Poster No:
PO3-3-30

COMPARISON OF ECG PARAMETERS USING GE GETEMED CONTINUOUS ECG HOLTER AND MAC-1200 BEDSIDE ECG

Jörg Täubel[1,2], Teresa Del Bianco[1], Sara Fernandes[1], Boaz Mendzelevski[3], Dilshat Djumanov[1], George Ferber[4]

[1]Richmond Pharmacology Ltd, UK; [2]St George's, University of London, UK; [3]Cardiac Safety Consultants, UK; [4]Statistik Georg Ferber, Switzerland

Background

Most published studies reporting ECG findings use standard 10-second 12 lead ECG and the must be regarded as the benchmark in cardiology. This incudes the assessment of physiological responses to new investigational medicinal products [1].

During clinical trials only a limited number of ECG recordings can be performed and as a consequence long intervals may elapse between assessment timepoints, particularly in longer trials. These limitations have led to the frequent use of 12L Holter recorders in clinical trials as these provide continuous data with much less burden to patients and freeing time for staff performing trials. The recordings allow for the capture of all cardiac events and provide data for in depth interval measurements at defined time-points by way of extracting a "quasi" 12L standard ECG for in depth evaluation, including interval measurements.

For thorough QT studies, 12L Holter recordings have become an accepted standard and are more frequently used than the conventional 10-second 12L ECG recorded in triplicate. However, there is paucity of data comparing the two approaches comparing ECG recorded from the same source and at the same time. The aim of the current study was to compare bedside with continuous Holter ECG with a focus on the estimate of the QT interval.

Methods

Design

Data from a randomised, double blind 4-period crossover Thorough QT study (TQT) study in 40 healthy subjects was used [2]. The study aimed to assess the effect of an intravenous compound on the QTc interval. The *Getemed* Holter device (GE Healthcare, Boston, USA) and a bedside device were used on Day-1 and Day 1 of each period. 12L Holter was recorded continuously and in parallel to standard 12L 10s bedside ECG using dual leads thereby recording the exact same signal. Timings and methodology were described elsewhere [2].

Data Extraction, Cleaning and Filtering of 12L Holter data

Heart Rate (HR) and QT interval estimates were extracted by averaging 3 consecutive beats. The estimate of QT was adjusted for HR according to the Fridericia Correction formula (QTcF) [3]. Each value was compared to the adjacent 22 data points (1 minute moving average filter). Values exceeding sample average by more than 5% were tagged as outliers and excluded from the analysis. Additionally, we compared the median values at sampling rates of 1 to 10 minutes to explore the effect of different sampling rates on noise and outliers in the Holter signal. The Holter samples were extracted as close to the conventional ECG timepoint as possible manually adjudicated by an experienced cardiologist.

Results

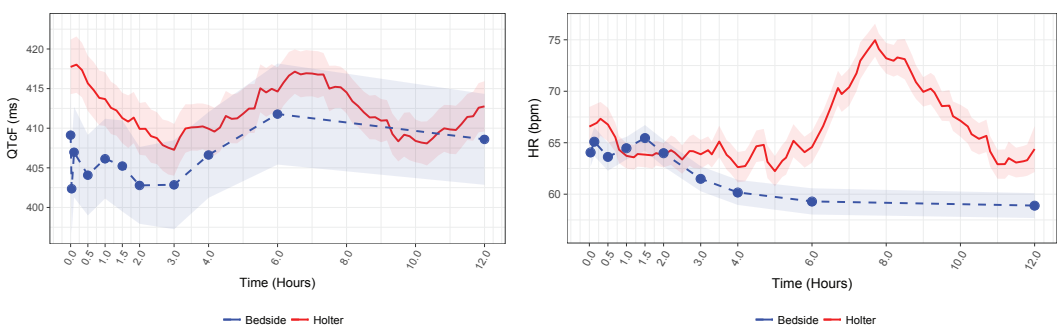

Figure 1: *line plot with 97.5% confidence intervals of average adjudicated bedside and raw Holter QTcF (right) and HR (left) on time (Day -1 of Period 1).*

The visual inspection of Holter signal clearly shows the potential of obtaining a continuous rather than a discrete signal.

