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Research article

Detecting drug-induced changes in ECG parameters using jacketed telemetry: Effect of different data reduction techniques

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ABSTRACT

Introduction: Continuous cardiovascular data is routinely collected during preclinical safety assessment of new medicines. This generates large datasets, which must be summarised to analyse and interpret drug effects. We assessed four methods of data reduction of continuous electrocardiogram (ECG) data and examined the impact on the statistical power of the assay.

Methods: Continuous ECG data were collected from a validation study in 6 cynomolgus monkeys using jacketed telemetry. Animals received either vehicle or vehicle followed by ascending doses of moxifloxacin each on a different dosing day. Recordings made for 25 h on each dosing day were reduced to discrete time-points using: 1-min average snapshots, 15-min average snapshots, large duration averages (0.5–4 h) or super-intervals (3.5–9 h averages).

Results: There was no difference in the ability to detect moxifloxacin-induced QTc prolongation between the 1- and 15-min snapshots and the large duration averages data reduction methods (minimum detectable change in QTca of 20, 17 and 18 ms, respectively at 80% power). The super-intervals method detected slightly smaller changes in QTc (15 ms), but did not detect a statistically significant increase in QTc after the lowest dose of moxifloxacin, in contrast to the other methods. There were fewer statistically significant differences between dosing days in animals given vehicle when the large duration averages and super-interval reduction techniques were used.

Discussion: There is no marked difference in the power of detection of drug-induced ECG changes in cynomolgus monkeys when using either small duration average or large duration average data reduction techniques. Use of larger duration averages or super-intervals may facilitate data interpretation by reducing the incidence of spurious significant differences that occur by chance between dosing days.

1. Introduction

Telemetry systems, either invasive or non-invasive, are used in preclinical studies to record cardiovascular data during the safety assessment of new medicines. Continuous recordings are made, usually for at least 24 h, to capture the onset and offset of any test compound-induced effects resulting in the generation of large amounts of data, e.g. >100,000 cardiac cycles for a dog or monkey. Such large datasets are unwieldy and it is desirable to summarise the data to allow clear visualisation, to enable statistical analysis to be performed and, ultimately, to enable a clear interpretation of the cardiovascular effects of the test compound to be made.

There is, however, no standard best practise recommended for reducing and summarising continuous preclinical cardiovascular data sets. In some studies, 24 h of data have been summarised by taking snapshots at predefined regular time-points, each snapshot being a short duration average of the raw data (e.g. 30–60 s for haemodynamic variables or 10–15 cycles for electrocardiogram [ECG] parameters) (Hanson et al., 2006; Toyoshima et al., 2005). The advantage of this approach is that the quality of raw data in each snapshot can be readily checked to ensure it is free from noise or artefact and placement of individual ECG interval markers can be verified. However, this method uses only a very small fraction of the continuous raw data captured, which may adversely affect sensitivity (Sivarajah et al., 2010). Alternative

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CDSER, Center for Drug Safety Evaluation and Research; CI, confidence interval; DSI, Data Sciences International; ECG, electrocardiogram; HR, heart rate; ICH, International Conference on Harmonisation; JET, jacketed external telemetry; NHP, non-human primates; SIMM, Shanghai Institute of Materia Medica.

