Problems in finding the best primary endpoint of dedicated QT studies:

Largest mean increase, mean of maximum increases, mean change at $C_{\text{max}}$, categorical analyses, and many others....

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• Usual disclaimer: The views expressed in this presentation are those of the author and do not necessarily reflect the opinions of Swissmedic or the International Conference on Harmonisation (ICH) Expert Working Groups or Steering Committee
The ECG of Berner Oberland
Overview

• Background:
  – Why we care about the QT-interval
  – What we are looking for
  – Why we can’t find it

• What we look for instead in Phase I
  – No choice: Surrogates!
    • Number of large prolongations / high absolute values
    • Means of prolongations

• Why I am afraid here
Why we care about the QT-interval

- Excessive (drug-induced) prolongation of the QT-interval: rising probability of:
  - Cardiac arrhythmias
    - Torsade de pointes
    - Sudden cardiac death

- Probability also dependent on:
  - Electrolyte disturbances, hypokalemia
  - Health status
  - „repolarization reserve“ „last drop to full tub“
Why we care about the QT-interval

Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death

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uncommon. Our results suggest that 320 cases of sudden cardiac death can be attributed to the use of non-cardiac QTc-prolonging medication in The Netherlands on a yearly basis.\textsuperscript{16,17} This is important because regulatory authorities have to evaluate the clinical significance of QTc prolongation observed in relatively small clinical trials without cases of sudden cardiac death.
What we are looking for

• Identify drugs which cause arrhythmias, Torsade de pointes, and Sudden Cardiac Death in treated patients
  – QT-prolongation one indicator

• Risk of 1 in 10‘000 patients for most drugs already much too high
Why we can‘t find it

• Identify such small risks on a background of „naturally“ occurring TdP or sudden deaths = prohibitively large patient numbers

• Susceptible patients (e.g. with Long QT Syndrome) difficult to identify, probably rare
What we look for instead in Phase I

• **No choice: Surrogates!**

• **But: Big choice of surrogates**

• **Most popular: More or less sophisticated analysis of ECG**
  – Categorical analysis
  – Analysis of central tendency
Categorical analysis

- Number of patients with
  - Prolongations (delta signals)
  - Absolute values

above a certain threshold

Deltas > 30msec, >60 msec

Absolute values e.g. >480 msec, >500 msec (sex dependent, but under discussion how relevant)
Categorical analysis

• Advantages:
  – Closest to what we look for: excessive prolongations
  – Not very sensitive to measurement method
  – Relatively easy to analyse (statistically)
  – Easy to interpret (clinically)
  – Relatively robust correlation to TdP and arrhythmias
Categorical analysis

• Disadvantages:
  – Lot of (quantitative) information lost
  – because it is a rare event (more frequent than TdP, but still very rare), the numbers of patients / volunteers needed to show statistically significant differences to placebo are **much too high = prohibitive**
    • not enough power in Phase I studies
  – but important in Phase III
Analysis of central tendency

• One of the ideas behind analysis of means:
  • In view of normal variation (day to day, diurnal, dependence on electrolytes, posture, food) of at least 40 msec, we obviously would not be concerned so much if a drug would cause in all patients a prolongation of only 10 msec, although the mean would still be above the „threshold of regulatory concern“

• However, don‘t forget the „last drop“ effect
A simplified mechanistic illustration

The actors: Drugs A, B

A potassium channel, with some genetically determined variation

Drug A has in the normal population some small effect, fits poorly. Drug B doesn’t fit at all, no effect

Drug A could have a huge effect in a small percentage of the population
Analyses of central tendency

- E 14: Largest mean increase
- Mean of largest increases
- Increase at population Cmax
- Increase at individual Cmax
- Increase at protocol specified time point
- Time-averaged increase
- Area under QT/QTc interval time curve
Analyses of central tendency

• Disadvantages common to all:
  – Already quite distant surrogate, not sufficiently validated
  – Based on assumptions which don‘t have to be true for all drugs
  – Disregarding more than 50% of data of studies (pk/pd relationship)

Small break to address some of yesterday‘s (mis)conceptions
E 14: Largest mean increase

- easily evaluable in x-over as well as parallel group studies

- Biased to higher values (statistics)
- Biased to lower values (pharmacokinetics)
- Big problems with sample size calculation
- Unwanted effect of more thorough investigation (influence of more time points)

Imho, choice driven by many studies with drugs with uncomplicated pharmacokinetics
Mean of largest increases

- Not sensitive to complicated pk

- Biased to even higher values (statistics)
- Even bigger problems with sample size calculation
- Even stronger unwanted effect of more thorough investigation (influence of more time points)
- Problem with Parallel Group design (difference to which placebo time point)
A Problem with Parallel Group design

• Common to e.g.:
  – Mean of largest increases
  – Increase at individual Cmax

• If the primary endpoint is not at the same time point for all subjects, the placebo correction needs to be defined
A Problem with Parallel Group design

• One proposal: If e.g. the prolongation at the individual Tmax is used, the difference to placebo at population Tmax should be used

• My proposal: Match pairs of subjects, use the QT-difference to baseline for the „placebo-subject“ at the Tmax (or Emax) of the „verum-subject“ for control of diurnal effects
Increase at population Cmax

- Easily evaluable in x-over as well as parallel group studies
- In most cases very well suited for intravenous administration, if without relevant metabolism
- Easy statistics, including sample size calc.

- Sensitive to complicated pk, in particular after oral administration
- Accumulation in tissues? Delayed effects?
Increase at individual Cmax

- Easily evaluable in x-over studies
- Easy statistics, including sample size calc.
- Not sensitive to absorption differences, but:

- Accumulation in tissues? Delayed effects? Active metabolites?
- The Parallel Group Problem
Time-averaged increase
Area under QT/QTc interval time curve

– In my view not suitable as primary endpoint, only as supplemental information
– Difficult to interpret and compare across studies, „threshold of regulatory concern“?
– Biased by data at time points with no effect
Conclusion (which is the introduction in the following paper)

„The optimal approach for quantifying peak QT/QTc prolongation is not a simple matter and may in fact be dependent on the pharmacokinetic and pharmacodynamic characteristics of the investigational drug in question."

* Highly recommendable further reading on this and many other subjects:

Colette Strnadova (Therapeutic Products Directorate, Health Canada): The assessment of QT/QTc interval prolongation in clinical trials: A regulatory perspective

In: DIJ, 2005
Why I am afraid here

My recommendation will probably not be welcome, as it means a lot more work for most of you:

Evaluate at least:
  • E 14: Largest mean increase
  • Mean of largest increases
  • Increase at individual Cmax

Discuss and find explanations for any discrepancies between these endpoints
Why I am afraid here

And also because this will not be welcome, I guess:

It cannot be expected that regulators don‘t look at and don‘t take into account potentially concerning, significant results, just because it was not the primary endpoint in a clinical trial