

Thorough QTc studies: patients at heart...

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ABSTRACT

Regulatory authorities increasingly focus their attention on the cardiac effects of non-cardiac drugs, and especially on their potential impact on cardiac repolarization. Delay of cardiac repolarization can lead to cardiac arrhythmias and sudden death by ventricular fibrillation. A generally accepted indicator of the delay of cardiac repolarization is the QT interval prolongation on the surface electrocardiogram (ECG). International Conference on Harmonization guidance E14 defines the 'thorough QT/QTc study', a dedicated study with the primary objective to quantify the effect of a drug on the QT interval, as standard.

Some of the requirements set by the guidance cause serious challenges in clinical trials. In the scope of Parkinson's disease, the supratherapeutic doses requested by the guidance prevent the use of healthy subjects, and affected patients require handling the effect of the disease on the quality of ECG recordings. This paper presents an original study design that offers accurate, thorough QTc (TQT) analysis in patients.

INTRODUCTION

The early detection of potential serious side effects linked to a drug is a key element of patient safety. For example, TQT studies are a requirement to establish the (absence of) potentially lethal effect of non-antiarrhythmic drugs on cardiac rhythm.

When the drug is tested for conditions known to affect the ECG recordings, or when the use of healthy subjects as control is not possible (due to high drug doses or ethical concerns) setting up such a study might become a real challenge.

This paper examines the potential difficulties and proposes a model for TQT studies conducted in clinical populations with diseases that substantially affect the character and quality of the ECG.

WHY DO WE WANT TQT STUDIES?

DRUG-INDUCED CARDIAC ARRHYTHMIA

An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, an effect that can be measured as prolongation of the QT interval on the surface ECG. The QT interval represents the duration of ventricular myocardial depolarization and subsequent repolarization, and is measured from the beginning of the QRS complex to the end of the T wave. As the QT interval is affected by the preceding RR interval (which is equivalent to the heart rate), the rate-corrected QT (QTc) interval has been used as a substitute index.

A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly torsade de pointes (TdP), but possibly other ventricular tachyarrhythmias as well. TdP is a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline. A feature of TdP is pronounced prolongation of the QT interval in the supraventricular beat preceding the arrhythmia. TdP can degenerate into ventricular fibrillation, leading to sudden death.

Investigating the potential risks early in the drug development process is critical in ensuring patient's safety. In the past, cardiac repolarization liability of some drugs was too often only discovered after regulatory approval when they had already caused fatal complications in the patient population.

In response to that issue, the International Conference on Harmonization (ICH) developed E14 Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. This document, endorsed by the FDA, defined the concept of "Thorough QT/QTc Study" as a way to identify the proarrhythmic risk of a drug.

THE TQT STUDY

The TQT study as defined in ICH E14 Guidance is intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation. The threshold level of regulatory concern is around 5ms as evidenced by an upper bound of the one-sided 95% confidence interval (CI) around the mean effect on baseline and placebo-corrected QTc of 10ms for at least one timepoint of the study. Contrary to a frequent misunderstanding, these studies are not aimed at quantifying the risk of drug-induced torsade de pointes tachycardia. Rather, the purpose of TQT study is to exclude proarrhythmic risk due to the study drug. A negative TQT study (i.e. one that does not show an effect of the drug on cardiac repolarization) is interpreted as proof that extensive ECG safety evaluation during the later stages of drug development for the investigated drug is not necessary, and that the collection of baseline and periodic on-therapy ECGs is sufficient. On the other hand, a positive TQT study will mean further detailed ECG monitoring studies are needed.

The TQT study objective is best achieved by the maximum tolerated dose. In cases where the maximum tolerated dose has not been identified prior to conducting TQT study, the correct dose is the largest dose that can be safely administered and which is expected not to invalidate the ECG readings (e.g. because of tolerability and/or autonomic adverse effects). At a minimum, the investigated dose should cover the expected increase in steady-state drug and metabolite exposures due to intrinsic (e.g. renal, hepatic, age-related) and extrinsic (e.g. metabolic inhibition, food effects) factors in the patient population taking the labeled dose. A number of torsadogenic drugs prolong QTc interval only minimally when administered at standard therapeutic doses, while showing very clear QTc signal when overdosed and/or metabolically multiplied.

