Comparison of digital 12-lead ECG and digital 12-lead Holter ECG recordings in healthy male subjects: Results from a randomized, double-blinded, placebo-controlled clinical trial

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Running Head: Comparison of Digital and Holter ECG Recordings

**Background**: Electrocardiogram (ECG) variability is greatly affected by the ECG recording method. This study aims to compare Holter and standard ECG recording methods in terms of central locations and variations of ECG data.

**Methods**: We used the ECG data from a double-blinded, placebo-controlled, randomized clinical trial and employed a mixed model approach to assess the agreement between two methods in central locations and variations of eight ECG parameters (Heart Rate, PR, QRS, QT, RR, QTcB, QTcF and QTcI intervals).

**Results**: A total of 34 heathy male subjects with mean age of 25.7±4.78 years were randomized to receive either active drug or placebo. Digital 12-lead ECG and digital 12-lead Holter ECG recordings were performed to access ECG variability. There are no significant differences in least square mean for all ECG parameters between the Holter and the standard method. The total variance is consistently higher for the Holter method than the standard method for all ECG parameters except for QRS. The intraclass correlation coefficient (ICC) values for the Holter method are consistently lower than those for the standard method for all ECG parameters except for QRS, in particular, the ICC for QTcF is reduced from 0.86 for the standard method to 0.67 for the Holter method.

**Conclusions**: This study suggests that Holter ECGs recorded in a controlled environment are not significantly different but more variable than those from the standard method.

Keywords: standard 12-lead ECG, Holter 12-lead ECG, mixed model, cardiac safety

# INTRODUCTION

Thorough QT/QTc (TQT) studies (TQT) studies are currently the accepted method for investigating QTc interval changes of therapeutic and supratherapeutic doses of new compounds [1]. However, Phase I studies often use doses up to the maximum tolerated dose (MTD) achieving plasma concentrations above those that will be seen during later stages of development, making single ascending dose and multiple ascending dose studies the ideal candidates for incorporation of early QT assessment. Traditionally ECG monitoring in these studies was very limited, primarily addressing subject safety, and looking to exclude only large electrocardiographic abnormalities, mainly because smaller changes may be dwarfed by electrocardiogram (ECG) variability which would be the result of trial design issues such as number and duration of ECGs, lack of ECG replicates and difficulty in control external environmental conditions such as subject stress. In addition, QT-RR hysteresis (the time lag of QT interval adaptation to heart rate changes) following changes in heart rate is an important factor considerably influencing the variability of recorded ECG data and the outcome of QTc analysis [2, 3, 4].

The power of Phase I studies to detect QT interval changes can be improved by reduction of variability in the QT interval measurements. It has been speculated that quality QT data in single ascending dose and multiple ascending dose, first in human studies can be collected without compromising the QT assessment by modifying the trial design features to integrate robust ECG monitoring and analyses [5-7]. ECG recordings should be performed at time points around Cmax and the assessment should be conducted according to a controlled, standardised procedure. Introduction of continuous Holter recordings has also become advantageous despite the issue of common noise associated with the electrocardiographic signal, collected via this route. Furthermore, Holter ECG recordings can be available for retrospective analysis in a more rigourous QT assessment in clinical trials and snapshots can be extracted according to the drug pharmacokinetic profile. Holter ECG recordings have considerable advantages over static 12 lead snapshots giving information on the potential for drugs to cause chronotropic incompetence (ability of subjects to increase heart rate with activity), frequency of ventricular ectopics which could give rise to atrial and ventricular tachyarrhythmias, loss of nighttime bradycardia during sleep or excess bradycardia during sleep and heart rate variability in a crude format. Proving data quality standards are met here would therefore be helpful.

The use of an appropriate method for the measurement of QT and RR interval is therefore critical for the detection of small QTc effects in Phase I studies. The first study to compare the standard 12-lead ECG and digital 12-lead Holter recorders showed that these different methods provide equal value in the assessment of drug-induced changes from baseline in QT/QTc and RR intervals [8]. A meta-analysis study investigating the effects of (a) the baseline correction method (b) the design (c) the ECG recording method demonstrated that only the ECG recording method had a significant impact on data variability and that digitally recorded 12-lead Standard bedside ECG was superior to capturing electrocardiographic changes when compared to digital 12-lead Holter ECG recordings [9].

In this study, the central level and variability of two commonly used digital ECG recording methods: 12-lead bedside ECG and 12-lead Holter ECG that were recorded simultaneously in the same subject, were compared and assessed using a mixed model approach.

