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Not-In-Trial Simulation II:
Predicting Cardiovascular Risk From Clinical Trial Data

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ABSTRACT

Model-based techniques have become an established approach in drug development. Less attention however has been paid to the role of simulations for the evaluation of safety data, which is fraught with ethical and clinical hurdles. Here we materialise the implementation of Not-In-Trial Simulations as an inferential tool for predicting and translating drug-induced effects from clinical settings to real life situations. We illustrate the concept using QTc-interval prolongation as example of safety concern for both industry and regulatory agencies. In a previous work, we have demonstrated that observed QTc prolongation in a patient population can be only partially explained by the underlying treatment effects. Using a series of simulations, the current investigation shows how QTc-intervals can be modelled as a function of baseline QT-interval, drug exposure, concomitant medications and comorbidity conditions. Our method offers the basis for improved risk management, dissecting drug-specific contribution to pre- or post-approval safety findings.
6.1 Introduction

Generating safety data that reflects the actual risk (and consequently risk:benefit ratio) for the target population during the course of drug development is fraught with practical and ethical hurdles, particularly if safety concerns regard low frequency or rare events. Such information can only be derived from epidemiological or pharmacoepidemiological studies, which are planned and performed after drug approval. Furthermore, inclusion and exclusion criteria are imposed on clinical trial protocols to mitigate risk and prevent the most vulnerable patients from exposure to an experimental agent for which the risk:benefit ratio is unknown at the time of the investigation. Subsequently, however, drug prescription is not restricted or contra-indicated for those patients who were excluded during the clinical development phase. Implicitly, such practice imposes the assumption that such inclusion/exclusion criteria do not alter treatment outcome. Inferential methods offer an opportunity to address this issue in a more quantitative and systematic manner.

With the exception of signal detection methodologies used for pharmacovigilance purposes [1, 2], the integrated use of clinical trial and epidemiological data for the prediction and interpretation of safety findings in clinical drug development remains very limited [3, 4]. Simulation techniques can play an important role in the implementation of such methods. Unfortunately, the use of simulations has been rather limited in the evaluation of the safety profile whether in epidemiological cohorts or in randomised clinical trials [5].

Using a model-based approach that allows the integration of pharmacokinetic-pharmacodynamic relationships for the evaluation of drug-induced QTc-interval prolongation, we illustrate the concept of Not-In-Trial Simulation (NITS) as an inferential tool for the quantification of the contribution of intrinsic and extrinsic factors on the risk of pro-arrhythmic events, i.e. QTc-interval prolongation. In contrast to typical clinical trial simulations [6-8], we make use of simulations to characterise the role of design factors which have been omitted or excluded from a randomised trial, among which those listed under the exclusion criteria or diverging from the clinical conditions relevant for the target population. Thus, our approach will represent a natural extension of ongoing efforts within the pharmaceutical industry to improve safety signal detection [9-15]. This
approach provides the pharmacological basis for the assessment of causality, discriminating drug-induced from other (drug-unrelated) effects.

The objective of this study was therefore to show how clinical findings translate into real life observations and resolve some of the discrepancies commonly observed between pre- vs. post-market estimates of the pro-arrhythmic effects associated with a new therapeutic agent. Drug-induced QTc-interval prolongation has become one of the most widely debated topics in the past decade [16-19], given its presumed association with increased risk for ventricular arrhythmias, which can potentially lead to sudden cardiac death [20, 21]. \( \text{d,l-} \)Sotalol was selected as a paradigm compound for the purposes of our investigation. Based on simulation scenarios we explain the impact and clinical implications of additional factors on QTc-interval prolongation for the real life population.

