

Safety pharmacology studies for cardiovascular systems in ferrets conform with 'Best Practice Considerations for In Vivo Studies'



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Introduction

In recent years, the spread of coronavirus infection has influence on supplying monkeys and dogs as experimental animals. Therefore, we examined whether ferrets could be used to assess the circulatory system in this study, as part of a safety pharmacology study. We used moxifloxacin as a positive control, and carried out this study according to the Q&A of "best practice considerations for in vivo studies". All experimental operations followed the Laboratory Animal Ethical Code of Shiga Institute of Nissei BilisCo., LTD.

Materials and Methods

Animals

In this study, four male telemetered ferrets weighing about 1.5 kg were used.(Marshall Bio Resources Japan Inc.). The animals were housed in a room kept at a temperature 15.5 to 24.4°C, a humidity 29.5 to 80.4%, 12-hour light/dark cycle (7:00 to 19:00).

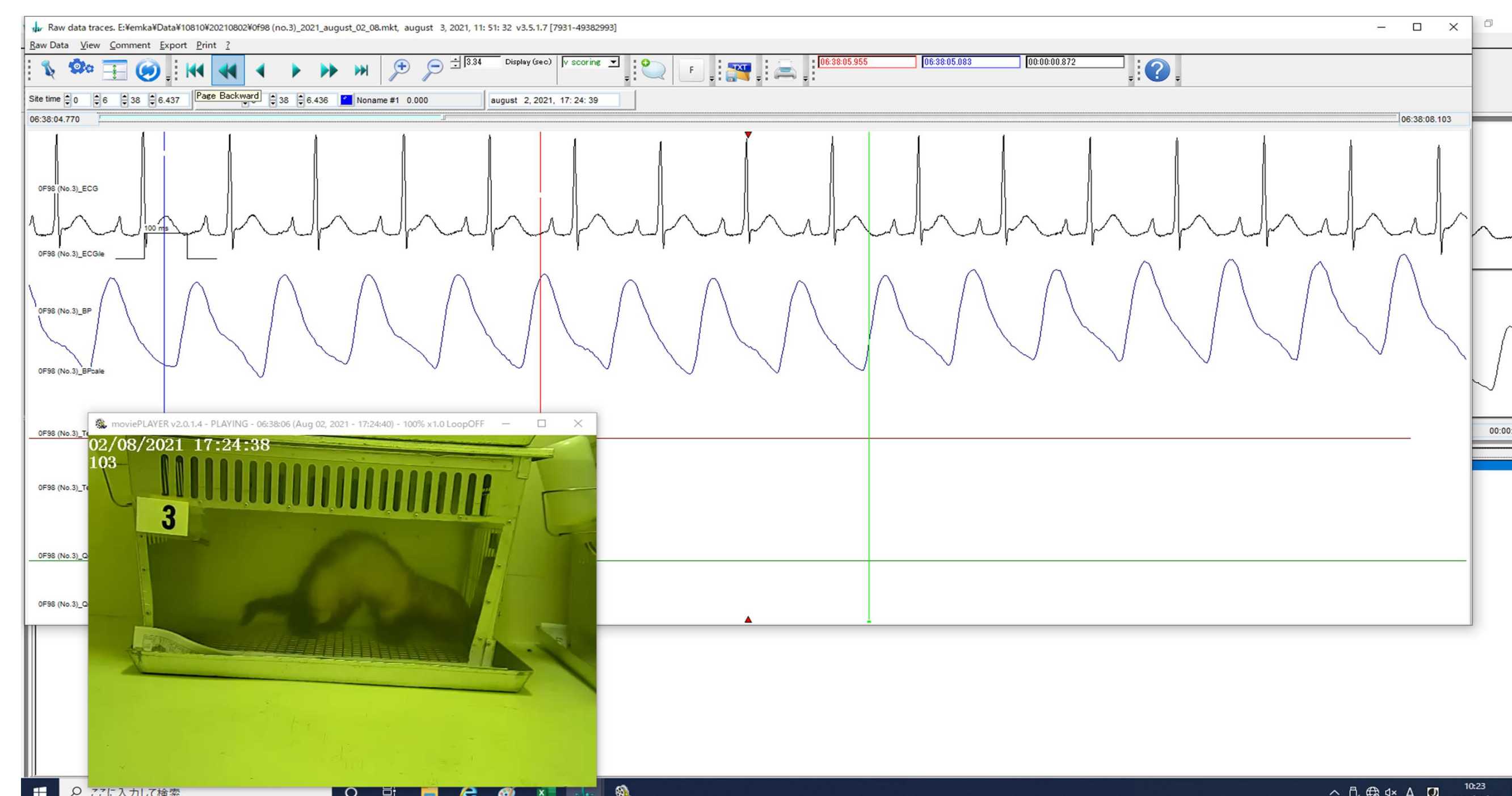
Method

A telemetry transmitter (+M2-EPTA, emka technology) was implanted intraperitoneally and was fixed inside the abdominal wall of each animal. The leads of the ECG were fixed in accordance the intra-thoracic implant method (Holzgrefe, Cavero, Gleason, Warner et al., 2007), in order to acquire a high amplitude ECG recording largely devoid of noises.

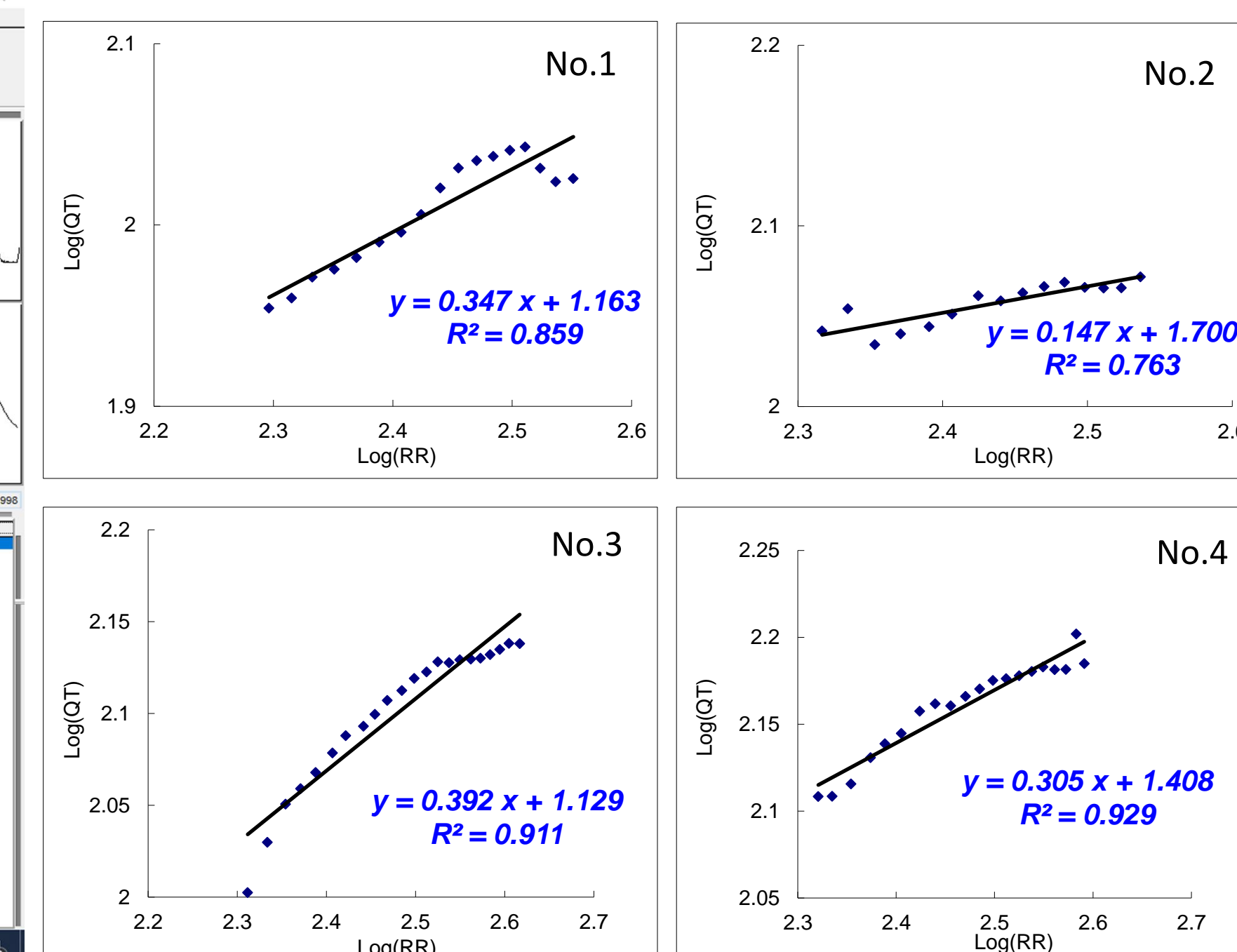
The experiment designed a cardiovascular experimental phase that included vehicle and moxifloxacin treatment at three dose levels (25, 50 and 100 mg/kg) and a pharmacokinetic (PK) experimental phase that included treatment at the same three dose levels. Management is based on a 4x4 standardized Latin square design, which was adopted as a robust design during the cardiovascular experimental phase. A period of at least an one week after each treatment was maintained as a washout period.

