Evaluation of Minimum Detectable Difference via Moxifloxacin-Induced QTcH Prolongation in the Telemetered Beagle Dog

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Background

Model sensitivity and validity are both of the utmost importance when evaluating the safety and efficacy of novel therapeutics. The ability of a preclinical model to accurately determine a drug candidate's potential is critical with regards to its future success in clinical trials, as well as providing an assurance in the substantial financial investments involved in developing these compounds. Current preclinical guidelines (International Conference on Harmonization, ICH E14/S7B) indicate that, in order to avoid the potential for further clinical safety analysis, the effect of a novel therapeutic compound on the heart rate (HR)-corrected QT interval (QTcH, Holzgrefe et. al, 2007) must be interrogated via high fidelity nonclinical safety pharmacology studies.

Moxifloxacin is a fluoroquinolone antibiotic characterized by a reliable and dose-dependent induction of QT prolongation, a well-known risk factor of both life-threatening arrythmias and sudden cardiac arrest. Thus, the pharmaceutical industry, along with its associated regulatory agencies, have widely recognized moxifloxacin as an important positive control in the evaluation of model sensitivity within both clinical and preclinical cardiovascular drug development studies via QT prolongation assessments (Chen et. al., 2009).

The minimum detectable difference (MDD) is a quantitative measure of the variance that occurs between treatment groups as compared to a control to identify a statistically significant result. Therefore, in this telemetered-dog study, MDD was evaluated via moxifloxacin-induced QTcH interval prolongation, in order to assess this model's sensitivity and reliability.

Objective

To use escalating doses of moxifloxacin to assess the effect on the QTcH interval in male beagle dogs, thus providing a model to examine the reproducibility and validity of our procedures.

Methods

Telemetered Dog Study Design: Non-naïve male beagle dogs (n = 8; range: 8.0−8.7 kg) were single-housed and fed a 25% protein dog diet. Animals were kept in a room maintained at approximately 18–27°C, with humidity set at 30–70% and illuminated to simulate a 12-hour light, 12-hour dark cycle. Body weights were obtained immediately prior to dosing, and each animal was observed regularly for clinical signs.

At least 2 weeks prior to study initiation, dogs were implanted with a Data Sciences International (DSI; St. Paul, MN) telemetry device (model L11) for electrocardiographic (ECG) evaluation. Each animal was orally administered vehicle (0.5% methylcellulose [MC] in deionized water) and escalating doses of moxifloxacin (10 mg/kg, 30 mg/kg and 100 mg/kg) in a Latin square design. ECG (PR interval, QRS duration and QT interval) and heart rate (HR) data were continuously recorded for 24 hours after each dose.

Overall Data Analysis: Individual beta constants for the corrected QTcH calculations were made as 10-second data blocks. Both ECG parameters and HR were analyzed using 15-minute averages; these values were then averaged into 1-hour superintervals from predose to 24-hours post dose. Values from each individual animal were pooled to determine an average for each variable at individual doses. Change from time-matched vehicle comparisons were used as the primary analysis method for test compound data. The median standard error (STDERR) was calculated on the mean QTcH interval values as the difference in least square means between the control group and across all treatment groups.

MDD Calculations: MDD was calculated as: MDD = Min{[t(0.05, ddf) + t(0.80,ddf)] x STDERR}, where "ddf" is equal to the treatment denominator degrees of freedom. MDD was calculated using this formula both for all animals on the study combined as well as for each individual animal throughout each of its 24-hour dosing epochs. Using the individual animal MDD values, dogs were then ranked as the most and least sensitive n = 4 and n = 6 on study, with shorter MDDs receiving a better ranking. Once ranked, these condensed groups were interrogated for their new MDD values. Additionally, individual QTcH:RR plots (a calculation that relates the corrected QT interval to the RR interval, which is the time between heartbeats) for each animal were subsequently created using 10-second data. Alternative rankings (more sensitive/less sensitive n = 4 and n = 6 on study) using the QTcH:RR plots were then assigned to each animal by either the proximity of the data across treatment groups (density), the absolute values of the complete study slope, or the absolute values of the prestudy slope. New MDD values for these condensed groups were once again calculated for comparison.