Investigations of drug-induced QTc changes should be performed long enough to also capture the potential effects of the main metabolites of the drug. A single dose testing is generally not acceptable, unless the tested drug is not extensively metabolized and has time-independent pharmacokinetic. The TQT study design of choice should allow reaching steady-state concentration of the investigated drug and its metabolites.

The study is typically carried out in healthy volunteers. However, some compounds (e.g. neurological agents) are not tolerated by healthy subjects when administered in high doses. TQT studies of such compounds need to be investigated in target populations, but in that case, susceptible patients with other complicating conditions (e.g. those with prolonged QTc interval at baseline) are usually excluded. Compared with patients, a high level of ECG precision is more easily achievable in healthy subjects, and their autonomic conditions and responses to environment are easier to control.

Following the ICH E14 requirements, every TQT study needs to demonstrate ECG assay sensitivity. That is, it has to show that the study conduct and ECG processing is capable of documenting small drug-induced QTc changes. At present, this is achieved by administering a drug with known QTc effects as a positive control. While other possibilities have been investigated, it has become customary to use a single 400 mg dose of moxifloxacin. Indeed, in carefully conducted studies, the population mean QTc changes after a single 400 mg dose of moxifloxacin not only closely follow the plasma concentration of the drug, but their one-sided lower 95% CI also exceeds a 5ms QTc prolongation in at least one of the study timepoints, which is the presently accepted test of moxifloxacin-based assay sensitivity.

Placebo control is also required as it has been shown that the placebo (so just the conduct of the study on its own) could either shorten or extend the QTc interval. Even if the exact mechanism is not known yet, it is clear that the QTc interval is under the influence of the autonomic nervous system, which is in turn affected by the TQT study procedures. This influence could be mitigated by very careful clinical handling but not totally suppressed. In consequence, placebo adjustment of the results is a mandatory part of the design.

Sensitivity of the ECG readings to experimental conditions also means that these conditions should closely replicate each other between subjects receiving active treatment, placebo and positive control. For example, when studying a drug that requires a prolonged titration period, placebo must be "titrated" over an equally prolonged period. The same is true with the schedule of ECG collection.

The baseline correction in TQT studies is needed because, even with the same environmental conditions, QTc intervals vary substantially from subject to subject. Since the primary objective of a TQT study is to compare the mean difference of the study drug and placebo over the entire time course, adjustment for baselines is necessary. The simplest – albeit costly – solution is to collect at least 1 full day, time-matched baseline on the day preceding the (first) dosing day. Since the circadian rhythm of QTc is not the same in each subject, and since the clinical conduct and environmental conditioning of the study can change the circadian profile even on placebo, both false positive and false negative results might be obtained if time-matched baseline adjustment is not used in parallel studies.

A TQT STUDY EXAMPLE

Real-life studies unfortunately cannot always fit into the tightly defined conditions of a “perfect” TQT study setup. An example of these difficulties is found in the study on dopamine agonist rotigotine in the treatment of Parkinson's disease (PD).

First, the ICH E14 TQT Guideline requires use of supratherapeutic doses of the drug. Given that such high doses of dopamine agonists are not tolerated by healthy volunteers with no dopaminergic deficit, the TQT study had to be conducted in patients affected with advanced stage PD.

PD is also known to affect the ECG quality, due to the electrical effects of muscle tremors, skin conditions, and disease-related autonomic disturbances. The muscle tremors create electrical currents that get recorded by the ECG and could create artifacts that complicate the interpretation of the recordings, sometimes even mimicking cardiac rhythm affections. The QT interval is affected by a complex interplay between sympathetic and parasympathetic nervous systems, which are both altered by the disease. One consequence of that is a prolongation of this interval in parkinsonian subjects, independent of any drug treatment.

