QT interval correction for drug-induced changes in body temperature during integrated cardiovascular safety assessment in regulatory toxicology studies in dogs: A case study

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Abstract

Introduction: Cardiovascular safety assessment requires accurate evaluation of QT interval, which depends on the length of the cardiac cycle and also on core body temperature (BT). Increases in QT interval duration have been shown to be associated with decreases in BT in dogs.

Methods: An example of altered QT interval duration associated with changes in body temperature observed during a 4-week regulatory toxicity study in dogs is presented. Four groups of Beagle dogs received the vehicle or test item once on Day 1, followed by a 4-week observation period. Electrocardiogram (ECG) parameters were continuously recorded on Days 1 and 26 by jacketed external telemetry (JET). Core body temperature (BT) was measured with a conventional rectal thermometer at appropriate time-points during the Day 1 recording period.

Results: Decreased BT was observed approximately 2 h after treatment on Day 1, along with increased QT interval duration corrected according to the Van de Water formula (QTcV), but the effect was no longer observed after correction for changes in BT [QTcVcT = QTcV − 14(37.5 − BT)] according to the Van der Linde formula. No significant changes in QTcV were reported at the end of the observation period, on Day 26.

Discussion: The present study demonstrates that core body (rectal) temperature can easily be monitored at appropriate time-points during JET recording in regulatory toxicology studies in dogs, in order to correct QT interval duration values for treatment-related changes in BT. The successful application of the Van der Linde formula to correct QTc prolongation for changes in BT was demonstrated.

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1. Introduction

Cardio-toxicity is a major cause of drug attrition in pre-clinical and clinical drug development. To detect any potential risk of cardio-toxicity, safety pharmacology studies use QT interval as a surrogate marker of proarrhythmic liability (De Ponti, Poluzzi, Cavalli, Recanatini, & Montanaro, 2002; Couderc & Lopes, 2010), which could lead to the possible development of fatal arrhythmias, including torsade de pointes (TdP). Accurate assessment of an effect on repolarisation requires QT interval correction for changes in heart rate, as QT interval is dependent on the duration of the cardiac cycle. Therefore a dedicated formula, the Van de Water formula (QTcV) (Van de Water, Verheyen, Xhonneux, & Reneman, 1989), is routinely used in dogs.

Abbreviations: BT, Core body temperature; JET, Jacketed external telemetry; ECG, Electrocardiogram; GLP, Good laboratory practices; HR, Heart rate; QTcV, QT interval corrected according to the Van de Water formula; QTcVcT, QTcV corrected for changes in body temperature according to the Van de Linde formula; SEM, Standard error of the mean; TdP, Torsade de pointes; TI, Test item.

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QT interval, which represents ventricular depolarization and repolarization, is not only dependent on cardiac cycle length. Core body temperature (BT) may also influence the duration of the repolarisation period. Decreases in body temperature have been shown to be associated with increases in QT interval duration, and vice versa, in dogs (Alhaddad, Khalil, & Brown, 2000; Van der Linde, Van Deuren, Teisman, Towart, & Gallacher, 2008). Consequently, a correction formula to compensate for changes in BT [QTcVcT = QTcV − 14(37.5 − BT)] was proposed by Van der Linde et al., 2008.

Continuous accurate monitoring of QT interval and core body temperature is usually performed in fully implanted (telemetry) animals in GLP-compliant stand-alone safety pharmacology studies (ICH S7A, ICH S7B). This “gold standard” approach for the assessment of a potential adverse effect on cardiovascular function in non-restrained animals allows simultaneous recording of QT interval and core body temperature.

When cardiovascular assessment is integrated into regulatory toxicology studies involving, for example, candidate drugs, biotechnology-derived pharmaceuticals (ICH S6) or anticancer drugs (ICH S9), jacketed external telemetry (JET) is generally considered to be the most appropriate approach. This non-invasive telemetry approach allows...
continuous measurement of ECG parameters and accurate evaluation of potential effects on QT lengthening in non-restrained animals, but does not allow accurate assessment of core body temperature as this technology is based on measurement of skin temperature.

In the course of our everyday work, we encountered a candidate drug for which the evaluation of QT increases was complicated by effects on core body temperature. The identity and mechanism of action of the drug candidate cannot be disclosed for confidentiality reasons.