# METHODS

This study used data collected from a Phase I, single-center, double-blinded, placebo-controlled, randomized, single-ascending oral dose and food interaction study to investigate the safety, tolerability and pharmacokinetics of ACT-280778 in healthy male subjects [10]. Each subject participated in one treatment period only (fasted), with the exception of subjects in the food effect group who participated in two treatment periods (fed/fasted).

Tolerability and safety was evaluated by adverse events (AEs), serious adverse events (SAEs), physical examination, body weight, vital signs, ECG, and clinical laboratory tests. At various time-points before and after the administration of study drug, venous blood samples were collected for safety and pharmacokinetic analysis.

## ECG assessment

Standard 12-lead paper ECG and Holter ECG were recorded with subjects at rest in the supine position for a 10-minute period (in triplicate) on Day -1, and on Day 1 at pre-dose and at 1, 2, 4, 8 and 24 hours post dose. Bedside and 12-lead Holter recording methods were employed simultaneously. Electrodes were placed for each system as close to each other as possible without interference. Subjects were connected to a 24-hour Getemed Holter ECG device (GE Healthcare) for simultaneous 12-lead ECG recording using a CardioMem® CM 3000 digital recorder. The recorded data was used for retrospective 12-lead ECG snapshot extraction and analysis at the time-points specified in the clinical study protocol. In addition standard 12-lead ECGs were recorded using a MAC1200®/MAC1200ST® ECG recorder (GE Healthcare) and stored electronically on the Medical MUSE® information system (GE Healthcare). Before any ECG recording, the subjects maintained an undisturbed supine resting position for at least 10 minutes and avoided postural changes during the ECG recordings. At each time point, the ECGs were recorded in triplicate, to reduce variance and improve the precision of measurement. Each ECG lasted 10 seconds. The triplicates were performed at 1-minute intervals during 3 minutes and the average of triplicates for each parameter was calculated and used for the statistical analyses. Mason-Likar ECG lead placement was used for both the standard recordings and Holter recordings. Dual ECG electrodes were utilised so that two leads can be attached to the same electrode. The Holter leads were connected to the top stud of the electrode, and the standard ECG leads to the bottom stud. In each case the ECG leads were connected via a ‘crocodile clip’.

Prospective 12-lead ECG snapshot extraction from the 24-hour 12-lead Holter ECGs (GE Getemed) was done from within the 10-minute rest period recording by a qualified cardiologist ensuring that the subject had had a minimum of 2 minutes of stable HR.

Automatic ECG analysis was performed by the Marquette® 12SL™ ECG Analysis Program (MEAP). All ECGs and their associated automated interval measurements were subsequently reviewed by qualified cardiologists. If manual adjustments of the automated measurement became necessary, a second cardiologist confirmed the assessment. Any disagreement between first and second reader was adjudicated by a third and most senior cardiologist. Details of this process have been described in [11]. This provided an opportunity to explore variability in the data which, owing to the simultaneous acquisition, are attributable to experimental noise.

## Statistical analysis

Eight ECG parameters were analyzed: Heart Rate (bpm), PR interval (ms), QRS interval (ms), QT interval (ms), RR interval (ms), QTcB interval (ms), and QTcF interval (ms), and QTcI interval (ms) with particular emphasis on Fridericia and Bazett’s QT correction formulae: QTcI, QTcF and QTcB. The ECG variables QTcB (ms) and QTcF (ms) were calculated based on the QT and RR data retrieved from the standard 12-lead ECG and the 12-lead ECG obtained by snapshot extraction. QTcI was calculated using individual correction methods described in Wang et al 2012 [12]. To select the best correction method among six commonly used QT correction formulae, we used the least least-square regression method to choose the model with the minimum of the root mean squared error.

The main purpose of the statistical analysis was to assess the agreement between Holter and standard ECG recording methods in central locations and variations of these ECG parameters. Arithmetic mean was used to describe the central level of an ECG parameter whereas standard deviation (SD) and range (maximum-minimum) were used to describe its variation. For inferential statistical analysis, a linear mixed effect model was employed. Let yijk be an ECG parameter value of *i*th subject (*i*=1, 2,…,n) on Time *k* on *j*th Day. The mixed model can be expressed as:

yijk = α + Methodi + Dayik + Timeij + Si + εijk,

where

α = the intercept;

Methodi = the fixed effect of method for *i*th subject, taking A and B for Holter and standard ECG recording method, respectively.

