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Validation Of Not-In-Trial Simulation:
Predicting Cardiovascular Risk From Clinical Trial Data Using Cisapride

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ABSTRACT

Previously, a tool was developed to translate clinical trial findings to real life settings by resolving the discrepancies between pre- vs. post-market estimates of QTc-interval prolongation using d,l-sotalol as the paradigm compound. The tool consisted of a prediction model for QTc measurements based on baseline values, QTc model for drug effect from clinical population and effects of concomitant drugs and comorbidities. The objective of this study was to apply the same model to cisapride, as a form of external model validation. There were 87 new cisapride users in the Rotterdam Study cohort (60 female and 27 male) with the average observed QTc of 432.4 msec and 423.5 msec for women and men respectively. The average simulated QTc for female was 435.8 (sd. 15.83) and 424.1 (sd. 19.5) for male. It was verified that same tool can be used to predict real life QTc values for cisapride users gaining confidence in the use of Not-In-Trial Simulation as a risk mitigation tool.
7.1 INTRODUCTION

One of the main objectives of clinical trials is to test whether a new chemical entity (NCE) is efficacious towards the condition it is targeted to treat and whether it is safe for human usage. Together, evidence on efficacy and safety allow for the assessment of the expected risk-benefit ratio [1]. However, such estimates are only readily available for events which occur frequently enough, i.e. those with high incidence. Less frequent or rare events require larger populations or longer trials and are usually evaluated during the post-approval phase [2]. On the other hand, there are cases in which it is not the frequency of an adverse event, but its magnitude that cannot be accurately determined during the clinical development phase. In these circumstances the observed risk-benefit ratio may not reflect the actual implications of the therapeutic intervention in the target population; QTc-interval prolongation is an example of such a case.

QTc-interval has been considered a risk factor for torsade de pointes (TdP), and has become a major cause for drug withdrawal [3]. Mitigation measures have been implemented by the International Conference on Harmonisation (ICH) [4], which proposes the use of thorough-QT (TQT) studies to detect QTc-interval prolongation as part of the clinical evaluation package for regulatory submissions. Despite these efforts, important limitations are being overlooked because of the mandatory status these studies have. In addition to the lack of quantitative evidence, i.e., the absence of explicit details on the underlying concentration-QTc effect relationship, the current approach often relies on data from healthy subjects who are enrolled according to strict inclusion / exclusion criteria, which does not necessarily reflect the demographic characteristics in the patient population. Moreover, in a TQT trial, supra-therapeutic levels of the drug are used under the assumption that the resulting effects would be representative of the risk in patients, who may be more vulnerable or sensitive to the pro-arrhythmic effects.

Nonetheless, mounting evidence suggests that current TQT protocols may provide biased estimates of the actual risk of QTc-interval prolongation, with high rates of false positive results due to the accepted data analysis method [5]. These findings raise important questions both from a drug development and from a pharmacovigilance perspective. It is in everyone’s best interest to ensure accurate assessment of the risk-benefit ratio, so that decision making
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regarding the development, approval or risk management is effective and timely.

Recently, to address this issue we have developed a model-based approach that allows better translation of clinical trial findings into real life conditions. Thanks to the use of a Bayesian hierarchical model, it is possible to integrate pharmacokinetic-pharmacodynamic relationships with disease and other patient-specific characteristics, discriminating drug-induced effects under controlled and uncontrolled conditions [6]. In fact, we have shown that the use of model parameter estimates in conjunction with Not-In-Trial-Simulations (NITS) provides a framework for evaluating drug vs. disease-specific properties, which facilitates the assessment of causality.

Unfortunately, those who defend the status quo, i.e., the requirement for a TQT study as the best approach to gather evidence on the propensity for QTc-interval prolongation, continue to use patient safety as a cogent argument for adhering to current practices. There is an urgent need to consider alternative methods which do not only ensure lower false positive rates, but also provide accurate estimation of the pro-arrhythmic risk taking into account other factors relevant to the target population in clinical practice. Essentially, there needs to be an increase in operational effectiveness in drug development. We envisage therefore the use of a Not-In-Trial Simulation as a risk management tool for the evaluation of causality and assessment of the impact of mitigation measures as shown in Figure 1.

