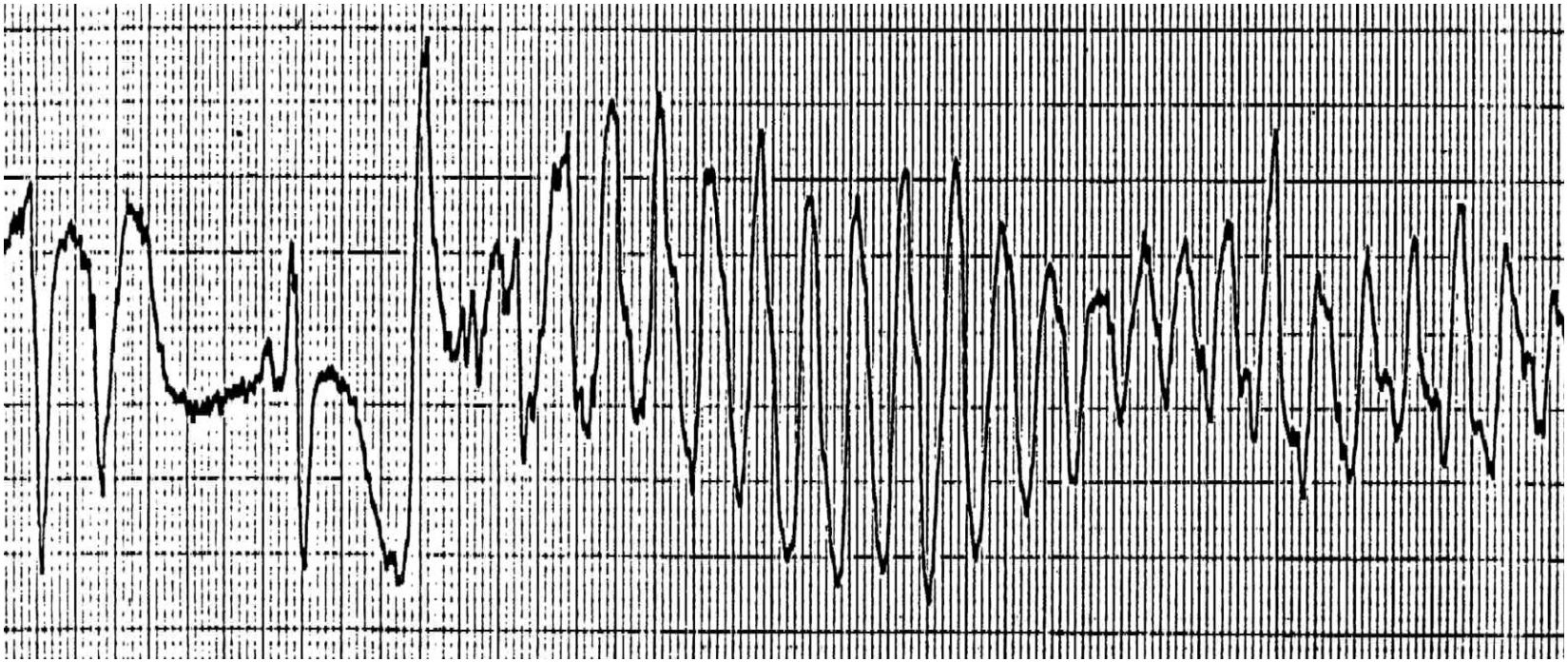
Drug-Induced Torsade de Pointes (TdP)



QT Prolongation: Abbreviated Hx

- Symposium: 'QTc Interval Prolongation: Is It Beneficial or Harmful?'
  - Amer Jnl of Cardiology 1993

--Mechanisms and Models to Predict a QTc Effect
--Relation of QTc Prolongation on the Electrocardiogram to Torsades de Pointes: Definitions and Mechanisms
--How to Measure QT Interval-- What is Normal?
--Rate-Corrected QT Interval: Techniques and Limitations

Abbreviated Hx (cont)

- 1990-2000: 5 drugs withdrawals due to QT (hismanal, cisapride, grepafloxacin, LAAM, terfenadine)
- Late 1990's- 2005: work on approaches to identify and assess risks of TdP and E14
- 2005- present: 248 TQT studies later, can we do better?

QT in Larger Safety Context

PHOTO: JB REED/BLOOMBERG VIA GETTY IMAGES

Societal Interest in Drug Safety

- Societal expectations higher than ever:
  - Faster development of needed therapeutics, but…..
    - Safer therapies
    - More safety information with less uncertainty faster
    - Comparative safety and effectiveness

FDA Approach to Common Safety Concerns Affecting Drug Development

- Examples:
  - TdP
  - Hepatotoxicity and other organ toxicities
  - Genotoxicity

FDA Approach to Common Safety Concerns Affecting Drug Development (cont)

- Initially: systematic testing
  - Guidance—ICH S7A, S7B, S(2)R and E14, FDA Guidance on Hepatotoxicity…
  - Review standards and process: TQT team, Safety Review template, CAC
- Experience Collection
- Re-Assessment

What About the TQT?