Dayik = the fixed effect of the *k*th day, where *j*=1, 2 for Day -1 and 1, respectively;

Timeij = the fixed effect of the *j*th time-point, where *k*=1, 2,.., 6 for pre-dose, 1, 2, 4, 8, and 24 hours post-dose, respectively.

Si = the between-subject effect of *i*th subject.

εijk = the random error in observing yijk.

It is assumed that {Si} are independently and identically distributed with mean 0 and variances σsA2 and σsB2, and {εijk} are independently distributed with mean 0 and variances σeA2 and σeB2. {Si} and {εijk} are assumed mutually independent. The estimate of σsA2 and σsB2 are usually used to explain the inter-subject variability while σeA2 and σeB2 are used to assess the intra-subject variability for Holter and standard ECG recording method, respectively. The above model is sometimes called the heterogeneous variance mixed model.

Based on the above mixed model, the least square (LS) means of an ECG parameter for each ECG recording method, the differences between two methods together with 95% confidence interval was derived. In addition, inter-subject and intra-subject variability was estimated. The inter-subject correlation coefficient (ICC) from the heterogeneous mixed model was also calculated. The ICC is an index of the reliability of the measurement for ECG recording method: it can be reasoned that the larger the ICC value, the more reliable the method. The mixed regression model was estimated using SAS PROC MIXED.

# RESULTS

A total of 34 heathy male subjects were included in the study and were randomized to receive either ACT-280778 or matching placebo in five treatment periods (2 mg, 5 mg, 15 mg, 40 mg and fed/fasted condition with 5 mg or matching placebo). Overall, subjects had a mean age of 25.7±4.78 years and a mean body mass index of 24.6 ±2.28 kg/m2. Of the 34 subjects included, 26 were Caucasian, 3 were Asian and 5 were Black/African American. No serious adverse events were reported throughout the study and the novel non-dihydropyridine dual L/T-type calcium channel blocker ACT-280778 was shown to be well tolerated [10]. Those subjects contributed with 413 ECGs recorded by Holter method and 406 ECGs by standard method.

The descriptive statistics of the 7 ECG parameters by ECG recording method are presented in **Table 1**. These results indicate that no major differences in 7 ECG parameters between Holter and standard ECG recording methods were detected. The mean values for standard ECGs showed slightly higher PR, RR, QT, and QTcF. When the standard deviations (SD) from two methods are compared, some differences were observed **Table 1**. HR and PR showed more variability when recorded using Holter ECG compered to standard ECG. QRS was the only parameter showing greater SD value for the standard ECG. SDs for QT, QTcB, and QTcF Holter recordings showed up to 3 ms greater variability compared to standard ECG.

**Table 2** displays the mixed model analysis results of differences in LS mean ECG parameters between Holter and the standard method. There is no evidence to suggest that two methods produce different ECG readings in terms of LS mean values. For example, the difference in LS mean for QTcF between the Holter and the standard method is -0.69, 95%CI=-6.69, 5.31, p-value = 0.8193 and the difference of -26.51 ms (95%CI: -70.24, 17.22, p-value = 0. 2305) in LS mean RR was due to chance.

From the mixed model analysis results of variations in ECG parameters between Holter and the standard method, four observations of relevance can be pointed out **Table 3**. First, the total variance is consistently higher for Holter method than the standard method for all ECG parameters except for QRS. For example, Holter method results in over 50% increase in total variance for Heart Rate and QTcB. The variance for QTcF derived from the Holter traces is 25% higher in comparison to the standard method. Second, the intraclass correlation coefficient (ICC) values for the Holter method are consistently lower than those for the standard method for all ECG parameters except for QRS. For example, the ICC for QTcF is reduced from 0.86 for the standard method to 0.67 for the Holter method, about 22% reduction. Third, the Holter method has the largest impact on heart rate in terms of total variance and ICC. Finally, ICC values are consistently higher for QTcI than the QT, QTcB, and QTcF for both Holter and the standard method.

# DISCUSSIONS

Integration of intensive cardiac assessments in early-phase trials and collection of quality ECGs is highly desirable to assess QT effects at supratherapeutic doses usually evaluated in Phase I studies.