In the present study, a 4-week GLP regulatory toxicology study in dogs, the measurement of rectal temperature to assess core body temperature in restrained animals during cardiovascular safety assessment via JET is presented as an alternative approach to ensure the evaluation of key parameters. Electrocardiography recordings and QT interval measurements were performed by JET technology in freely moving animals, and rectal temperature was measured with a conventional thermometer under restrained conditions during the recording period at time-points in accordance with the toxicokinetic profile of the test item. In this case example, the test item, which had no effect on HERG current, produced significantly increased QTcV with significantly decreased core body temperature on the first day of treatment. When QTcV was corrected for changes in rectal temperature, no significant alteration in QTcV was reported, thus demonstrating an application of the QTcV correction method (Van der Linde et al., 2008).

2. Materials and methods

2.1. Animals

Twenty-four healthy Beagle dogs (12 males and 12 females) from Marshall Farms, North Rose, New York, USA were used in the present study. At the beginning of the treatment period, the animals were approximately 7 to 10 months old and had a mean body weight of 9.2 kg (males; range: 8.3 kg to 10.1 kg) or 6.8 kg (females; range: 5.5 kg to 7.5 kg). During the acclimation period (~3 weeks), the animals were submitted to hematological, blood biochemistry and veterinary examinations, and were allocated to groups (by sex) using a stratified randomization procedure.

The animals were housed in pens containing wood shavings (SICSA, Alfortville, France) for bedding material in a dedicated dog unit (room temperature: 20 ± 5 °C, relative humidity: 50 ± 30%, light/dark cycle: 12 h/12 h and ventilation ≈ 12 cycles/h of filtered, non-recycled air). The dogs were group-housed in threes (same sex and group) except during the telemetry recordings, when they were individually housed in pens located in sound-insulated telemetry rooms containing less than 4 animals (so that entry into one telemetry room did not cause disturbances in the other telemetry rooms). The time spent by technicians in each telemetry room was kept to a minimum to reduce recording disturbances. To avoid contamination, one cage was left empty between two monitored animals during evaluation.

Animals had free access to tap water, and food was distributed no sooner than 4 h after treatment.

2.2. Jacketed external telemetry (JET)

The dogs were equipped with a JET system (Data Science International (DSI)) and were monitored using the Ponemah Physiology Platform (DSI) in individual pens situated in small telemetry rooms, with a limited number of animals (3 to 4) per room.

The animals were habituated to wearing an external telemetry jacket on at least two occasions during the pre-treatment period. During the habituation period, a check for the ECG quality and the presence of arrhythmias was performed for each animal, and the animals were also habituated to the rectal temperature measurement procedure with a conventional thermometer under restrained conditions.

The animals were prepared for telemetry recording as follows: The sites of electrode placement were shaved, cleaned and dried with alcohol. Then ECG electrodes were placed on the thorax of the animal (lead II configuration) using adhesive patches and protected by an under-jacket. The ECG electrodes were connected to the telemetry transmitter, which was placed inside the pocket of the jacket. The jacket was placed over the under-jacket. Jackets were fitted onto the animals on the day before recording or at least 2 h before administration of the test item.

ECG signals were digitized and recorded continuously at a sampling rate of 500 Hz. Data were analyzed using dedicated software (Ponemah v. 5.0, DSI). All ECG parameters were extracted from the lead II configuration.

ECG parameters were continuously recorded on Days 1 and 26 by JET. On Day 1, ECG recordings began no less than 2 h before dose administration and ended no sooner than 24 h afterwards. On Day 26, the Day 1 ECG and BT recording times were used as time-points, based on the theoretical treatment time. Heart rate and ECG parameters [PQ, QRS, QT and QTcV (QT corrected for heart rate according to the Van de Water formula)] were quantified in all groups before (mean of the measurements obtained at −90, −75 and −60 min) and after (at 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 h) the beginning of the actual or theoretical infusion time.

At each time-point on Days 1 and 26, ten consecutive beats were visualized and analyzed: heart rate (HR) was measured in beats per minute (bpm), and ECG parameters: PQ interval duration, QRS complex duration and QT interval duration were measured in milliseconds (ms). RR interval was also measured, allowing calculation of the corrected QT interval.

QT interval corrected for changes in HR was calculated according to the formula of Van de Water (Van de Water et al., 1988): QTcV = QT − 0.087 (60/HR − 1), where QT and QTcV are expressed in milliseconds and HR in beats/min. QTcV was corrected for the influence of BT according to the Van der Linde formula (Van der Linde et al., 2008): QTcV = QTcV − 14 × (37.5 − BT), where QTcV is expressed in milliseconds and BT corresponds to the rectal temperature in °C.