It is noticeable that the segment between 6 and 8 hours presents a peak in QT: such a trend is missed by bedside ECG, as it does not provide intermediate estimates between 6 and 12 hours. Furthermore, the minimum HR values correspond to the 3 and 4 hours timepoints – when the bedside ECG was recorded. Hence, unlike the Holter, bedside ECG profile shows a smooth decline missing the effects of a meal on heart rate and QTc interval completely.

Meal-induced effects on QTcF and HR occurring between 2-4 hours from meal intake.

As shown in the plot in Figure 2, the average raw, holter QTcF shows a marked QT shortening 3-4 hours after the start of each meal and a steep increase in mean HR was observed following the meal. This inverse relation between HR and QTcF has been previously reported after food intake [4].
As previously stated, it is unlikely that the bedside ECG would have shown a meal-induced effect in the same period, as it lacks intermediate values at later timepoints (Figure 3).

Adjudication/ Non-adjudication

At the individual level, the estimates of bedside versus Holter QTcF showed a fair correlation by timepoint, but also large differences of ≥ 10ms at some timepoints. Using the same method, manual adjudication, for adjusting the Holter estimates significantly improved the correlation, both at the individual (Figure 3) and at the general level (Figure 4).

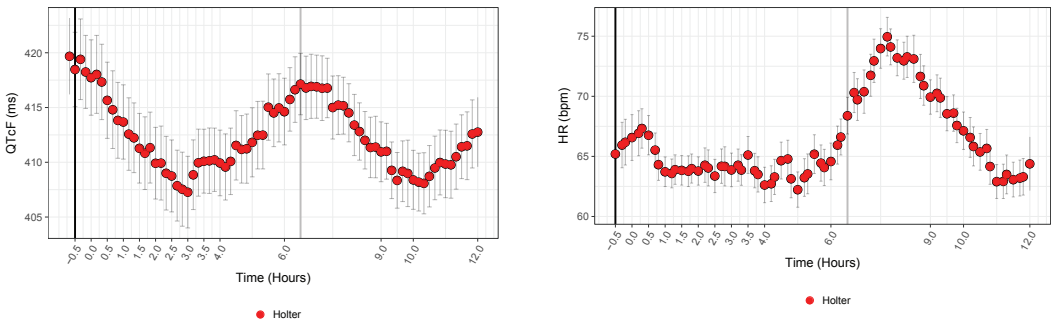

Figure 2*: plot of average,* ***raw Holter*** *QTcF (right) and HR (left) on Day -1 until the 12 h, with 97.5% confidence intervals. The black and the grey lines respectively indicate breakfast and lunch time.*

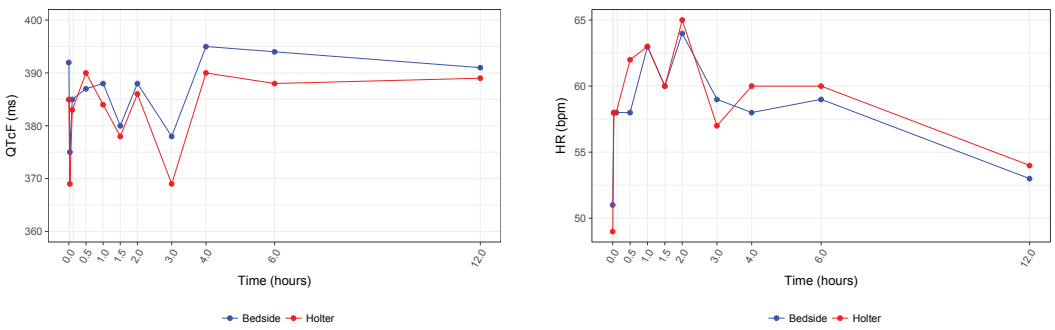

Figure 3: *comparison of a bedside versus Holter QTcF and HR of one subject (Day -1 of Period 1)* ***after adjudication****.*

A reasonable concordance after Holter ECG adjudication is also evident from the boxplot (Figure 4): the medians of QTcF and HR calculated by timepoint are overlapping. Furthermore, the degree of variation, represented by the height and the whiskers of the boxes, is comparable across groups and timepoints.