![Diagram](image)

Figure 1. Not-In-Trial Simulation can be used as a framework for risk management and assessment of the impact of mitigation measures. Most importantly, it provides quantitative estimates of the contribution of drug-related vs. drug-unrelated factors.
In a previous publication we have shown that the method resolves the discrepancies in pre- vs. post-market estimates of QTc-interval prolongation. *d,l*-Sotalol was used as the paradigm compound in which QTc changes are described as a function of baseline QTc measurements, drug-induced effects, and contributions of concomitant drugs and comorbidities. Furthermore, the model also demonstrated that the relationship between exposure and QTc-interval is best characterised in terms of drug concentrations rather than the traditional concept of defined daily dose (DDD) in epidemiology studies. The objective of the current investigation is therefore to demonstrate the generalisability of the approach to other areas of drug development by performing an external validation. External validation is an essential step for the use of predictive or prognostic tools in clinical practice [7].

Here we apply hierarchical modeling and Not-In-Trial Simulations to characterise the impact of pro-arrhythmic effects of cisapride in real life conditions. Cisapride is a gastroprokinetic agent which is used to increase motility in the upper gastrointestinal tract. It was first introduced in 1990 after showing promising clinical trial results in healing and producing symptomatic improvement among patients with esophagitis [8-12] as well as improving symptoms among those with symptomatic heartburn [13, 14], preventing the provocation of heartburn by a fatty meal in susceptible individuals [15] and reducing relapse rates among those with healed esophagitis [16].

From a safety perspective, evidence including post-marketing data from two study groups totaling over 23 000 patients suggested that the drug was safe, with diarrhea, abdominal pain, nausea or vomiting, headache and constipation being the most frequent reported adverse events [17]. Furthermore, serious cardiac rhythm disorders were not found to be associated with cisapride use in a review of almost 37 000 patients who were prescribed cisapride in the UK and Canada [18]. However, reports of cardiac events began to accumulate, beginning with a report of palpitations [19], followed by culminating instances of unusual tachyarrhythmia, torsades de pointes, ventricular fibrillation and sudden death [20]. Eventually, it came to be recognised that cisapride use could result in the prolongation of the QT-interval and, thereby increasing the risk of arrhythmia. It was later revealed that cisapride’s arrhythmogenic potential existed at the cellular and molecular level. In *in vitro* studies, cisapride was found to be a potent and dose-dependent blocker of the human ether-a-go-go-related gene (hERG)
channel [21], which is the main channel responsible for the repolarisation phase of the cardiac action potential [22].

In 1995, a black box warning contraindicating the use of cisapride among those taking drugs that affected its metabolism was issued by the FDA; at that time thirty-four cases of torsades de pointes, twenty-three of prolonged QT-interval and four deaths had been reported (103). A further warning was issued in 1996 regarding to its use with medications that also prolonged the QT-interval and in patients with conditions that predisposed to cardiac arrhythmias. The black box warning was again expanded in 1998. However, the subsequent realisation that serious adverse cardiac events could occur even among low-risk groups, including children, coupled with the documentation of continued cisapride use in contraindicated situations (112) led to the withdrawal of the drug worldwide in July 2000. Thus cisapride is an example, given its sensational rise and demise, where a tool should be in place that can anticipate events, such as QT-interval prolongation, in the future for new compounds in clinical development.

7.2 METHODS

Evaluation of the effect of age on QTc-interval

Baseline information from healthy subjects participating in seven Phase I studies was used for the development of the relationship between baseline QTc-interval and age. The meta-data consisted of approximately 1000 subjects. 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. The Bazett formula was used as the RR correction factor for QT-intervals as it was a consistent output for all the data used in the study. Only QTc values vs. age relationship was explored for this analysis while the effect of age on RR-interval was not explored.

In the original simulation model, 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/), where QTc = 0.5096(Age) + 386.52 for the male population and QTc = 0.8617(Age) + 371.34 for the female population.

**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 [28-30]. MEANS determines common onsets and offsets for all 12 leads together for one representative averaged beat, with the use of template matching techniques [29], until the end of the T wave. To adjust for heart rate, Bazett's formula (QTc = QT / RR ^ ½) was used [31].

