**INTRODUCTION**

It is well known that accurate assessment of effect on repolarisation requires QT interval correction for changes in heart rate using a dedicated formula such as the Van de Water formula in dogs (QTcV). In addition, changes in core body temperature (BT) may also influence the duration of the repolarisation period as decreases in BT have been shown to be associated with increases in QT interval duration in dogs and vice versa (1, 2). Consequently, a correction formula to compensate for changes in BT (QTcV=QTcV-Ia(37.5-BT)) was proposed by Van der Linde et al. in 2008 (2). Changes in BT are usually observed during several pathological situations and following treatments with pharmacological agents and most importantly during regulatory toxicology studies. Most of these studies do not involve fully implanted telemetry animals, a situation where QT-interval and BT can be accurately measured. Jacketed external telemetry (JET) animals are used in toxicology studies to evaluate potential effects on QT lengthening. JET does not allow accurate assessment of BT as this technology is based on measurement of skin temperature and not core body temperature. In the present study we measured rectal temperature by a thermometer in restrained animals at relevant time points (in accordance with toxicokinetic data), while QT interval is collected via JET in freely moving animals. An example of a 4-week toxicity study associating significant alterations in QT interval duration with transient changes in body temperature is presented.

**MATERIALS AND METHODS**

Four groups of 5 male and 3 female Beagle dogs (24 animals in total) received one single intravenous infusion (1 minute) of the test item (TI) at dose-levels of 0 (vehicle), 10, 20 or 30 µg/kg, followed by a 4-week observation period. Treatment was performed as a slow IV bolus with a dose volume of 0.5 ml/kg. Arterial blood pressure (systolic, diastolic and mean arterial blood pressure) was measured by High Definition Oscilometry cuff system (HDO). Body temperature (BT) was measured by a conventional thermometer (rectal temperature). Arterial blood pressure and rectal temperature were measured before treatment on a minimum of one occasion, then approximately 15 min and 2, 4, 12 and 24 hours after the beginning of the infusion on day 1 and day 26. ECG parameters (lead II) were continuously recorded on days 1 and 26 by jacketed external telemetry (JET) using Ponemah Physiology Platform (Data Science International). Animals were habituated to wearing the external telemetry jacket for several days 1 and 26 by jacketed external telemetry (JET) using Ponemah Physiology Platform (Data Science International). Animals were habituated to wearing the external telemetry jacket for at least two occasions during the pre-treatment period. During the habituation period, a quick check for the quality of ECG and arrhythmias was performed for each animal over a 1-hour ECG recording. A time-point analysis was performed to check that ECG parameters were within the normal range prior to the beginning of the study. ECG recordings began no less than 2 hours before dose administration and ended no sooner than 24 hours afterwards. ECG parameters (PQ, QRS, QT and QTc) were measured from the ECG complexes measured before dose and at 10, 20, 30 and 60 min post-dosing (mean of measurements obtained at -90, -75 and -60 minutes) and approximately 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours after the beginning of the infusion.

**RESULTS**

Week 1 (day 1)

Single intravenous administration of TI at 0, 10, 20 or 30 µg/kg had no noticeable effect on QT interval duration and core body temperature in male or female dogs. Transient increases in heart rate were observed 30 minutes after intravenous infusion in all groups. TI produced dose-dependent decreases in body temperature in all animals when compared to the vehicle group (Figure 1). Two hours after dosing with TI on day 1, collected BT values were: 38.4 ± 0.2 °C, 37.0 ± 1.0 °C (p<0.01), 35.1 ± 0.4 °C (p<0.05) and 34.1 ± 0.6 °C (p<0.01) in vehicle and test item treated groups at 10, 20 and 30 µg/kg, respectively.

TI had no effect on PQ interval or QRS complex duration. However, dose-dependent increases in QTcV (Figure 2) and QTcV intervals were observed (Figures 3 and 5) following intravenous administration of TI. Two hours after dosing, QTcV values were 227±18, 265±28 (p<0.05); 285±22 (p<0.001) and 284±12 ms (p<0.001) in vehicle and test item treated groups at 10, 20 and 30 µg/kg, respectively.

**DISCUSSION AND CONCLUSION**

- These results demonstrated that QT lengthening observed after TI administration was mainly related to the decrease in body temperature.
- This conclusion is in accordance with the absence of HERG inhibition observed with high concentrations of TI.
- The present study demonstrates that rectal temperature (BT) can easily be monitored at relevant time points during external telemetry recording in regulatory toxicology studies in dogs.
- In addition, Van der Linde’s formulae can be used to correct QTcV for treatment-related changes in BT using rectal temperature.
- Ignoring correction for BT may lead to a mis-interpretation of changes in QTcV interval, especially when treatment-related changes in BT are observed.

**REFERENCES**


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