Despite numerous efforts aimed at improving signal detection of cardiovascular events for new medicines [22-24], none of them has focused on what actually happens after the drug has been approved and released into the general population. Although many post-marketing surveillance trials and spontaneous adverse events reporting have been used to monitor the incidence of (supra)ventricular arrhythmias, torsade de pointes and other safety events [25-27], there is still an important advantage to knowing what can be expected so that mitigation plans can be made in advance. Thus, we anticipate that our approach will widen the views on risk management beyond the evolving perspective from clinical pharmacology experts and regulators, i.e., that the liability for QTc-interval prolongation cannot be assessed accurately without an assessment of the concentration-effect relationships [28]. Not-In-Trial Simulations will enable quantitative evaluation of the implication of other factors contributing to QTc-interval prolongation in real life population, as compared to the observed drug effects in clinical trials. Among various factors [15], our example reveals how gender [29], congestive heart failure [30] and baseline QT-intervals [31] can have equally important impact on treatment outcome.
6.2 METHODS

**Evaluation of the effect of age on QTc-interval**

Baseline information from seven healthy volunteer studies was used for the development of the relationship between baseline QTc-intervals and age. These data were combined with elderly patient data that were classified as healthy in the Rotterdam Study cohort described below. The healthy elderly subjects were defined as those who were not on any medications and not have any comorbidity conditions recorded at the time of the ECG measurement. Only the Bazett correction factor was used for the assessment of the effect of age on QT-interval due to the consistency availability of data across all datasets. Other correction factors were not explored nor did we explore the effect of age on RR-intervals. Finally, a quadratic regression was used to describe the age-dependent QTc data. Based on the resulting parameter estimates, the regression was reduced to a linear relationship in R².8 (The R project - http://www.r-project.org/).

**Evaluation of drug-induced effects in healthy volunteers**

Data from a Phase I healthy volunteer study with d,l-sotalol was selected from GlaxoSmithKline’s clinical data repository (study number EXP20001). The study was performed according to a placebo-controlled, three-way crossover design with two placebo periods. The study population comprised of 30 subjects (12 females, 18 males), between the ages of 19 and 47. Other relevant eligibility criteria for inclusion into the study for the purposes of our investigation were non-smoking status, body mass index between 19-30 kg/m², with a weight of 50 – 95 kg, inclusive. Subjects with a history of hypertension, asthma, bronchial hyperactivity or peripheral vascular disease, including diabetes or previous alcohol or drug abuse were excluded at screening. In addition, subjects showing abnormal QRST complex morphology, sinus bradycardia (HR<45 bmp, PR > 210 msec) or QTc-interval values above 420 or 440 msec (for male and female, respectively) were also excluded.

**Modelling of QTc-interval prolongation:**

The primary outcome of this study was to demonstrate the use of the Not-In-Trial Simulation concept as a tool to quantify the contribution of additional
factors to QTc-interval prolongation. The simulation of QTc-intervals was performed in a two-step approach. First, drug exposure in the target population (i.e., d,l-sotalol users) were derived using a pharmacokinetic model previously published [37]. Briefly, the pharmacokinetics of d, l-sotalol was described by a two compartment, first-order absorption model with weight as a covariate on clearance using nonlinear mixed effects modelling, as implemented in NONMEM (v5.1, ICON Development Solutions, Ellicott City, MD, USA) [38].

Heart-rate corrected QT-intervals were described by a pharmacokinetic-pharmacodynamic (PKPD) model using a Bayesian approach in which physiological (QT and RR) and drug specific (concentration) parameters are parameterised in an independent manner (Equation 1) [39]. A detailed description of model development was presented in a previous publication [37].

\[
QT_c = QT_0 \cdot RR^\alpha + A \cdot \cos \left( \frac{2\pi}{24} (t - \phi) \right) + \text{slope} \cdot C
\]

*Equation 1*

where, QT\textsubscript{0} [msec] is the intercept of the QT-RR relationship. Sex was included as a covariate for this parameter whenever applicable. RR [sec] is the interval between successive R waves, \(\alpha\) is the individual heart rate correction factor, A [msec] is the amplitude of circadian rhythm, t is the clock time, \(\phi\) is the phase, slope [msec/concentration] is the linear pharmacodynamic relationship, and C is the predicted concentration of drug at the time of QT-interval measurements.