- No new drugs withdrawn for TdP risk since E14
  - Pathway for assessing older drugs with potential QT liabilities has assisted post-marketing assessment of adverse events reports
- TQT study
  - Additional dedicated study
  - Labor-intensive process of data collection and analysis
- Features of QT prolongation suggest it could be a target for alternate testing

Alternate Assessment of Arrhythmic Risk: Why it Makes Sense

- Mechanistic toxicity (i.e., largely K-channel blockade mediated)
- Mechanism reasonably well-defined, concentration-dependent, and shared between animals and humans
- Other data routinely collected can potentially inform risk ID and assessment
- Recognize that QT interval prolongation is an imperfect surrogate for arrhythmic risk

Alternate Assessment of Arrhythmic Risk: Why It's Hard

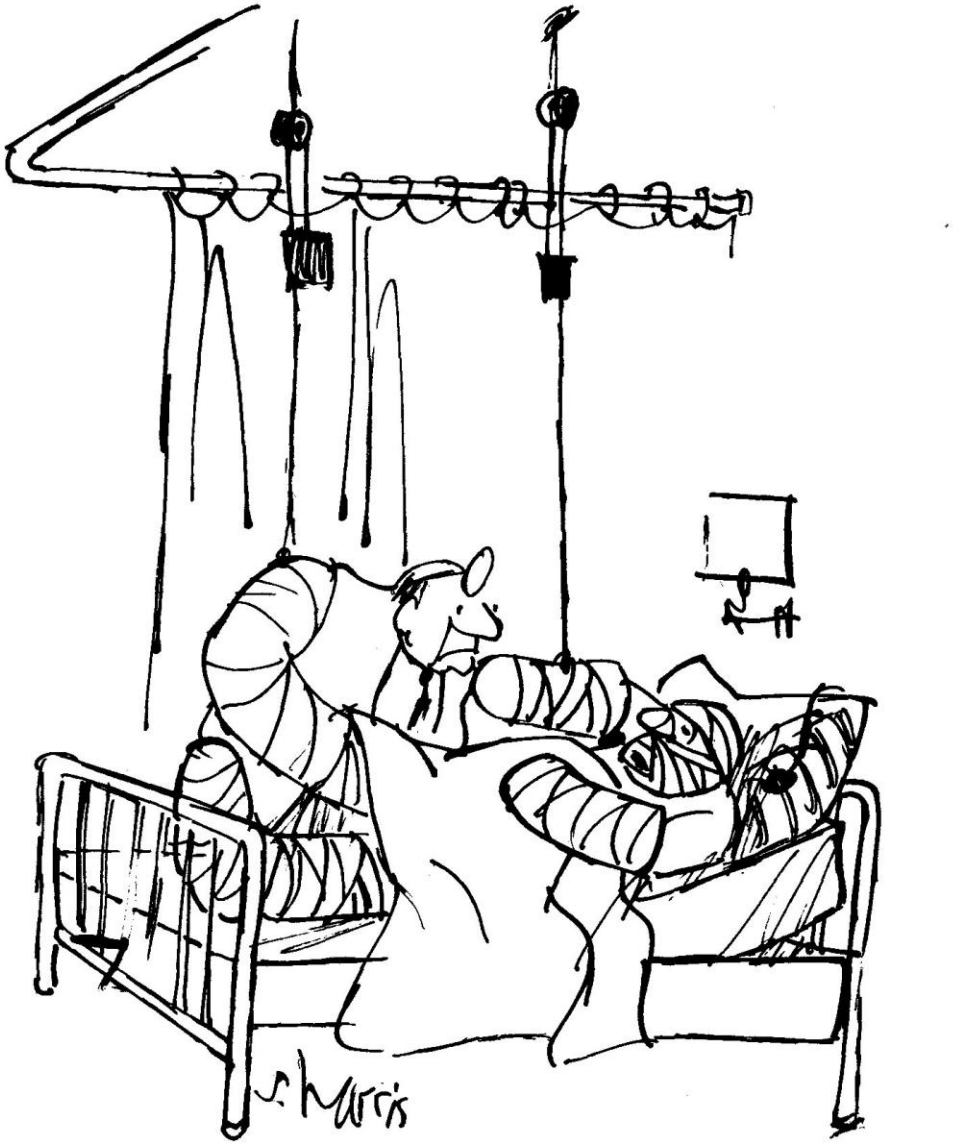
- More than one mechanism for drug-induced QT prolongation
- Protocols for data collection in non-clinical and early-phase data variably standardized between labs
- Rigorous analysis of correlation between non-clinical and early-phase data not done
- High degree of surety required for a non-clinical test in the area of CV safety in order to eliminate the need for clinical testing
  - Few worked examples in drug development

Paths Forward: Cardiac Database

- Collaboration: HESI, industry, academia and FDA
- Quantitative comparison of nonclinical QT data with clinical QT interval trial results, with the purpose of determining how well nonclinical studies predict clinical QT study results
- > 75 compounds in the database at present
- Can early phase data clinical help?
  - Focus of this meeting
  - Intensive monitoring of small #s of subjects
  - Standardized data collection?

Summary

- Current approach has been successful at preventing the need to remove drugs from the market, but at a cost
- Identification and assessment of arrhythmic risk fits within normal approaches to drug safety
- Advances in data collection and characteristics of TdP suggest it's time to re-evaluate assessment methods:
  - Use of non-clinical data alone most efficient change if possible
  - Early phase data another target for important information



You call this an adverse drug reaction?