Results

Escalating Doses of Moxifloxacin Resulted in Dose-Dependent QTcH Prolongation, with No Notable Changes in PR Interval, QRS Duration or HR

- Baseline values were within typical ranges for the male beagle dog. No vehicle-related (0.5% methylcellulose in deionized water) changes were noted in either ECG or HR.
- As expected, orally administered moxifloxacin increased the QTcH interval in a dose-dependent manner, with the maximum effect ranging from +4% to +21% with increasing doses when assessed as percent change from time-matched vehicle values.
- The PR interval, QRS duration and HR remained similar to the vehicle control throughout dosing, when assessed as percent change from time-matched vehicle values.

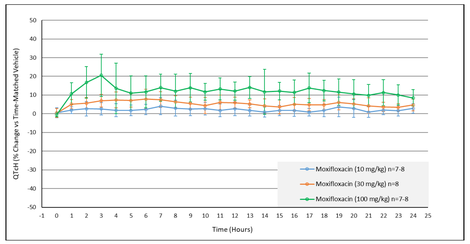
Table 1. Effects of Escalating Doses of Moxifloxacin Administered via Oral Gavage on ECG and HR Parameters in Telemetered Beagle Dogs (Min/Max Mean Range Over 24 Hours)

Parameter	Vehicle (n=8)	10 mg/kg Moxifloxacin (n=8)	30 mg/kg Moxifloxacin (n=8)	100 mg/kg Moxifloxacin (n=8)
QTcH (ms)	214-224	217-229	221-240	219-262
HR (bpm)	74-105	71-103	77-103	79-108
PR Interval (ms)	95-103	92-101	90-104	88-102
QRS Duration (ms)	38-41	39-42	38-43	39-43

Table 2. Effects of Escalating Doses of Moxifloxacin Administered via Oral Gavage on ECG and HR Parameters in Telemetered Beagle Dogs (Percent Change from Time-Matched Vehicle Data)

Parameter	10 mg/kg Moxifloxacin		30 mg/kg Moxifloxacin		100 mg/kg Moxifloxacin	
	Change (%)	Time Point of Maximum Change (hours post dose)	Change (%)	Time Point of Maximum Change (hours post dose)	Change (%)	Time Point of Maximum Change (hours post dose)
QTcH	+0 to +4	7, 19	+0 to +8	6, 7	+0 to +21	3
HR	-11 to +10	17	-12 to +13	10	-7 to +33	14
PR Interval	-5 to +1	5	-8 to +1	7, 10	-11 to +1	4, 5
QRS Duration	-5 to +6	9	-5 to +6	13, 14	-4 to +7	9, 15

Figure 1. Effects of Escalating Doses of Moxifloxacin Administered via Oral Gavage on ECG and HR Parameters in Telemetered Beagle Dogs



Evaluation of MDD via Moxifloxacin-Induced QTcH Prolongation in the Telemetered Beagle Dog Model Yielded Remarkable Sensitivity

The MDD of the overall study for moxifloxacin-induced QTcH interval prolongation in this telemetered beagle dog model was found to be notably sensitive at 3.2 ms.

Ranking the Most Sensitive and Least Sensitive Animals Via Individual MDD Values, QTcH:RR Plot Density or QTcH:RR Plot Slope Yielded Similar Overall MDD Results

When animals were ranked either via their individual MDD values, their QTcH:RR plot density across treatments, the absolute values of the complete study slope, or the absolute values of the pre-study slope, all ranking methods produced similar results in terms of both individual animal order and overall MDD values.

Table 3. Individual Animal MDD Values

Animal No.	MDD (ms)
001	3.2
002	4.1
003	3.6
004	4.3
005	4.0
006	6.0
007	3.9
008	7.9