To overcome these difficulties, extra attention should be given to collection and processing of ECG data, as explained later in this paper.

STUDY DESIGN

The eligible subjects are affected by advanced-stage PD on stable levodopa medication for over 7 days prior to baseline. To avoid interference on study results, the patients should not have received any other dopamine agonists for at least 7 days (or five or more elimination half-lives if longer) before baseline measurements. For the same reason they could not have received any drug known to prolong the QTc interval for 5 elimination half-lives and have no pre-existing serious cardiac rhythm alteration (no more than 20 ectopic beats per hour during a 24-h holter recording at screening). After a 4-weeks run-in period, the patients were randomized one-to-one to rotigotine or placebo in a parallel group, double-blind study design once they have provided their written informed consent.

The investigational drug was administrated via transdermal patches. Since the patients could not tolerate the target dose of 24mg/24h right from the start of the study, a 6-week drug escalation period was required. Starting with 4mg/24h, the dose was escalated in weekly 4mg/24h increments. This treatment phase was followed by a 10-days de-escalation period, where the dose is reduced by 4mg/24h every 2 days, and by a 2-weeks safety follow-up. The patches were applied every day at 20:00 on a site which was rotated between different body locations (to avoid local skin reactions): shoulder, upper arm, flank, abdomen (twice weekly), hip, and thigh.

It is necessary in TQT study to show assay sensitivity of ECG measurements. Therefore, each patient in the parallel study group receiving placebo patches was randomized to receive an infusion of 400 mg of moxifloxacin (a known QT prolonging drug) on either day 32 or day 39 and a placebo infusion on the other of those two days. The patients who received rotigotine patches were given infusions of placebo on both day 32 and day 39. Previous studies have shown that the difference in levels between days 32 or 39 and the respective subsequent placebo monitoring days (days 35 or 42) exceeded seven terminal half-lives of moxifloxacin, thereby providing a sufficient washout period. The 1-h moxifloxacin/placebo infusions were initiated at 10:00, that is, 14 h after the previous patch application. Non-translucent infusion sets were used to maintain double-blindness.

ECG RECORDING AND PROCESSING

ECGs are obtained using continuous 12-leads monitors that created recordings made of 10-s ECG samples. The 24-h ECG recordings were started immediately after the patch application on days 14, 21, 28, 35 and 42 of the study. Similar 24-h tests were performed on 2 baseline days, preceding the first drug application by 24 and 48h, respectively. Also, ECGs were recorded during positive control days 32 and 39.

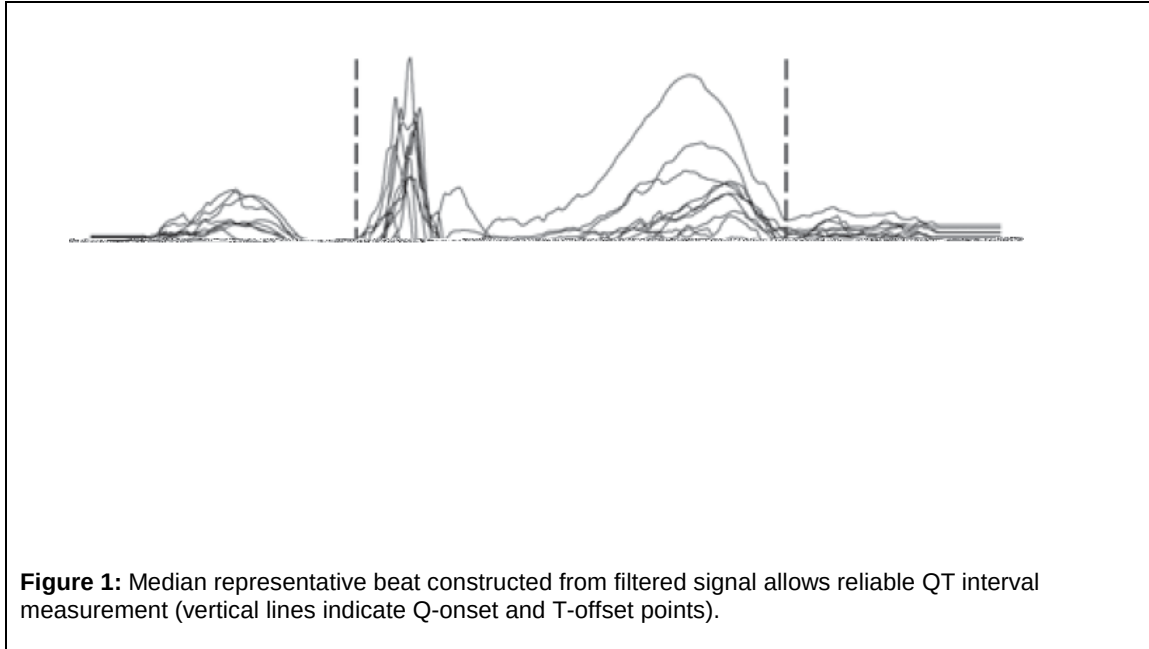
During daytime, the patients have to sit in a semi-reclined position for 5 min at intervals of 20 min (during investigational drug peak concentration, between 13 and 19 h after patch application) or 30 min (at any other time). The semi-reclined position allows the patient to achieve a stable heart rate during measurements.