2.3. Study design

This study was chosen as it is good example of a regulatory toxicology study demonstrating the method for integration of core body temperature over the same period as JET recordings. The identity and mechanism of action of the drug candidate cannot be disclosed for confidentiality reasons.

Four groups of 3 male and 3 female Beagle dogs received a single intravenous infusion (i.v.) of the test item (TI) at dose-levels of 0 (vehicle), 10, 20 or 30 μg/kg on Day 1, and were then kept for a 4-week observation period. Treatment was performed as a slow (1-minute) intravenous bolus under a dosage volume of 0.5 mL/kg.

Rectal temperature was measured on Day 1 using a conventional thermometer in all groups at 0, 0.5, 2, 4, 12 and 24 h after the actual or theoretical treatment time. The body temperature measurement procedure took approximately 1 min. ECG data were collected 5 to 10 min before body temperature measurement.

Arterial blood pressure was collected immediately after the measurement of rectal temperature, before treatment, then approximately 15 min and 2, 4, 12 and 24 h after treatment, using a high definition oscillometry cuff system (data not shown). Blood pressure was measured over approximately 2–3 min. Dogs had been previously trained to the procedure and were restrained in order to reduce excitement as much as possible. Respiratory parameters were recorded using external telemetry and respiratory inductive plethysmography and a functional observation battery was performed before treatment then approximately 4 and 24 h after treatment (data not shown). On Day 1, blood samples for toxicokinetic were collected from each animal before treatment, at the end of the infusion of the test item, then at 15 min, 30 min, 1, 2, 6 and 24 h after treatment (data not shown). Clinical pathology data were recorded before treatment (for the inclusion of the animals in the study) and 24 h after treatments (Day 2).
2.4. Statistical analysis

Statistical analysis was performed on the ECG parameters using SAS software (SAS Institute Inc.). All parameters were expressed as mean ± SEM. Two-way (time and treatment) analysis of variance (ANOVA) for repeated measurements was performed using SAS PROC MIXED. In the case of statistical significance, additional one-way ANOVA, followed by a Dunnett test, was implemented at each time point. P values less than 5% were considered as significant.

2.5. Regulatory compliance

This investigation was conducted under Good Laboratory Practice conditions and in compliance with Animal Health regulations, in particular: Council Directive No. 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes.

3. Results

The test item had no effect on HERG current as 2% HERG inhibition had been obtained at 100 μM in a GLP manual patch-clamp study using HEK293 transfected cells (data not shown).

ECG parameters collected during the pre-dose period were homogenous in all groups. No statistically significant changes were observed in any of the parameters measured for any of the groups (Table 1), and no arrhythmias were reported in any of the study animals.

No significant changes in arterial blood pressure, respiratory function or functional observation battery parameters were reported after treatment with the test item (data not shown).

### Table 1

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Vehicle</th>
<th>TI (10 μg/kg)</th>
<th>TI (20 μg/kg)</th>
<th>TI (30 μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>76 ± 4</td>
<td>80 ± 4</td>
<td>81 ± 4</td>
<td>87 ± 7</td>
</tr>
<tr>
<td><strong>QRS (ms)</strong></td>
<td>39 ± 1</td>
<td>37 ± 1</td>
<td>40 ± 3</td>
<td>37 ± 1</td>
</tr>
<tr>
<td><strong>PQ (ms)</strong></td>
<td>97 ± 4</td>
<td>88 ± 3</td>
<td>91 ± 2</td>
<td>88 ± 2</td>
</tr>
<tr>
<td><strong>QT (ms)</strong></td>
<td>219 ± 5</td>
<td>215 ± 4</td>
<td>213 ± 4</td>
<td>209 ± 6</td>
</tr>
<tr>
<td><strong>QTcV (ms)</strong></td>
<td>235 ± 3</td>
<td>235 ± 2</td>
<td>233 ± 5</td>
<td>233 ± 4</td>
</tr>
<tr>
<td><strong>QTcVcT (ms)</strong></td>
<td>253 ± 3</td>
<td>255 ± 3</td>
<td>246 ± 7</td>
<td>249 ± 3</td>
</tr>
<tr>
<td><strong>BT (°C)</strong></td>
<td>38.7 ± 0.1</td>
<td>38.9 ± 0.1</td>
<td>38.5 ± 0.1</td>
<td>38.6 ± 0.1</td>
</tr>
</tbody>
</table>

TI: test item, n = 6 animals in each group (3 males and 3 females).