Drug-induced QTc-intervals in patients was simulated assuming full compliance to treatment. Population parameter estimates were used for the simulations (slope = 0.02 msec/\text{ng/ml}, and intercept (QT\textsubscript{0}) = 380 msec).
**Evaluation of effect of intrinsic and extrinsic factors on QTc-interval in real life patients**

Data from a real life population setting was obtained from the Rotterdam Study. The study is a prospective population-based cohort study, which started with a baseline visit between 1990 and 1993. All inhabitants of a suburb in Rotterdam, Ommoord, aged 55 years and over were invited to participate. Of the 10,275 subjects invited, 7,983 (78%) gave their written informed consent and took part in the baseline examination. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands. Objectives and methods of investigation have been described in detail in other publications [40]. All participants were visited at home for a standardised questionnaire and 7,151 were subsequently examined at the research center. A second, third and fourth follow up visit took place, respectively, between 1993 - 1995, 1997 - 1999 and 2002 - 2004. In addition to follow-up examinations, the cohort is continuously monitored for major morbidity and mortality through linkage with general practitioner and municipality records.

All subjects who started treatment with d,l-sotalol during follow-up were included in the present study, with the exception of prevalent users and subjects with left ventricular hypertrophy (LVH), right bundle-branch block (RBBB) and left bundle-branch block (LBBB), who were excluded. The reason for the exclusion of these patients is that LVH, RBBB and LBBB can cause secondary repolarisation changes and atrial fibrillation can cause difficulties in measuring QT-intervals. From the remaining population, “new” d,l-sotalol users were identified as those receiving their first prescription after enrolment into the study. Our analysis included all QTc measurements after the start of d,l-sotalol for all new users.

Comorbidities were screened and identified according to standard clinical criteria. Hypertension was defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg and/or use of antihypertensive medications, encompassing grade 2 and grade 3 hypertension compounds according to the World Health Organisation (WHO) criteria [41]. Diabetes mellitus was defined as the use of blood glucose-lowering medication and/or a non-fasting or post-load serum glucose level of 11.1 nmol/L or higher according to the WHO [42]. A history of myocardial infarction was assessed by self-report, checked with records from the general practitioner or
cardiologist and/or electrocardiographic evidence. All reported myocardial infarctions were verified against the medical records as described in detail previously [43]. Assessment of heart failure at baseline and during follow-up was assessed by reviewing all medical records for the occurrence of at least two signs and symptoms suggestive of heart failure or the use of medication for the indication heart failure and hospital discharge letters. Cases of incident heart failure were obtained by continuously monitoring the participants [44, 45]. The ankle arm index (AAI) was used as potential predictor of cardiovascular diseases and mortality [46].

The impact of co-medications and comorbidities were evaluated using a linear regression in R2.8 where the absolute differences in QTc prolongation between taking d,l-sotalol alone and in conjunction with co-medications and comorbidities were calculated with standard deviation. The same evaluation was performed for non-users.

**ECG measurement in clinical trials and real life population**

A 10 sec 12-lead ECG, resulting on average 8-10 heart beats, was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements. The MEANS program has been evaluated extensively and reported elsewhere [47-49]. MEANS determines common onsets and offsets for all 12 leads together for one representative averaged beat, with the use of template matching techniques [48], until the end of the T wave. To adjust for heart rate, Bazett’s formula (QTc = QT / RR ^ ½) was used [50].

**Not-In-Trial Simulation**

The final distribution of QTc values associated with all causal factors was simulated stepwise in R2.8. Differences between observed and expected QTc-intervals were compared non-parametrically by visual inspection.

### 6.3 Results

From the Rotterdam Study cohort, 158 “new” d,l-sotalol users were identified which was defined as only those who have started a prescription
for the drug after the beginning of the study in 1990. The final simulated QTc-interval (expected) distribution of the real life d,l-sotalol users is composed of four parts. It is a cumulative function of age-dependent baseline QTc values, drug effects from d,l-sotalol, contribution from concomitant medication and comorbidity conditions as well as a between-subject variability term. The Bazett formula has been used throughout this study for the heart rate-corrected QT values as this was a consistent output between various data used for the investigation.