To mask the sequence of the recordings (and so drug exposure info), the ECG records were recorded to a random date, assigned according to a table provided by the sponsor. The only information transmitted to the ECG lab is whether the record was obtained at baseline or not, since the baseline recordings were used for the determination of individual heart rate correction for the QT interval.

The 24-h records are separated into their 10-s components, for which underlying heart rate and noise content were measured. Subsequently five non-adjacent 10-s samples were selected from within each of the 5 min semi-reclined sitting periods, preceded by at least 90s of stable heart rate with fluctuation below 2 bpm. Within records matching the aforementioned requirements, the five with the lowest noise content were selected.

The same procedure was applied to 20-min records repeated during nighttime every 30 min. As there were no periods of prescribed stable position at night, ECGs preceded by stable heart rate were selected for measurement at regular intervals: straight after patch application and thereafter every 30 min up to 11.5 h later.

Recordings with the lowest noise content are then selected along the entire baseline long-term records for accurate measurement. That allows the construction of a median representative beat, which in turn is used to determine QT interval with an advanced version of a pattern-matching algorithm. The combination of the study specific filtering process with the median-beat construction allowed for QT interval measurement even in ECGs with substantial noise pollution.



The measurements were verified and if needed corrected by two independent cardiologists doing manual measurements. The results obtained by the two cardiologists were compared and the ECGs in which they differed, either in their decisions on measurability or by $>6\text{ms}$ in the QT interval measurement, were identified. These ECGs were returned to the same pair of cardiologists for repeated verification. After the second measurement, the results provided by the two cardiologists were again compared, and the instances where they still disagreed were reconciled by a senior cardiologist.

After obtaining these manually verified and reconciled measurements, all the measured ECGs of each of the patients were pattern-classified with an adjustment algorithm to ensure that similar ECG morphological patterns of QRS onset and T-wave offset were measured systematically. Thereafter, the measurement was again visually checked and, where necessary, manually corrected either by one of the initial observers or by the senior cardiologist, depending on whether the pattern adjustment suggested a change in the QT interval by $\leq$ or $>10\text{ms}$. Finally, as an ultimate quality control, all the measured ECGs were reviewed by a senior cardiologist for making final corrections where required. All the ECGs relating to any given patient were processed by the same pair of cardiologists and by the same senior cardiologist.

For the heart-rate correction required to compute QT_c , drug-free QT/RR patterns were obtained for each patient from all baseline ECG recordings. The measured QT intervals were related to the RR intervals representative of the stable heart rate preceding the measured ECGs. In each subject, the daytime and nighttime QT/RR patterns were considered separately, and each was converted into an individualized heart-rate correction formula including QT/RR curvature optimization. These individualized formulae were subsequently applied to the daytime and nighttime data for each subject to obtain the principal QT_c values.