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

Data on the pharmacokinetics and pharmacodynamics of cisapride was derived from a randomised, placebo-controlled, dose-escalating Phase-I trial with up to 6 sessions. The primary objective was to assess the cardiovascular safety of single doses of 10, 20, 40, 80, 130 and 200 mg cisapride. Secondary objectives were to determine the pharmacokinetics of cisapride at these single doses, to search for a correlation between pharmacokinetics and cardiovascular parameters, and to evaluate an experimental beat-to-beat computerised analysis of electrocardiograms (ECGs) recorded by Holter monitoring in comparison with the analysis of traditional 12-lead timed ECGs taken at pharmacokinetic blood sampling times. Subjects were randomised in 4 blocks to treatments so that for each block and for each dose, 5 subjects received cisapride and 1 subject received placebo. There was a 48-hour wash-out interval between consecutive doses. A total of 24 healthy subjects participated in the trial. The dose escalation was stopped after dosing with 130 mg cisapride (or placebo) on Day 9, because of the investigator's medical judgment of a potential risk if dose escalation would proceed to the highest dose level of 200 mg of cisapride.

Other relevant eligibility criteria for inclusion into the study for the purposes of our investigation were non-smoking status and body mass index between 18-28 kg/m², inclusive. Subjects with a history of syncope and a family history of sudden death or long QT syndrome were excluded at screening. In
addition, subjects showing an increase in number of premature ventricular beats at a heart rate of >120 bpm, >500 premature ventricular beats per 24 hours, abnormal STU dynamics, a RR-interval > 3 sec, an average heart rate < 50 bpm or > 95 bpm, apparent QT prolongation, ventricular tachycardia of >3 beats at a rate of 100bpm, QRS-interval > 0.12 sec, apparent ST abnormalities, second degree atrioventricular block, supraventricular tachycardias with rates > 150 bpm, QTc-intervals above 450 or 430 msec (for male and female, respectively) were also excluded.

**Modeling of QTc-interval prolongation**

The pharmacokinetic model (PK) as well as the pharmacokinetic pharmacodynamic (PKPD) model of cisapride was taken as reported from the analysis report for the study to demonstrate that Not-In-Trial Simulations can be applied to the current workflow. In the report, it was indicated that the models were fitted to the data using NONMEM V software version 1.1, by applying the first-order conditional estimation (FOCE) method. The package was installed on a PC platform using Compaq Visual Fortran version 6.6 under Microsoft Windows 2000.

A two-step sequential approach was adopted, including a pharmacokinetic modeling step followed by a pharmacodynamic modeling step. The pharmacokinetic model included a two-compartment disposition and a sequential zero- and first-order absorption with a lag time. The relationship between cisapride concentration in plasma and heart rate, RR-interval, uncorrected QT-intervals, corrected QT-intervals using the Bazett and Fridericia formulas as well as other correction formulas, was explored graphically, and by means of linear regression.

The ECG parameters were fitted linearly on the cisapride concentrations. The regressions were based on the ECGs taken immediately before the corresponding pharmacokinetic blood sampling. Plasma concentrations that were below the lower limit of quantification (5 ng/mL) were replaced by zero. Since both heart rate and QT-interval tended to increase with higher cisapride concentrations, all QT corrections also increased with concentration. The tests for the model parameters were always statistically significant (p=0.0001), indicating that the relationship between ECG parameters and cisapride concentrations was most likely not an observation by chance.
Drug-induced QTc-intervals in patients was simulated assuming full compliance to treatment. Population parameter estimates were used for the simulations (slope = 0.179 msec/ng/ml, and intercept (QT0) = 393.5 msec).

**Evaluation of the 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, 7983 (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 [32]. All participants were visited at home for a standardised questionnaire and 7151 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 cisapride 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” cisapride users were identified as those receiving their first prescription after enrolment into the study. Our analysis included all QTc measurements after the start of cisapride 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 [33]. 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 [34]. 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 [35]. 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 [36, 37]. The ankle arm index (AAI) was used as potential predictor of cardiovascular diseases and mortality [38].

The impact of co-medications and comorbidities were evaluated using a linear regression 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. In the original model, the increases of QTc-interval values were derived from non-d,l-sotalol users. Therefore, the same values can be applied here for the validation of the simulation model using cisapride. These values are indicated in table 1.

<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>
<tr>
<td>Hypertension</td>
<td>0.117 (+/- 0.08)</td>
<td>-0.142 (+/- 0.05)</td>
</tr>
</tbody>
</table>

Table 1. Increase in QTc [msec] due to various concomitant medications and comorbidity conditions

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.
7.3 RESULTS

**PKPD modeling of QTc-interval prolongation**

Drug effect-concentration relationships are routinely investigated as part of the drug development process. The relationship of cisapride, shown in Figure 2, has been directly taken from the original Phase I clinical trial report. This illustrate that Not-In-Trial Simulation can be applied in addition to the current workflow, rather than changing the drug development paradigm.

