Bridging Cardiovascular Risk from Clinical Trials to Real Life Population

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Background

Regulatory guidelines impose the need to assess drug-induced QT prolongation in early drug development. In fact, QTc prolongation has become the second most common cause for market drug withdrawal, since abnormal QTc prolongation has been associated with a threefold increased risk in sudden cardiac death (SCD). Despite the efforts towards harmonizing the technical requirements in the clinical evaluation of QT/QTc prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs, little attention has been paid to the predictive value of such trials. Furthermore, no systematic evaluation has been performed to demonstrate whether QTc prolongation in a real-life patient population can be fully attributed to the pharmacological effect. The first step to address this question is to identify and resolve patient parameters that have not been taken into consideration in clinical trials.

Method & Aims

Sotalol was chosen as a paradigm drug to compare QTc_B outcomes from a thorough QT- study using data from healthy subjects and from an epidemiological study. The pharmacokinetics of sotalol can be described using a two-compartment, first-order absorption pharmacokinetic model with weight as a covariate on Vd.[1] Drug-induced QTc prolongation in healthy subjects was modeled using the relationship: QT = baseline + circadian rhythm + drug exposure.[2] In contrast, to describe real life epidemiology observations, one needs to consider more than just drug effect. It is believed that $QT_{real\ life}$= function (baseline, circadian rhythm, drug exposure + other factors).

The aim of this exploratory study is to identify and explain discrepancies in QTc prolongation observed in healthy subjects in a clinical trial and in patients in real life.

Using NONMEM v.5.1, drug exposure in both populations is simulated assuming a single, full compliance scenario. Both groups are then compared non-parametrically using QTc distributions from observed and simulated data. Relative risks are also estimated to discriminate drug effect from other explanatory covariates.

Epidemiology Study Summary

Study Population

- All "new" sotalol users from the Rotterdam Cohort Study (ERGO) with at least one ECG assessment during the period 1990-2004
- The ERGO study is a longitudinal prospective cohort study with baseline and repeated follow-up visits including ECG assessment
- A maximum of 4 ECG measurements per subjects are included
- Patients with ECG evidence of left ventricular hypertrophy, left or right bundle branch block are excluded

Dates of baseline and follow-up measurements

Available Data

From a total of 676 sotalol users, 608 are "new" users. A total of 1387 ECG records are used for the present study:

	Male	Sotalol Users	Female	Sotalol Users
Baseline	208	6	274	11
Follow-up 1	177	18	241	24
Follow-up 2	136	20	167	37
Follow-up 3	92	21	92	21

Covariates and Risk Factors

- Sex
- Age
- BMI
- Smoking habits
- Alcohol Abuse
- Heart failure
- Hypertension
- Diabetes mellitus
- Arrhythmia
- QT-prolongation drugs
- Drugs that affect HERG
- Low dose aspirin
- History of myocardial infarction, stroke, angina pectoris

Outcomes

Two different endpoints are investigated:

- QTc in ms for the linear regression analysis
- Relative risks for the association between covariates and QT prolongation

Results

Characteristics of Study Population Compared to Clinical Study

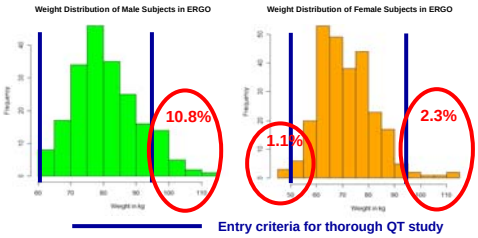

Fig 1 – Weight distribution in the ERGO population

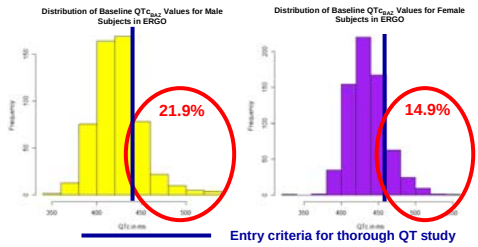

Fig 2 – Baseline distribution in the ERGO population

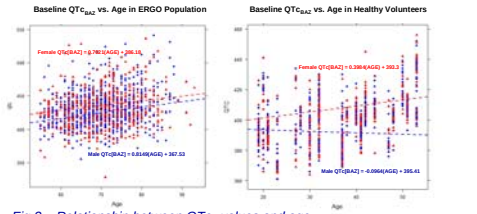

Fig 3 – Relationship between QTc_B values and age

Drug exposure is only one of the explanatory variables for QTc prolongation in real life.

We show how trial design contributes to bias in the estimation of the drug-induced effect. 1) Body weight. Given that body weight is a covariate on the PK of sotalol, the weight distribution of the ERGO population is compared to the inclusion / exclusion criteria for a thorough QT study (*Fig 1*). It is shown that 10.8% and 3.4% of the male and female population would not participate in a trial. 2) Baseline QTc is another important inclusion criterion. In *Fig* 2, it is shown that 21.9% male and 14.9% female would have been excluded from a clinical trial. 3) In addition, age does play a role in the elderly population. In *Fig* 3, the correlation between QTc_B and age is explored.

Drug-induced QTc Prolongation

Using the demographic data, simulations show how drug exposure would effect QTc in the ERGO population. In *Fig* 4, the distribution from simulated QTc_B is compared with data from sotalol users.

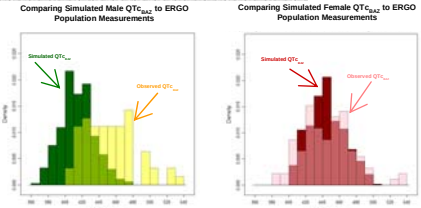

Fig 4 – Distribution of simulated QTc_B value using real life weight range

Relative Risks from Comorbidities

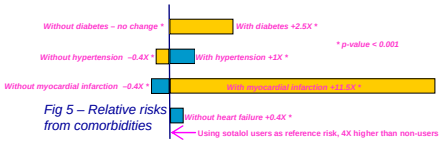

Fig 5 – Relative risks from comorbidities

Binary logistics are performed to find the increase in relative risks of having a QTc > 450 ms in males and QTc > 470 ms in females with various comorbidity conditions in sotalol users (*Fig 5*).

Discussions

The underlying assumption in conducting clinical trials is that findings about drug effect are generalisable to the real life population. In the case of sotalol, our results show that ***only part of*** the observed QTc distribution in the ERGO subjects can be attributed to the effect of d,l-sotalol. Furthermore, we have identified other important explanatory covariates (age and co-morbidities) of the upper range of QTc intervals. This study shows how PK/PD modelling can be incorporated into the analysis and interpretation of epidemiological data. The main challenge is to define the best and worst case compliance to infer drug exposure in the target population.

Ref: [1] Chain et al., PAGE 14 (2005) Abstr 782 [www.page-meeting.org/?abstract=782] [2]Krudys et al.,PAGE 16 (2007) Abstr 1125 [www.page-meeting.org/?abstract=1125]