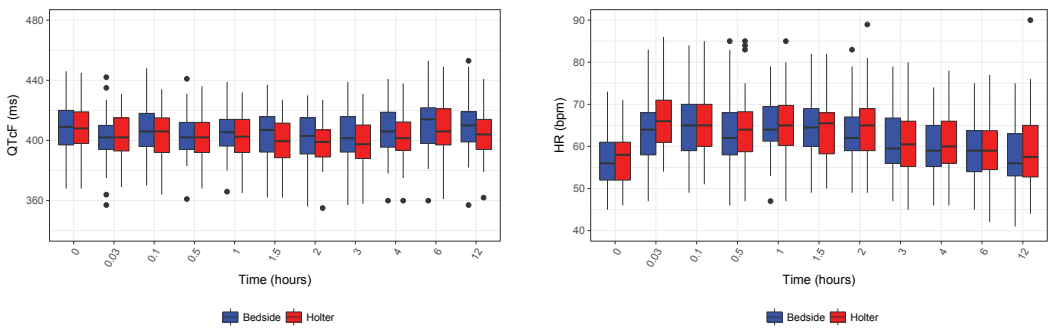

Figure 4: *boxplot of average* ***adjudicated bedside and Holter*** *QTcF (right) and HR (left) on time (Day -1 of Period 1).*

The variance observed before adjudication could be partly attributed to the different algorithms used for QT measurement, as the Holter and the bedside devices are provided with their own internal , specific algorithm. Bedside MAC1200 device uses 12SL algorithm where the QT is measured from a median complex reducing the influence of noise, it is also measured from global fiducial points from all 12 simultaneous leads. Getemed Holter utilises beat-to-beat QT measurement where the Qbegin, Jpoint and Tend are found using a threshold base method in the squared 1st derivative of the ECG. Therefore, an essential measure to avoid discrepancies between the two estimates in the future would be to use the same automated algorithm.

The success of manual adjudication suggests that the outliers in the Holter estimates may be due to either technical issues or movement artefacts. These artefacts can be automatically excluded by developing more robust filtering algorithms. However, a manual adjudication is essential to ensure that only artefacts are removed and no true signal is filtered out.

Conclusions

- The discrepancies between raw 12L Holter and a conventional bedside ECG using automated algorithms might be explained by the use of different algorithms resident in the different devices, even if these are supplied by the same manufacturer (GE Medical).
- Bedside and Holter estimates of QTcF and HR showed a reasonable correlation after extraction and manual adjudication of the 12L Holter. However, some differences in results persist in this study.
- Mixing ECG obtained by the two different systems may not be appropriate.
- Subjects carrying the Holter device are free to move and measurements are not as standardised as when undergoing a conventional bedside ECG recording.
- However a continuous ECG recording provide a more accurate reflection of ECG changes over a time period; usually 24 hours.
- Confirmation of sparsely placed single timepoints as used for concentration effect modelling against a continuous Holter is a useful quality measure.

References

1. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf
2. Täubel J, Ferber G, Fox G, Fernandes S, Lorch U, Camm AJ. *Br J Clin Pharmacol.* 2017;83(2):339-348.
3. Fridericia LS (1920). *Acta Medica Scandinavica* (53): 469–486.
4. Täubel J, Wong AH, Naseem A, Ferber G, Camm AJ. J *Clin Pharmacol*. 2012;52(10):1558-1565

Conflicts of Interests

Jörg Täubel, Sara Fernandes, Teresa del Bianco and Dilshat Djumanov are employees of Richmond Pharmacology Ltd. Georg Ferber is an employee of Statistik Georg Ferber GmbH and Boaz Mendzelevski is an employee of Cardiac Safety Consultants. Both have received honoraria for consulting from Richmond Pharmacology.

This study was funded by Richmond Pharmacology.

RICHMOND Pharmacology
www.richmondpharmacology.com

St George's University of London