To ensure accuracy, QT/RR pattern characterization must include a sufficient heart rate range with comprehensive sampling between the slowest and fastest rates. This is not achievable while using only recordings obtained in standardized stable positions because the range of heart rates would not be wide enough. Therefore, all 10-s ECGs were selected in baseline recordings preceded by $\geq 120\text{ s}$ of stable heart rate (variability $< 2\text{bpm}$).

ASSAY SENSITIVITY EVALUATION

Assay sensitivity was evaluated by a within-subject crossover comparison of the time-matched changes from baseline (average of days -2 and -1) in QTc at each separate daytime data point on day 32 or 39 between moxifloxacin and placebo. Changes from baseline were also analyzed after moxifloxacin and placebo infusion at each daytime data point.

STATISTICAL ANALYSIS

The primary outcome variables of the study were based on normalized areas under the QTc curve. This was used to avoid biased results due to the autonomic variability in patients with advanced stage Parkinson's disease. Time – matched QTc changes from baseline at separate data points of the study (Δ QTc values) are also presented. These are more detailed than the normalized areas under the QTc curve.

Parallel-group comparison of rotigotine vs. placebo was based on time-matched changes from baseline (average of days -2 and -1) at each daytime and nighttime data point ($\Delta\Delta$ QTc values) for the following dose levels: 8, 12, 16, 20, and 24mg/24 h.

The parallel-group analysis was based on non-inferiority comparisons of rotigotine vs. placebo using one-sided 95% CI (upper limits of two-sided 90% CI) for the time-matched changes from baseline at each data point. Point estimates and CI were calculated using analysis of covariance, with effects for site, treatment, gender, age, and time-matched baseline QTc as covariates. Analysis of covariance was performed for each data point separately. If the upper CI limit for the comparison of rotigotine vs. placebo was below 10ms at each data point, it is concluded that rotigotine has no effect on QTc.

Analysis of variance - with the factors being treatment, period, sequence, and subject (sequence) - was used to compare the positive control vs. placebo at each data point and calculate point estimates of the respective two-sided 95% CI for the difference in effects between use of placebo and moxifloxacin.

The sensitivity of the assay was considered established if the one-sided 95% CI (lower limit of two-sided 90% CI) at the maximum effect excluded the possibility of only 5ms QTc increase and if the profile of QTc changes corresponded to the expected drop in moxifloxacin plasma levels after the infusion.

RESULTS

Figure 2 shows the QTc differences (rotigotine minus placebo) in the time-matched changes from baseline at individual data points (intersection union test). All differences were close to zero. In particular, all upper limits of the 90% CIs were below +5ms, and all lower limits of the 90% CI were above -5ms.