Exposure/Response(E/R) analysis was performed from QTci of probabilistic method and blood concentration data.

Result

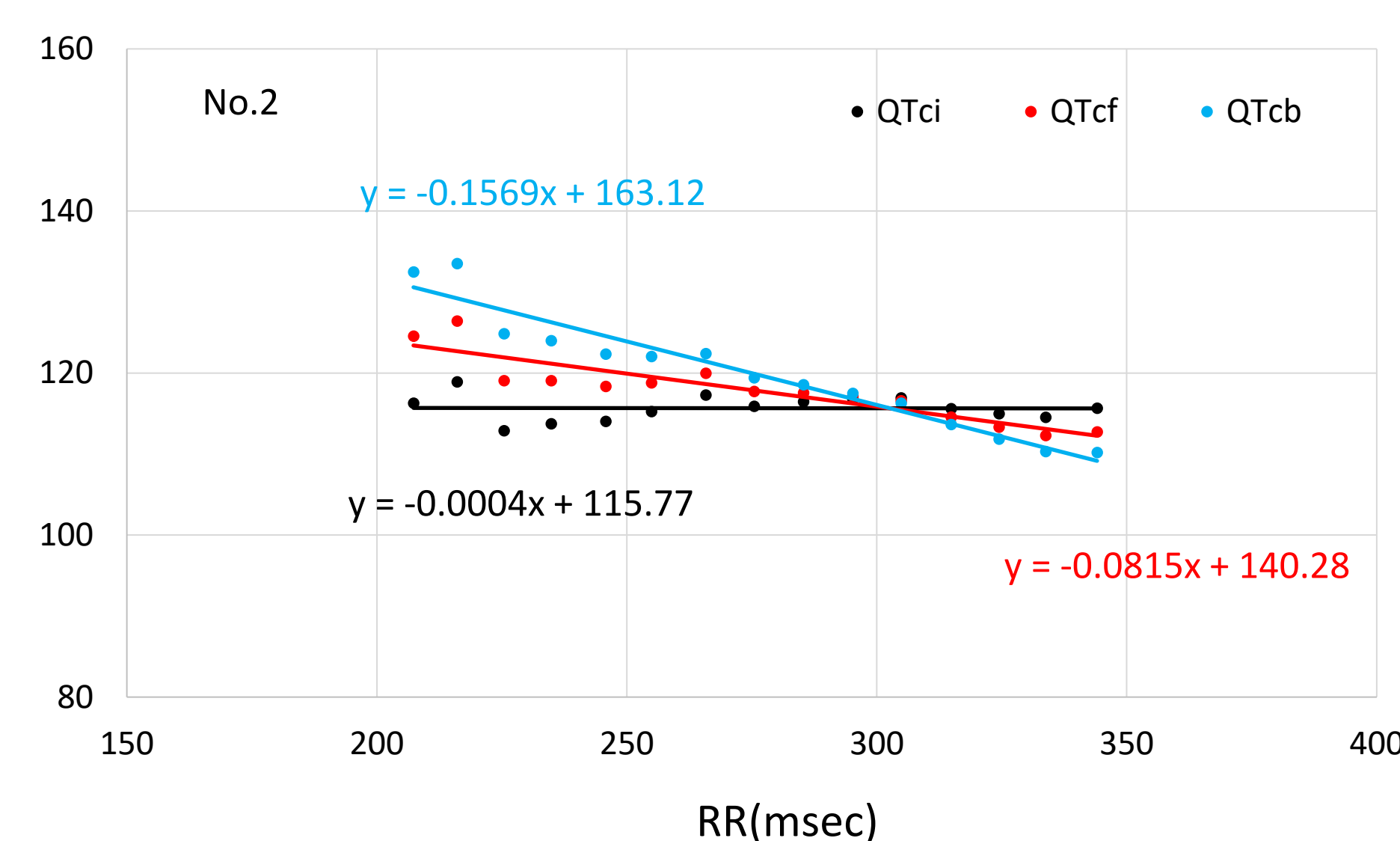


A high amplitude ECG with almost no noise was recorded.