**Age-dependent baseline QTc values**

Using all the available baseline QTc values for healthy subjects in this study, a linear relationship was found to best describe the data. The results are also separated by gender because of the known differences in cardiac outputs between men and women [32]. The correlation between age and baseline QTc was modelled according to equations: QTc = 0.5096(Age) + 386.52 for the male population and QTc = 0.8617(Age) + 371.34 for the female population as captured in Figure 1.

*Figure 1. The relationship between age and healthy baseline QTc values, separated by gender.*
**PKPD modelling of QTc-interval prolongation**

Pharmacokinetics (PK) was modelled separately where it was found that a two compartment model best described the time course of concentrations in plasma. The absorption phase was characterised by a lag time, and furthermore, it was found that body weight had a significant effect on the volume of distribution. The PKPD model, shown in Figure 2, allowed the system-specific parameters (i.e., those related to the individual correction for the QT-RR relationship and circadian rhythm) to be estimated separately from the drug-specific parameters (i.e., drug-induced QTc-interval prolongation).

![Figure 2. Pharmacokinetic-pharmacodynamic relationship of d,l-sotalol in healthy subjects following administration of 160 mg.](image)

**Effects of concomitant medications and comorbidity conditions**

Linear regression calculations assessing the impact of various concomitant medications and comorbidity conditions revealed different increase of QTc values in milliseconds. There was also no interactions found between d,l-sotalol and any of the conditions, thus the results found with the users and non-users were not statistically different. Since the power for the non-user group was greater, the results were used in the simulation and the increase in QTc values are summarised in Table 1.
Table 1. Increase in QTc [msec] due to various concomitant medications and comorbidity conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Male, (CI)</th>
<th>Female, (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>7.7 (+/- 4.02)</td>
<td>5.8 (+/- 3.49)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>3 (+/- 2.11)</td>
<td>3.2 (+/- 2.31)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>18.5 (+/- 9.24)</td>
<td>20.4 (+/- 9.51)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.0 (+/- 2.28)</td>
<td>5.4 (+/- 2.0)</td>
</tr>
</tbody>
</table>

**Not-In-Trial Simulation**

The newly proposed Not-In-Trial Simulation model yielded the results shown in Figures 3a-f. First using the ages of the 158 real life d,l-sotalol users in the Rotterdam Study, the baseline QTc values were simulated (Figure 3a) using age-dependent relationships shown above. In Figure 3b, the baseline QTc distributions of the real life population is compared with the baseline distributions from the Phase I clinical trial of healthy volunteers. From the comparison, it was found that there were discrepancies of 33 msec and 29 msec in male and female respectively. Then the effect of d,l-sotalol was added to the baseline distributions of the real life population. The QTc values were shifted by 22 msec in both genders in Figure 3c. Afterwards, taking the comorbidity and concomitant medications of the real life d,l-sotalol users were taken into consideration, the mean QTc values were increased by 3 msec in the male population and 1 msec in the female population (Figure 3d). In Figure 3e, the between-subject variability boundaries around the QTc distributions were added, which has until now been constructed using only the mean values from each step. Finally in Figure 3f, the observed QTc values from the 158 d,l-sotalol users were superimposed onto the simulated distributions. It can be visually confirmed that real life observed QTc measurements fell within the boundaries of the final simulated QTc distributions along with the between-subject variability found in the age-dependent baseline values.
Figure 3. Overall simulation model results (a-f). The left panel depicts results for the male population and female outcome is shown on the right. The lighter colours represent the actual observed QTc values as recorded in the Rotterdam Study while the simulated results are superimposed in a darker colour. The Gaussian distribution curve represents the lower and upper bound of the between-subject variability in baseline values.
6.4 DISCUSSIONS

In contrast to current practice which relies on the evidence from a thorough QTc study for the assessment of the risk of pro-arrhythmic events, we present a model-based approach for the characterisation of drug-induced effects which enables explicit assessment of causality, distinguishing drug-related effects from other factors contributing to the QTc-interval prolongation, namely that, QTc (real life population) = age-dependent baseline QTc values + fluctuation in QTc due to drug effects + effects on QTc due to concomitant medications and comorbidity conditions.