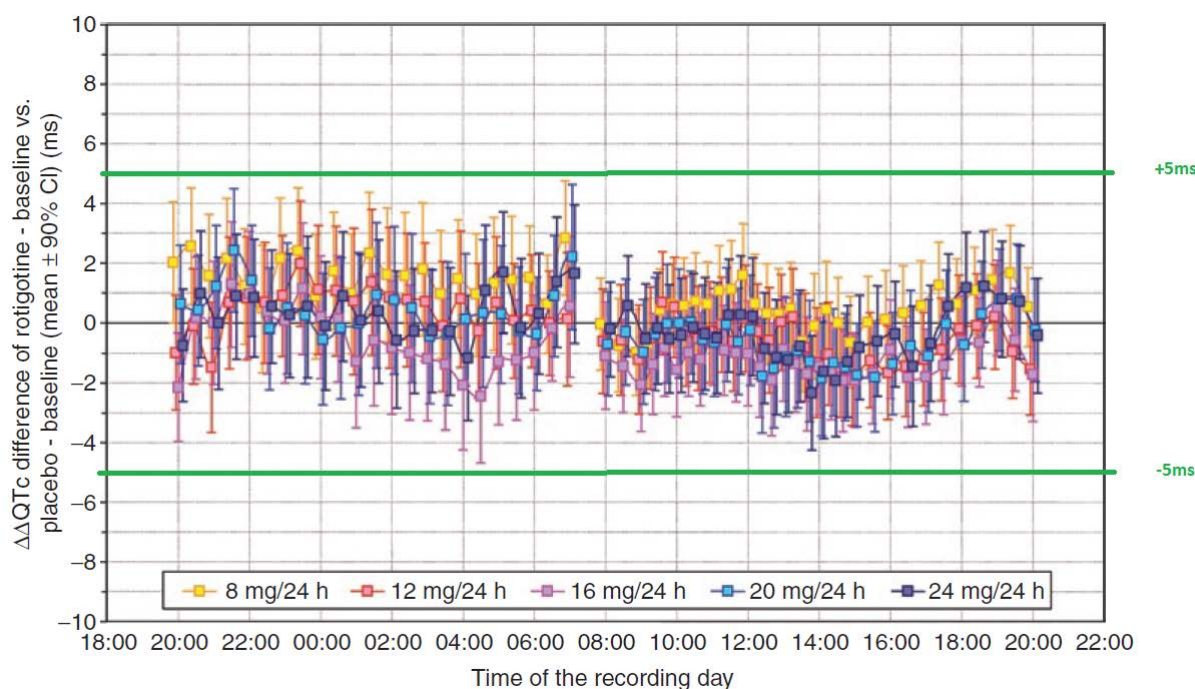


Figure 2: Mean time-matched differences of rotigotine minus placebo in QTc differences from baseline (shown with two-sided 90% confidence intervals (CIs)). The gap between 7.30 and 8:00 is due to the change of the electrodes.

All the analyses resulted in point estimates close to zero for the mean difference for the parallel-group comparison of the time-matched change from baseline between rotigotine and placebo at all investigated doses. As there were no Δ QTc differences observed between the rotigotine and placebo arms, it was not surprising that no relationship was found between rotigotine plasma values and the corresponding QTc changes.

The variability of the QTc data was very small in both placebo and rotigotine arms despite the long study duration, confirming the very tight ECG measurements.

Figure 3 shows the differences between values relating to moxifloxacin and placebo in the rotigotine-matched placebo arm of the study. After the infusion, the mean QTc differences between moxifloxacin and placebo in the changes from baseline ranged from 6.19 to 13.50ms. The largest difference of 13.50ms (95% CI 11.78–15.22ms) was observed directly at the end of the infusion, gradually dropping to 6.19ms (95% CI 4.94–7.45ms) at the end of the monitoring, 10 h after the start of the infusion.