Constant supervision and quality control is required to produce consistently high quality ECGs over a period of time and unfavorable signal to noise ratio is unwanted as Phase I studies normally include a lower number of subjects when compared with dedicated TQT studies. Such studies are key to allow therapies to move to Phase II studies without which the development of an agent is interrupted, delayed or even abandoned. The highest possible quality of ECG recordings should be ensured to help reduce unnecessary over analysis therefore. This study aimed to compare digital 12-lead ECG and digital 12-lead Holter ECG recordings in a Phase I study environment as ECG variability can affect the conduct and interpretation of Phase I trials. In this study, there were no statistically significant differences in least square mean for all ECG parameters between the Holter and the standard method. Nevertheless, the results from this study indicate that standard deviations for QT, QTcB and QTcF were higher for the data sets derived from Holter ECG traces except for QRS. Heart Rate and QTcB presented a total variance of over 50% using the Holter. This demonstrates that digitally recorded standard (12-lead bedside) ECGs are more accurate than digitally recorded Holter (12-lead) ECGs when using 10 second extraction with manual adjudication and that this is due to a combination of noise introduced during Holter recording as well as at the over-reading stage.

It was noted that the differences in mean values between the two methods (Holter and Standard) observed in this study were smaller than those observed in literature which showed QTcF differences in SD of up to 5-10 ms [9]. This is due to the fact that the recordings were made in the same subjects who were enrolled in the same study at the same time. The same ECG chest leads, same cardiologists and method of over-reading were used. Under these conditions, the Holter ECG data is improved compared to reported data, however, the challenge remains of selecting hysteresis free snapshots from Holter which even an experienced cardiologist may not always be able to do.

It was also observed in this study that the ICC values for the observed QT are higher than those for QTcB for both Holter and standard method although the total variances are still smaller for the QTcB. The Bazett's correction formula was derived based on a very small sample of 12 patients in 1920 [13] and has been shown to over-correct QT intervals at high heart rates and under-correct at low heart rates and therefore is not accurate method [14]. Fridericia’s correction (QTcF) has similar problems [14]. On the other hand, this study shows that among the uncorrected QT and the corrected QTc (QTcB, QTcF and QTcI), QTcI produces the smallest total variance and the largest ICC for both Holter and standard method. This is because QTc intervals are calculated from the individual correction formulae that best fitted the individual non-linear relationships between QT and RR in terms of the root mean squared error, resulting in the lowest total variability and highest intrasubject stability of all corrected QT intervals.

The advantage of using 12-lead Holter devices in clinical studies is that they provide a continuous data acquisition available for retrospective analyses which can be used for example in safety reviews or beat to beat analysis. On the other hand, they make precise ECG acquisition more difficult leading to an increased variability due to QT/RR hysteresis [9, 15] which is unwanted noise. Automated measurement becomes a necessity to provide large enough sample sizes to overcome this experimental noise, although it is acknowledged that it is sometimes difficult in practice to determine the end of the T wave which still limits the acceptability of automated ECG measurements.

The QT-RR relationship is primarily influenced by heart rate (HR) with rapid changes in HR often leading to QT-RR hysteresis resulting in greater variability of QTc measurements [2, 3, 15]. In addition, the autonomic nervous system is also thought to influence QT-RR which changes in response to sympathetic and vagal tone [16].

A limitation of this study was the relatively small set of ECGs analyzed. However, this limitation did not seem to affect the study findings as they are in close agreement with published data.

In this Phase I study, we have used the mixed model to assess the agreement between Holter and standard ECG recording methods in terms of central locations and variations of ECG parameters. Advantages of the mixed model approach over conventional methods [17, 18] are that it assesses the differences in locations and variations of ECG parameters simultaneously and it adjusts for the impact of covariates on the ECG measurements. In a Phase I study environment, we encourage the use of the mixed model for ECG data analysis.

**CONCLUSION**

Holter recording of electrocardiographic signal is usually disturbed by noise added to measured useful signal due to imperfect electrode skin electrode, body movements and uncontrolled external variants. Results from this study suggest that ECGs recorded in a controlled environment are no different but more variable than those from the standard method. Results also indicate that differences in mean ECG parameters between two methods are smaller than those reported in the literature. However more noise seems to be due to an inability to choose optimal ECG portions free of background noise for manual adjudication.

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**Table 1: Descriptive statistics of ECG parameters by Standard and Holter method**