![Fig. 1](image-url)

**Fig. 1.** Heart rate (HR) in vehicle and treated groups on Day 1 and Day 26. Data are expressed as mean ± SEM. The test item produced dose-dependent increases in HR on Day 1 when compared to the vehicle group (n = 6 animals; 3 males and 3 females); *p < 0.05; **p < 0.01; ***p < 0.001.
Clinical pathology data recorded before treatment and 24 h after treatment (Day 2) were within the normal baseline range and no significant changes in these parameters were observed on Day 2 when compared to pre-dose values (data not shown). No clinical pathology data are available for Day 1.

**Day 1:**

Single intravenous administration of the TI at 10, 20 or 30 μg/kg produced transient increases in heart rate around 30 min after administration when compared to the vehicle control group (Fig. 1a and b). No effects on PQ interval or QRS complex duration were reported. Increases in QT (Fig. 2a and b) and QTcV intervals (Fig. 3a and b) were observed following TI administration. At time-point 2 h after administration of the vehicle or TI at 10, 20 and 30 μg/kg, respectively, QTcV values were 227 ± 4, 265 ± 11 (p < 0.05), 285 ± 9 (p < 0.001) and 284 ± 5 ms (p < 0.001).

Statistically significant decreases in BT were observed in all treated animals when compared to the vehicle group (Fig. 4, Table 2). At time-point 2 h after administration of the vehicle or test item at 10, 20 and 30 μg/kg, respectively, BT was: 38.4 ± 0.1 °C, 36.6 ± 0.4 °C (p < 0.01), 35.1 ± 0.2 °C (p < 0.001) and 34.1 ± 0.2 °C (p < 0.001).

No arrhythmias and no major changes in J-wave or T-wave amplitude were reported in any of the TI-treated groups.

No effects on QTcVcT interval were observed when QTcV was corrected for BT according to the Van der Linde formula (Fig. 5). QTcVcT values obtained 2 h after administration of the vehicle or test item at 10, 20 and 30 μg/kg, respectively, were 240 ± 5, 253 ± 9, 252 ± 9 and 236 ± 4 ms.

The relationship between QTcV and BT was linear (y = −12.571x + 718.21) with a negative slope close to 13 ms per degree change in BT (Fig. 6).

The maximum plasma concentration (Cmax) was reached in all animals at the end of the test item infusion; no significant gender difference was observed (data not shown). The time to reach the highest plasma test item concentration (Tmax) did not coincide with the maximum effect (Emax) observed on body temperature or QT interval changes (data not shown).

**Day 26:**

On Day 26, at the end of the observation period, no statistically significant changes were observed in HR (Fig. 1a and b), PQ interval and QRS complex (data not shown), QT interval (Fig. 2a and b) or QTcV (Fig. 3a and b), when compared to the vehicle control group.

4. **Discussion**

Physiological changes in body temperature are routinely observed in human and laboratory animals. Minor changes can be observed in situations such as when the animals are under stress or during physical activities. Greater changes in body temperature may be observed after...
surgery, during illness or fever, or following treatment with a pharmacological agent.

Body temperature is not routinely monitored in GLP toxicology studies, despite the fact that alterations in body temperature have been reported in the literature with administration of several pharmacological agents, such as 5-HT1A receptor agonists (Seletti et al., 1995), dopamine (Clark, 1979), thyroxine derivatives, cannabinoids, opioid receptor activators, neurotensins, transient receptor potential vanilloid, adenine, adenosine, adenosine nucleotides (Zhang et al., 2013), interleukin (Gatti, Beck, Fantuzzi, Bartfai, & Dinarello, 2002), interferon-alpha (Kentner, Miguelez, James, & Bielajew, 2006), peptides, amino-acids (Clark, 1979) and hydrogen sulphide (H2S) (Zhang et al., 2013).

In stand-alone cardiovascular safety pharmacology studies (ICH S7A and ICH S7B) involving animals with fully implanted transmitters, core body temperature and QT interval are measured simultaneously. In contrast, when cardiovascular safety pharmacology assessments are integrated into regulatory toxicology studies, a non-invasive JET approach (Derakhchan, Chui, Stevens, Gu, & Vargas, 2014; El Amrani, El Amrani-Callens, Loriot, Singh, & Forster, 2015) is used for evaluation of the effects of drug candidates, such as biotechnology-derived pharmaceuticals (ICH S6) or anticancer drugs (ICH S9). While QT-interval can be monitored continuously and measured accurately in conscious dogs, the assessment of body temperature using JET technology allows accurate assessment of skin temperature but not core body temperature (Akgun et al., 2004). The use of fully implanted telemetry devices in regulatory toxicology animals might be an alternative, but this option is not yet fully acceptable for at least two reasons: (i) economical: fully implanted animals are costly when the number of animals involved in each study and the cost of the transmitters, surgery and follow-up procedures are taken into consideration; (ii) possible interaction with the surgical procedure: clotting, inflammation or tissue damage may sometimes be confounding factors in the toxicological and histopathological assessment of study data.