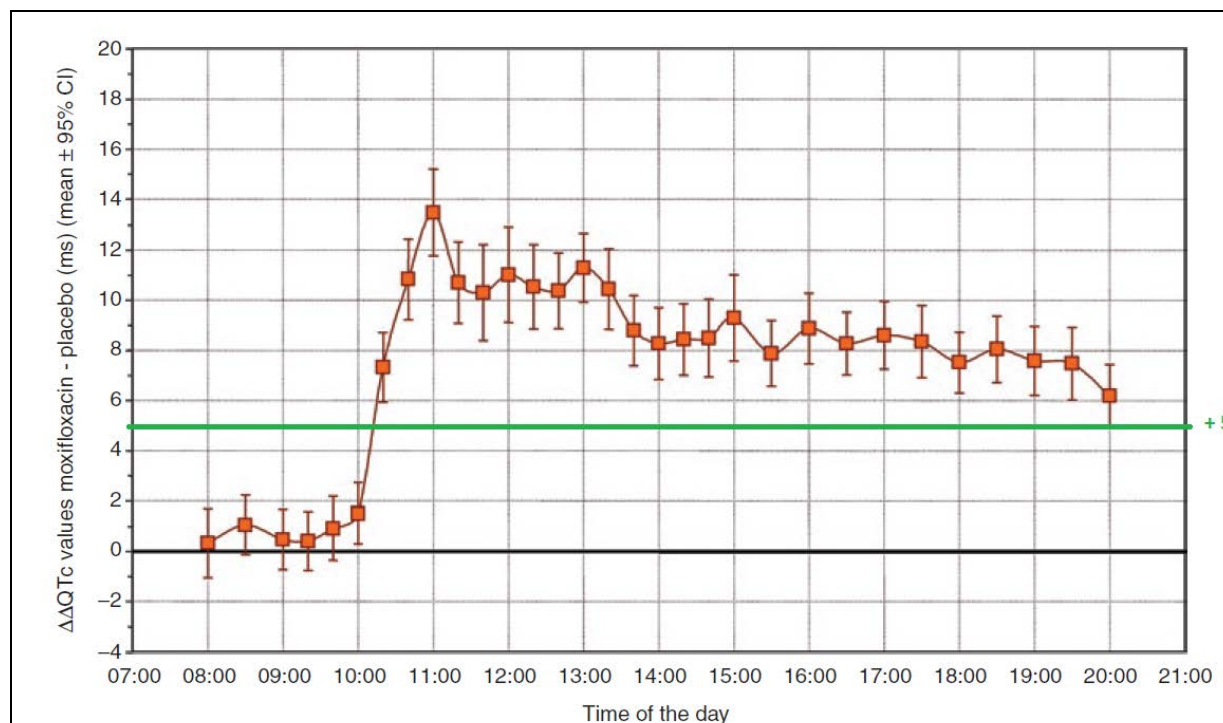


Figure3: Results of the assay sensitivity test. The time-matched QTc differences between moxifloxacin and placebo infusions. Graph show mean values with two-sided 95% confidence intervals (CIs).

The placebo infusion also appeared to have a small QTc effect. During the placebo infusion, QTc increased against baseline, reaching the maximum at the end of the infusion (average Δ QTc of 3.7ms, 95% CI 2.24–5.16ms).

CONCLUSION

This study showed that thorough ECG studies can be performed in patients with advanced-stage Parkinson's disease and, therefore, probably also in other patient populations with diseases that have profound effects on the quality of ECG recordings. This is very important, especially when considering the very tight results. Similar challenges may be faced when designing TQT studies for other pharmacological compounds that are not tolerable in healthy subjects.

The low Δ QTc variability and the narrow CIs observed both in the parallel comparison of rotigotine vs. placebo and in the assay sensitivity test are comparable to, if not substantially better than, those previously reported in similarly powered thorough ECG studies in healthy volunteers, including contemporary studies that used modern technologies. If the very low Δ QTc variability achieved in this study can be reproduced, much smaller thorough QT studies would still be sufficiently powered.

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The experience obtained during the course of the study suggests that the success of this study setup was attributable to the diligent care exercised during the clinical conduct of the study and the attention given to ECG processing.

The patients were kept in-house in a phase I-type setting for almost the entire duration of the clinical study and constantly received attentive nursing and medical care. The ECG-recording procedures, with the subjects placed in standardized semi-reclined positions without any external disturbance, were strictly observed.

The ECG processing pivoted on three essential aspects of the methodology: selection of the least noise-polluted ECG samples preceded by stable heart rate, repeated quality control and reconciliation of the manual corrections of ECG measurements, and pattern matching of the ECG waveforms for systematic measurement of ECG patterns with similar morphologies.

Also, the study was able to demonstrate that rotigotine application up to the supratherapeutic doses of 24mg/24 h did not induce any QTc interval changes, thereby indicating that the drug is not likely to have any cardiac-repolarization impact. The study demonstrated not only that the upper 95% single-sided CI of the difference in QTc change from baseline between rotigotine and placebo was <10ms at all times in the dosing interval, but also that all the upper and lower CIs were actually between -5 and +5ms.

RECOMMENDED READING

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