Designing SAD/MAD studies to generate TQT-like ECG data

Norman Stockbridge

Division of Cardiovascular and Renal Products, FDA/CDER

Issues

- Coverage of the exposure of interest—target dose, metabolites
- Sample size, data quality sufficient to constrain upper CI
- Substitute for positive control
- Systematic bias in exposure-response

Exposure

- Might my study fail to cover the dose I eventually decide is needed? Might it not be long enough (single or few doses) to get plasma levels of some active metabolite?
- Situation is not fundamentally different from the TQT. Interpretation of any results only valid for conditions of assessment. At least if one decides that higher doses need to be tested, you can graft the QT assessments onto any study.
- No novel concern about SAD/MAD approach

False positives

- Most suboptimal aspects of trial design and conduct will increase noise, which makes the study less likely to rule out a clinically relevant QT effect.
- Regulators' role is to ensure few false negatives; false positive problem is sponsor's.
- Sponsor can always address the issue by a second evaluation of QT effects.
- IQ/CSRC study only slightly helpful in evaluating this risk as a function of any design parameter.

No moxi (1)

- Risk was reading ECGs with a bias towards no effect. Purpose of moxi was to ensure assay sensitivity near threshold of regulatory interest.
- Moxi data seldom invalidate a TQT. This isn't entirely reassuring that very different data collection and evaluation won't be a problem.
  - Studies got bigger
  - Studies got more carefully managed

No moxi (2)

- Concern assuaged by
  - Fully automated ECG reading, but suppose the readings all 380 ms.
  - Seeing familiar QT-RR relationship
    - Same QT-RR at baseline and on-treatment
    - If crossover, same QT-RR in each period
    - Need to see full Holters

Systematic bias

- TQT selects the worst reading from several time points, resulting in a few-ms bias in the mean estimate and the upper CI relative to the exposure-response analysis. For similarly powered studies, TQT will declare more of them positive than will exposure-response.
- I consider this a benefit of exposure-response, but it is also “less conservative”, if you view the world as “positive” or “negative”.

Summary

Issue with exposure-response	Problem?
Exposure coverage	No more than TQT
False positives	Not for regulators
No moxi control	Alternative approach exists
No systematic bias	Less conservative