Steps should be taken to ensure that the best conditions are maintained while using the JET approach in integrated regulatory toxicology studies. To avoid disturbances during integrated JET monitoring in regulatory toxicology studies, core body temperature is not usually measured, as during the telemetry recordings for cardiovascular monitoring, access into the telemetry rooms is usually limited to feeding and physical checks. In the present study, we demonstrated how multiple interventions in the telemetry room can be conducted when all housing details and practical problems have been addressed.

Under the experimental conditions of our study, the dogs regained their normal heart rate within approximately 15 to 20 min after the technicians left the telemetry rooms (data not shown). When these observations are taken in consideration, several interventions in telemetry

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**Fig. 3.** QTcV in vehicle and treated groups on Day 1 and Day 26. Data are expressed as mean ± SEM. The test item produced dose-dependent increases in QTcV on Day 1 then compared to the vehicle group (n = 6 animals: 3 males and 3 females). *p < 0.05; **p < 0.01; ***p < 0.001.
room for body temperature measurement, blood collection or other clinical examinations could be allowed without prejudice to the telemetry recordings in the dogs.

On the first day of treatment in the 4-week toxicity study presented in this report, the test item produced significant increases in QT-interval duration and QT corrected for heart rate (QTcV) despite the absence of an effect on HERG current (data not shown). Rectal temperature measured within 5 to 10 min after the collection of QT-interval values was considered to be significantly and concomitantly decreased. When QTcV was corrected for changes in rectal temperature using the Van der Linde formula (Van der Linde et al., 2008), no significant alterations in QTcVcT were reported. At the end of the observation period, 26 days after treatment, no significant changes in QT-interval or QTcV were reported.

The range of body temperatures used by Van der Linde et al. (2008) to produce a QT correction formula for changes in body temperature was: 37.7 to 34.2 °C in cooled and 37.3 to 42.1 °C in heated anesthetized dogs. As our investigation was limited to effects of the test item only, the temperatures recorded in the present study ranged from 33.0 °C to 39.2 °C. We found the relationship between QTcV and BT to be linear, with a mean average decrease of approximately 13 ms per degree change in BT. Therefore, even though BT was measured shortly after the collection of QT interval values, the results were close to those reported by Van der Linde et al. (2008), where a mean average decrease of 14 ms was observed over a wide range of BT changes. This demonstrates the robustness of the QTcVcT formula, and shows that it can be applied to non-anesthetized animals.

Our results are in agreement with previous reports demonstrating that alterations in BT may have a direct effect on QT interval. For instance, BT decreases produced lengthening of QT-interval (Van der Linde et al., 2008) independently of any effect on HERG-current. Increases in BT may attenuate and decreases in BT may exacerbate any lengthening of QT interval related to HERG inhibition (Khan, Prasad, & Glancy, 2010).

The time to reach the highest plasma concentration of the test item (Tmax) did not coincide with the maximum effect (Emax) observed on body temperature or QT interval (data not shown). The absence of coincidence is probably related to the mechanism of action and pharmacological properties of the test item, which resulted in significant decreases in body temperature and significant increases in QTcV, with no significant changes in PQ interval, QRS complex, arterial blood pressure, respiratory parameters or functional observation battery parameters (data not shown).

Decreases in BT may not, in themselves, have a deleterious effect in terms of cardiovascular risk despite their effect on QT prolongation. In the present study, no arrhythmias were reported at any dose-level or BT. In dogs, lengthening and shortening of QTcV during cooling and warming, respectively, are not associated with arrhythmias (Van der Linde et al., 2008).