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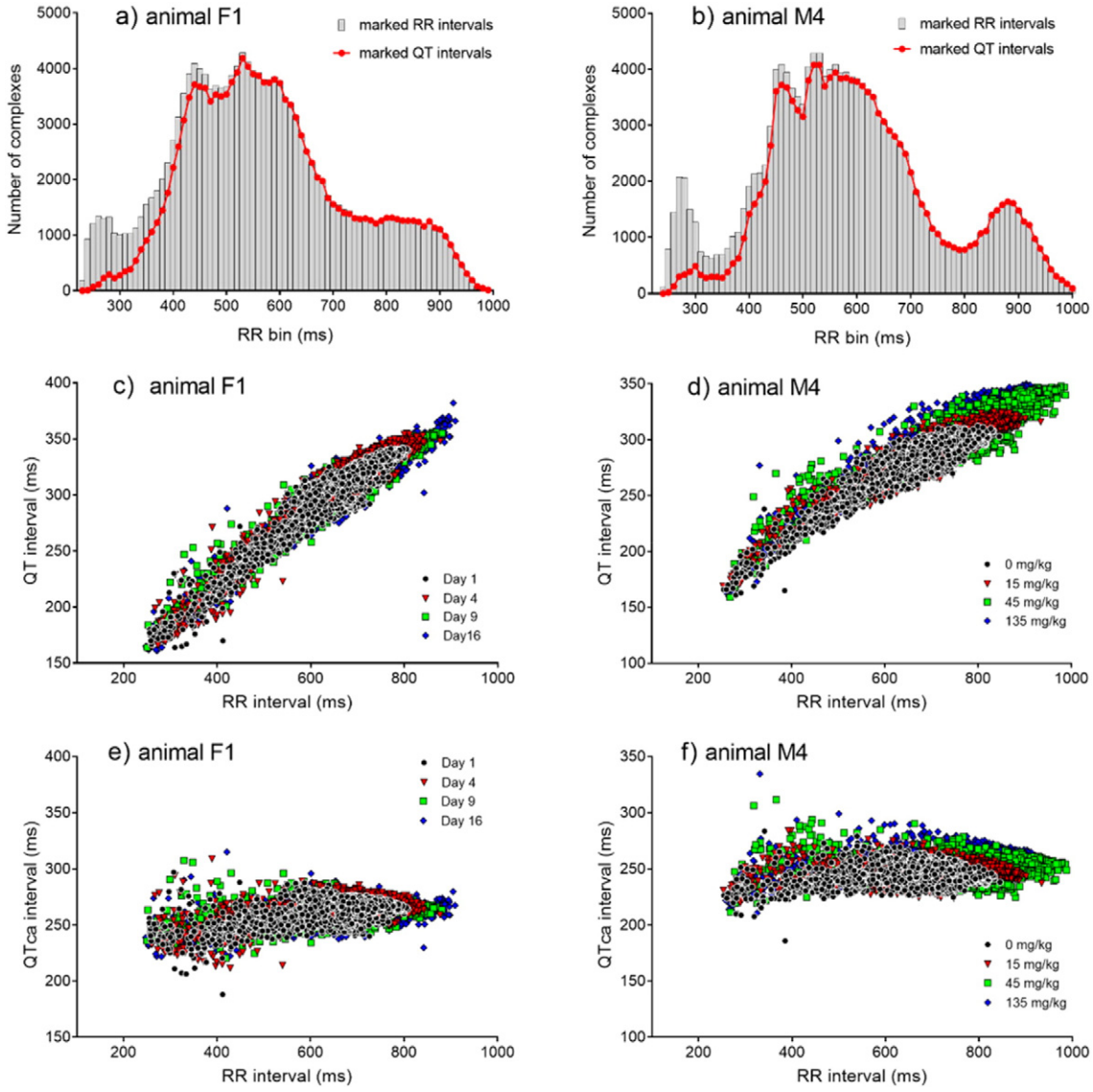

Fig. 1. Data from a) one female and b) one male monkey showing, as columns, the number of ECG complexes identified at different RR intervals (bin width 10 ms). The number of ECGs matched to templates to assign a QT interval is overlaid as a line. QT-RR and QTca-RR relationships are shown in c) and e) for one female after administration of four doses of vehicle and in d) and f) for one male after administration of vehicle and moxifloxacin. Data points plotted are from 1 min averages.

reduction methods have been employed that aim to maximise the amount of raw data used when preparing the summarised data set. In one study in telemeterised dogs, 24 h continuous recordings were divided into 21 time intervals (15 min duration for the first 3 h; 1 h duration for 3–6 h; 2 h duration for 6–12 h; and 4 h duration for 12–24 h) and median values for each interval were used to summarise the response (Chaves et al., 2007). Small drug-induced increases in QTc interval were detectable in this study. Averages of even larger time intervals of 5–8 h in duration, termed super-intervals, have been used to summarise continuous cardiovascular data and have detected small drug-induced changes in ECG and haemodynamic parameters in dogs (Guth et al., 2015; Sivarajah et al., 2010).

The statistical power of preclinical cardiovascular safety assessments has been reported in only a few studies in dogs (Chiang et al., 2007; Guth et al., 2009; Sivarajah et al., 2010) and recently in primates (Kaiser, Tichenor, Regalia, York, & Holzgrefe, 2015; Xing et al., 2015), but it is not clear how the different procedures used to reduce and summarise large datasets affect the assay sensitivity. Indeed, best practice articles by Cavero (2010) and Leishman et al. (2012) comment on the lack of published data relating to the optimum or minimum amount of cardiovascular data collection and suggest that the safety pharmacology community would benefit from more multi-laboratory validation of ECG data reduction methods. We therefore performed the current analysis to assess the effects of different data reduction techniques and examine the impact on the statistical power of detection using a previously validated dataset generated in conscious primates.

2. Methods

Data were collected from a previous validation study; methods used to generate the data have been described fully (Xing et al., 2015). Briefly, six cynomolgus monkeys (3 males and 3 females) (*Macaca fascicularis*) (Guangxi Weimei Bio-tech Co. Ltd., Guangxi, China and Guangdong Landau Biotechnology Co. Ltd., Guangzhou, China) aged 3–5 years, weight 3.70–6.39 kg were used. Animals were housed in single sex groups in pens that measured approximately 2 m × 1.5 m × 2 m. Data from group-housed animals were used in the main analysis, with data from single-housed animals also included in the power analysis.