| Parameter | Statistics | Holter | Standard |
| --- | --- | --- | --- |
| PR (ms) | N | 411 | 406 |
|  | Mean (SD) | 152.6(18.5) | 155.1(17.0) |
|  | Minimum-Maximum | 106.0-196.0 | 120.0-194.0 |
| Heart Rate (bpm) | N | 413 | 406 |
|  | Mean (SD) | 60.1(7.9) | 58.2(6.5) |
|  | Minimum-Maximum | 43.0-103.0 | 45.0-81.0 |
| RR (ms) | N | 413 | 406 |
|  | Mean (SD) | 1013.9(123.7) | 1043.2(111.5) |
|  | Minimum-Maximum | 583.0-1395.0 | 740.7-1333.3 |
| QRS (ms) | N | 413 | 406 |
|  | Mean (SD) | 97.3(7.4) | 96.5(8.5) |
|  | Minimum-Maximum | 76.0-118.0 | 72.0-118.0 |
| QT (ms) | N | 413 | 406 |
|  | Mean (SD) | 398.4(23.8) | 403.4(22.8) |
|  | Minimum-Maximum | 333.0-479.0 | 340.0-470.0 |
| QTcB (ms) | N | 413 | 406 |
|  | Mean (SD) | 396.8(15.7) | 395.7(12.8) |
|  | Minimum-Maximum | 349.6-451.4 | 357.8-430.7 |
| QTcF (ms) | N | 413 | 406 |
|  | Mean (SD) | 397.2(14.7) | 398.2(13.3) |
|  | Minimum-Maximum | 356.9-442.0 | 369.5-438.3 |
| QTcI (ms) | N | 413 | 406 |
|  | Mean (SD) | 397.8(14.3) | 397.1(12.1) |
|  | Minimum-Maximum | 360.9-443.4 | 367.2-433.4 |

**Table 2: Comparison of central level of ECG parameters between Standard and Holter method: Mixed model analysis**

|  | LS Means |  | 95%CI |  |
| --- | --- | --- | --- | --- |
| Parameter | Holter | Standard | Difference | Lower Limit | Upper Limit | Probability |
| PR (ms) | 152.11 | 154.00 | -1.89 | -9.99 | 6.22 | 0.6437 |
| Heart Rate (bpm) | 59.43 | 57.70 | 1.73 | -0.87 | 4.32 | 0.1887 |
| RR (ms) | 1025.10 | 1051.61 | -26.51 | -70.24 | 17.22 | 0.2305 |
| QRS (ms) | 97.50 | 96.82 | 0.68 | -2.66 | 4.01 | 0.6869 |
| QT (ms) | 400.80 | 404.95 | -4.15 | -13.85 | 5.55 | 0.3963 |
| QTcB (ms) | 396.81 | 395.66 | 1.15 | -4.41 | 6.71 | 0.6817 |
| QTcF (ms) | 397.98 | 398.67 | -0.69 | -6.69 | 5.31 | 0.8193 |
| QTcI (ms) | 398.95 | 397.70 | 1.24 | -4.40 | 6.88 | 0.6611 |

Mixed model includes day, time and method (Holter and Standard) as fixed effects and subject as random effect

**Table 3: Comparison of variability in ECG parameters between Standard and Holter method: Mixed model analysis1**

|  | Holter | Standard |  |
| --- | --- | --- | --- |
|  | Variance |  | Variance |  | Holter/Standard |
| Parameter | Between-subject | Within-subject | Total | ICC2 | Between-subject | Within-subject | Total | ICC | Total Variance | ICC |
| PR (ms) | 288.74 | 66.82 | 355.56 | 0.81 | 262.70 | 28.86 | 291.55 | 0.90 | 1.22 | 0.90 |
| Heart Rate (bpm) | 24.97 | 36.70 | 61.66 | 0.40 | 28.08 | 12.45 | 40.53 | 0.69 | 1.52 | 0.58 |
| RR (ms) | 6926.54 | 8196.87 | 15123.41 | 0.46 | 8301.69 | 3748.60 | 12050.29 | 0.69 | 1.26 | 0.66 |
| QRS (ms) | 39.95 | 9.15 | 49.10 | 0.81 | 53.48 | 6.49 | 59.97 | 0.89 | 0.82 | 0.91 |
| QT (ms) | 379.31 | 170.71 | 550.02 | 0.69 | 399.74 | 91.48 | 491.21 | 0.81 | 1.12 | 0.85 |
| QTcB (ms) | 115.27 | 142.74 | 258.00 | 0.45 | 132.00 | 39.12 | 171.13 | 0.77 | 1.51 | 0.58 |
| QTcF (ms) | 146.47 | 73.48 | 219.95 | 0.67 | 151.60 | 25.01 | 176.61 | 0.86 | 1.25 | 0.78 |
| QTcI (msec) | 145.66 | 60.77 | 206.43 | 0.71 | 122.01 | 17.65 | 139.66 | 0.87 | 1.48 | 0.81 |

1. Mixed model includes day, time and method (Holter and Standard) as fixed effects and subject as random effect.

2. ICC refers to the intersubject correlation coefficient and calculated by between-subject variation/total variance.