Although QT-interval prolongation is not necessarily harmful, it is at present perhaps the best and only surrogate marker for torsade de pointes, especially so because the definition of this arrhythmia requires prolongation of QT-interval as a preceding event. The crucial question from regulatory perspective is “How efficient and reliable are the pre-approval clinical trials in identifying the clinical risk of torsade de pointes, given the patient population enrolled, background noise arising from spontaneous intra-individual variability in QTc-interval and the relatively low frequency of the clinically significant drug-induced effect” [33]. For a variety of reasons, clinical trials may or may not detect the frequency and intensity of QT-interval prolongation but they are most unlikely to detect the risk of torsade de pointes. Firstly, safety trial designs are highly efficacy-oriented. Secondly, the number of patients exposed to the drug in the pre-approval phase is not large enough to detect a relatively rare but potentially fatal risk. Thirdly, many subgroups of patients most at risk of torsade de pointes during the uncontrolled clinical use to the drug in question are usually excluded from these trials. These subgroups include: females; the elderly, those with predisposing cardiac or noncardiac diseases associated with diminished repolarisation reserve (and therefore greater susceptibility to prolongation of the QT-interval); those with pharmacogenetic defects of drug metabolising enzymes or pharmacological targets such as the potassium channels; those susceptible to bradycardia or electrolyte imbalance; or those receiving drugs with a potential for pharmacokinetic or pharmacodynamic interactions. Therefore the scope for detecting drug-drug or drug-disease interactions in clinical trials is also very limited. And yet, experience has shown that these are among the most important risk factors.
Based on the aforementioned, one may question whether conducting the thorough-QT (TQT) studies yield the best indicator of risk for new therapeutic agents. This regulatory practice is further challenged by increasing clinical evidence that there is no fixed relationship between the extent of QT-interval prolongation and the risk of a patient developing torsade de pointes [34].

Our findings show that baseline QTc values are age and gender dependent. This correlation plays an important role in that observed QTc values will increase over time irrespective of drug treatment. Drug effect and comorbidity conditions also contribute to further increase in QTc values. In this study, simulation scenarios were implemented in such a way that all relevant causal factors affecting QTc prolongation are combined in an integrated manner. It is envisioned that this approach may provide more accurate estimates of cardiovascular risks and enable mitigation of these risks in the target population, preventing future drug-withdrawal due to cardiovascular safety.

Limitations

In this study we have successfully demonstrated the concept of Not-In-Trial Simulation. However, there are limitations in this present study that should be mentioned as this is the first attempt at realising the idea of using simulation as a technique to translate real life observations using clinical trial findings. First and foremost is the lack of hierarchical modeling techniques used in estimating the relationship between age and QTc values as well as the increase due to comorbidity conditions and concomitant drugs which can affect the accuracy or precision of effect sizes and the parameter estimations. Currently, we can verify that our simulation encompasses the range of values in real life situations, but to be able to improve the precision of the parameter estimations would lead to more confidence when performing the simulations for future compounds prospectively.

Another limitation to this study is that the age-QTc relationships in healthy subjects as well as the contributions from comorbidities and co-medications are limited to only the datasets used presently. This approach would no doubt benefit from a larger database to improve all the parameter estimates.
**Model-based risk management**

Currently, both the US and Europe regulatory agencies have produced guidelines that outline efforts in managing the safety and risk of pre- and post-market medical products [35, 36]. Enhancing internal and external epidemiologic and informatics capabilities, strengthening methods and tools of safety surveillance, developing and incorporating new quantitative tools in the assessment of benefit and risk are examples of ongoing activities.

To date, recommendations on how best to detect safety signals such as the introduction of the thorough-QT studies are being published. However, utilising modeling and simulation techniques as a quantitative tool to assess clinical relevance prior to implementation of mitigation measures or eventually as basis for appropriate recommendations is still not adequately advocated.
REFERENCES


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