In therapeutic approaches using clinically controlled therapeutic hypothermia (e.g. following cardiac arrest, hemorrhagic or ischemic stroke), hypothermia is considered as beneficial under certain circumstances, according to the extent of the decreases in body temperature

![Fig. 4. Rectal temperature (mean ± SEM). The test item produced dose-dependent decreases in rectal temperature on Day 1 when compared to the vehicle group (n = 6 animals: 3 males and 3 females) *p < 0.01; **p < 0.001.](image-url)

Table 2

<table>
<thead>
<tr>
<th>BT (°C)</th>
<th>QT (ms)</th>
<th>QTcV (ms)</th>
<th>QTcVcT (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>38.4 ± 0.1</td>
<td>219 ± 8</td>
<td>227 ± 4</td>
</tr>
<tr>
<td>TI (10 μg/kg)</td>
<td>36.6 ± 0.4** (-4.7%)</td>
<td>259 ± 14 (18%)</td>
<td>265 ± 11* (16%)</td>
</tr>
<tr>
<td>TI (20 μg/kg)</td>
<td>35.1 ± 0.2** (-8.6%)</td>
<td>265 ± 15 (21%)</td>
<td>285 ± 9*** (25%)</td>
</tr>
<tr>
<td>TI (30 μg/kg)</td>
<td>34.1 ± 0.2** (-11.2%)</td>
<td>265 ± 9 (21%)</td>
<td>284 ± 5*** (25%)</td>
</tr>
</tbody>
</table>

BT: Body temperature; TI: Test item; n = 6 animals in each group (3 males and 3 females).

* p < 0.05.
** p < 0.01.
*** p < 0.001.
and the duration of hypothermia. Therapeutic hypothermia using surface cooling, intravascular cooling or pharmacological cooling, is considered as a promising neuroprotective approach against ischemic brain injury (Zhang et al., 2013), although the mechanism of action underlying this effect is not yet fully understood. The prolongation of QT-interval during hypothermia might appear to be a physiological phenomenon without any pro-arrhythmogenic potential, and this has been clearly shown in anesthetized swine subjected to mild hypothermia, when increases in QT interval had no effect on ventricular arrhythmias and there was no occurrence of TdP (Kudlicka et al., 2015).

Despite the beneficial effect of hypothermia, concerns may arise concerning the pro-arrhythmogenic risk during concomitant effects on QT prolongation related, on the one hand, to hypothermia and, on the other hand, to inhibition of the HERG current in patients with inherited or acquired long QT (Long QT syndrome).

Intravenous infusion of a class III anti-arrhythmic drug, amiodarone, in a patient subjected to therapeutic hypothermia produced additional increases in QTc prolongation, but no life threatening arrhythmia was reported (Khan et al., 2010). In another case report of congenital Long QT syndrome, the induction of mild therapeutic hypothermia had no pro-arrhythmic effect, and no TdP was documented despite greatly increased QTc interval (Nishiyama, Sato, Aizawa, Nakagawa, & Kanki, 2012).

Further research is needed to evaluate the pro-arrhythmogenic risk potential of (i) drugs that may have combined effects on BT and HERG inhibition in healthy animals; (ii) pharmacological agents that might be associated with the therapeutic hypothermia procedure, especially in patients under medication who might be at risk during the procedure.

In pre-clinical drug development, and especially during regulatory toxicology studies, it seems prudent to recommend that the evaluation of any potential effects of drug candidates on BT should be performed on a regular basis, as any such issues should be identified during the non-clinical safety assessment. On the other hand, clinicians should be fully

![Fig. 5. QTcVcT (mean ± SEM) in vehicle and treated groups on Day 1 (QTcV corrected for changes in body temperature). When corrected for changes in body temperature, no effect of the test item on QT prolongation was observed.](image)

![Fig. 6. Rectal temperature versus QTcV on Day 1 in individual dogs (n = 24); regression analysis showed a linear correlation (y = −12.57tx + 718.21).](image)
aware of this issue and ready to take it into account, especially when changes in body temperature have been previously demonstrated. Ignoring correction for BT may lead to a misinterpretation of changes in corrected QT for heart rate in pre-clinical or clinical investigations.

One limitation to BT measurement under restrained conditions may be difficulty when dealing with non-human primates, unless a long-term training period is applied. Chemical restraint should not be used in BT measurement for QT correction, as the chemicals used, e.g. ketamine, may have an effect on BT.

5. Conclusion

We demonstrated (i) that the QT lengthening observed after administration of the test item was mainly related to a decrease in core body temperature, (ii) that core body temperature can easily be monitored during external telemetry recordings in regulatory toxicology studies in dogs, and (iii) that the QTcVcT formula (Van der Linde et al., 2008) can be applied to correct QTcV for changes in body temperature using measurements obtained with a conventional rectal thermometer in non-anesthetized dogs.

Conflict of interest statement

The authors declare no conflicts of interest.

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References