![Figure 2. Drug effect – concentration relationship of cisapride.](image)

**Not-In-Trial Simulation**

By combining the drug model with the age-dependent baseline relationship, along with the added contributions from comorbidities and concomitant medications, the progression of QTc-interval prolongation in the real life cisapride users is displayed in Figure 3. The distribution of the observed QTc
values (light colours) fell within the simulated distribution (dark colours). After applying the model developed using \(d,l\)-sotalol, it was verified that same tool can be used to predict real life QTc values for cisapride users.
Figure 3. Not-In-Trial Simulation of real life cispride users. From hypothetical age-dependent baseline values, to drug-induced QTc prolongation, to added effects from comorbidity conditions and co-medication and finally comparing the simulated values to observed measurements with between subject variability (BSV) shown.

7.4 DISCUSSIONS

Operational effectiveness

Understanding the actual benefit-risk ratio in the target population has become paramount for the development of successful candidate molecules and prevention of attrition at the post-approval phase. The assessment of the
propensity for QTc-interval prolongation is a very pertinent example of this requirement, as these events have become a major cause of drug withdrawal.

Current regulatory and clinical efforts regarding the effective use of drugs rely on the concept of positive benefit-risk ratio and as such depend primarily on the availability of oncoming evidence from clinical or observational trials [1]. These are often defined by Phase IV long term safety trials or more recently by progressive licensing proposal, which ultimately imposes the burden on patients and drug developers, with the caveat of the having the evidence after the facts [23-25]. Thus far, alternative methods to formalise prospective trials have been limited to “retrospective” meta-analytical approaches on data arising from empirical data, i.e., from clinical practice as well as from randomised clinical trials [26, 27].

In the current investigation we have shown once more that evidence synthesis can indeed be performed prospectively by the implementation of model-based approaches in which both fixed effects (drug-related as well as disease-related factors) as well random effects (including parameter and model uncertainty) are integrated. Our results reveal that Not-In-Trial Simulations can be used to predict real life impact of drug intervention on actual patients under real life conditions. QTc measurements in cisapride users were accurately described especially the extremely high values. The lower values were not as well described. One possible explanation that cannot be excluded is that those figures reflect measurement errors, despite quality control and review of the data entry. In fact, the readings showed values that are considerably low for an elderly population. Another possible explanation is due to the pharmacological effects of cisapride where short term usage would induce QTc prolongation; however, longer therapy might also cause a shortening phenomenon which cannot be anticipated by the model.

Validation procedures

Various requirements exist for the assessment of the predictive or prognostic value of a model. Predictive value refers to the ability to assess the probability of a target outcome while prognostic value defines the factors that predict prevalence. Among other things, internal and external validation procedures provide evidence of consistency, accuracy and precision of the estimates.
It is also essential to consider specificity and sensitivity of the model in discriminating drug-induced effects from other confounding factors, in particular when drug-drug interactions or drug-disease interactions may occur which are compound-specific and may not have been identified yet, i.e., where uncertainty exists about the actual effects.

The major limitation to our approach at this point of development is the exclusion of random effects. The inclusion of random effects and variabilities would further improve the assessment and predictability of the exposure-effect relationship. Further work will be required to incorporate various sources of variability and uncertainties in the model. Specifically, hierarchical modeling techniques can be applied to the relationship describing age and QTc values in healthy subjects. Alternatively, since age, concomitant medications as well as comorbidity conditions can all be considered systems-related factors affecting QT/QTc-intervals, a combined estimation approach can be taken with uncertainties built in.

In summary, having been able to successfully predict QTc values in real life for two different compounds using an age-dependent baseline QTc relationship, in conjunction with the effects from co-medications and comorbidities, we have gained confidence that Not-In-Trial Simulation will become a framework for signal detection in clinical development. Although our work has been limited to QTc-interval prolongation, we envision the application of the concept for any adverse event. This framework offers advantages compared to meta-analysis where the resulting model can only describe a large, pooled dataset rather than being predictive. Based on Not-In-Trial Simulation scenarios, investigators will have the freedom to explore hypothetical populations and test different doses which are not confined to the observed data.
REFERENCES