Figure 2. Individual Animal Pre-Study QTcH:RR Plots Ranked Via Slope

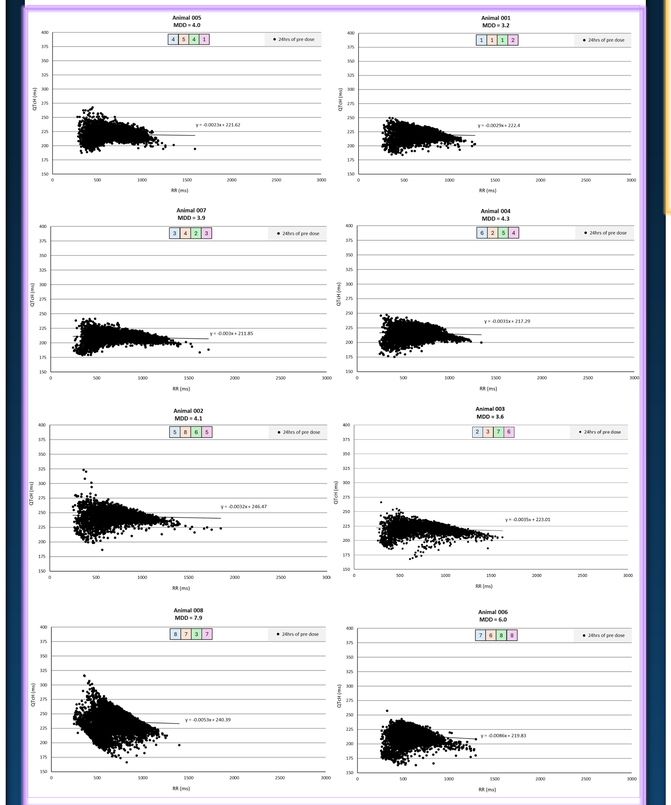


Table 4. Evaluation of MDD in Groups of Telemetered Beagle Dogs via Ranking with Alternative Methods

Animal No.	Ranking Method			
	Individual Animal MDD Values	Complete Study QTcH:RR Plot Density	Complete Study Slope, Absolute Values	Pre-Study Slope, Absolute Values
001	1	1	1	2
002	5	8	6	5
003	2	3	7	6
004	6	2	5	4
005	4	5	4	1
006	7	6	8	8
007	3	4	2	3
008	8	7	3	7

Figure 3. Individual Animal Complete Study QTcH:RR Plots Ranked Via Plot Density

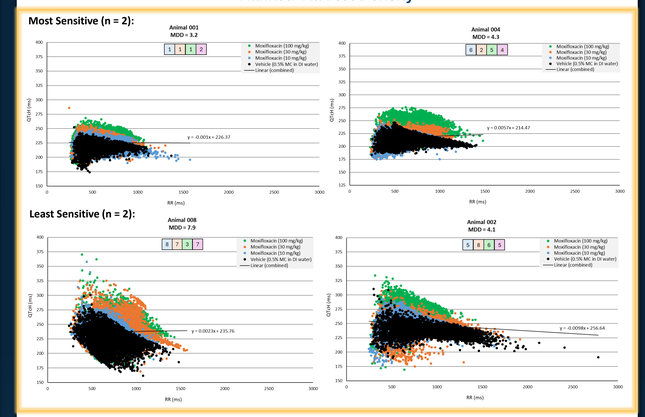


Table 5. Summary of Individual Animal Rankings Via Alternative Methods Overall Study MDD = 3.2 ms

Ranking Method	Most Sensitive Animals		Least Sensitive Animals	
	n = 4	n = 6	n = 6	n = 4
Individual Animal MDD Values	2.4	3.9	4.0	5.3
Complete Study QTcH:RR Plot Density	2.5	2.2	4.0	4.6
Complete Study Slope, Absolute Values	3.8	3.8	4.0	5.7
Pre-Study Slope, Absolute Values	2.7	3.9	4.3	5.0

Conclusion

Following evaluation via MDD, this beagle dog telemetry model was found to be remarkably sensitive to the detection of statistically significant changes in the QTcH interval, a vital component of novel compound development.

When this group of animals was ranked either by their individual MDD values, their QTcH:RR plot density across treatments, the absolute values of the complete study slope, or the absolute values of the pre-study slope, all ranking methods produced similar results in terms of both individual animal order and overall MDD values, adding support to the utilization of any of these methods.

When the animals on study were ranked by the absolute values of their pre-study slopes across treatments, correlations were noted between the pre-study slope rankings and individual animal MDDs following dosing, lending support to the prospect of researchers utilizing this method pre-study for optimal animal selection.

Finally, the more sensitive/less sensitive n = 4 and n = 6 groupings that were found following each ranking method generally followed a predictable pattern of new MDD values that were all within a highly sensitive range.

References

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COI Statement

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