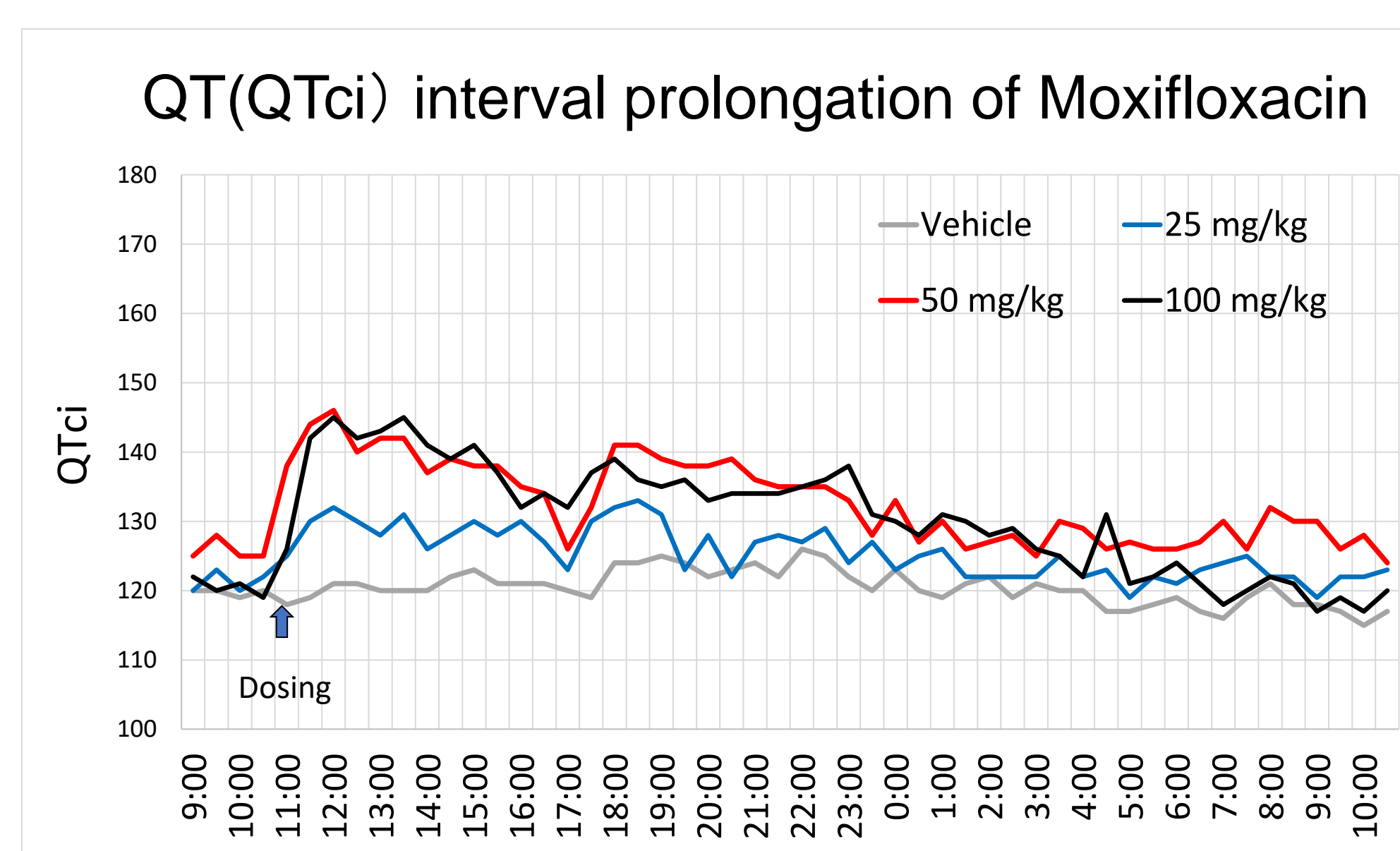
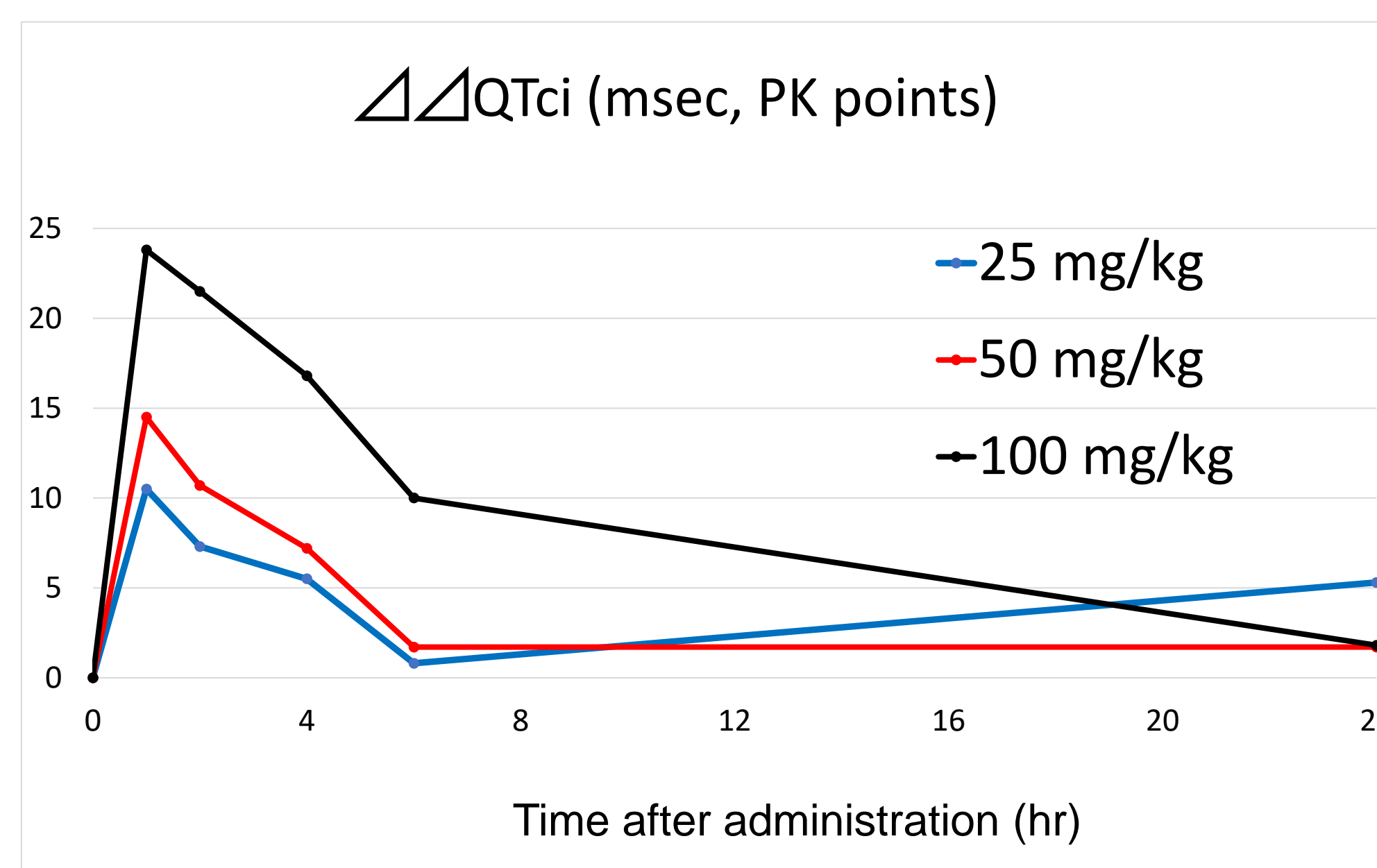


QT and RR showed a positive correlation.

Various correction formulas



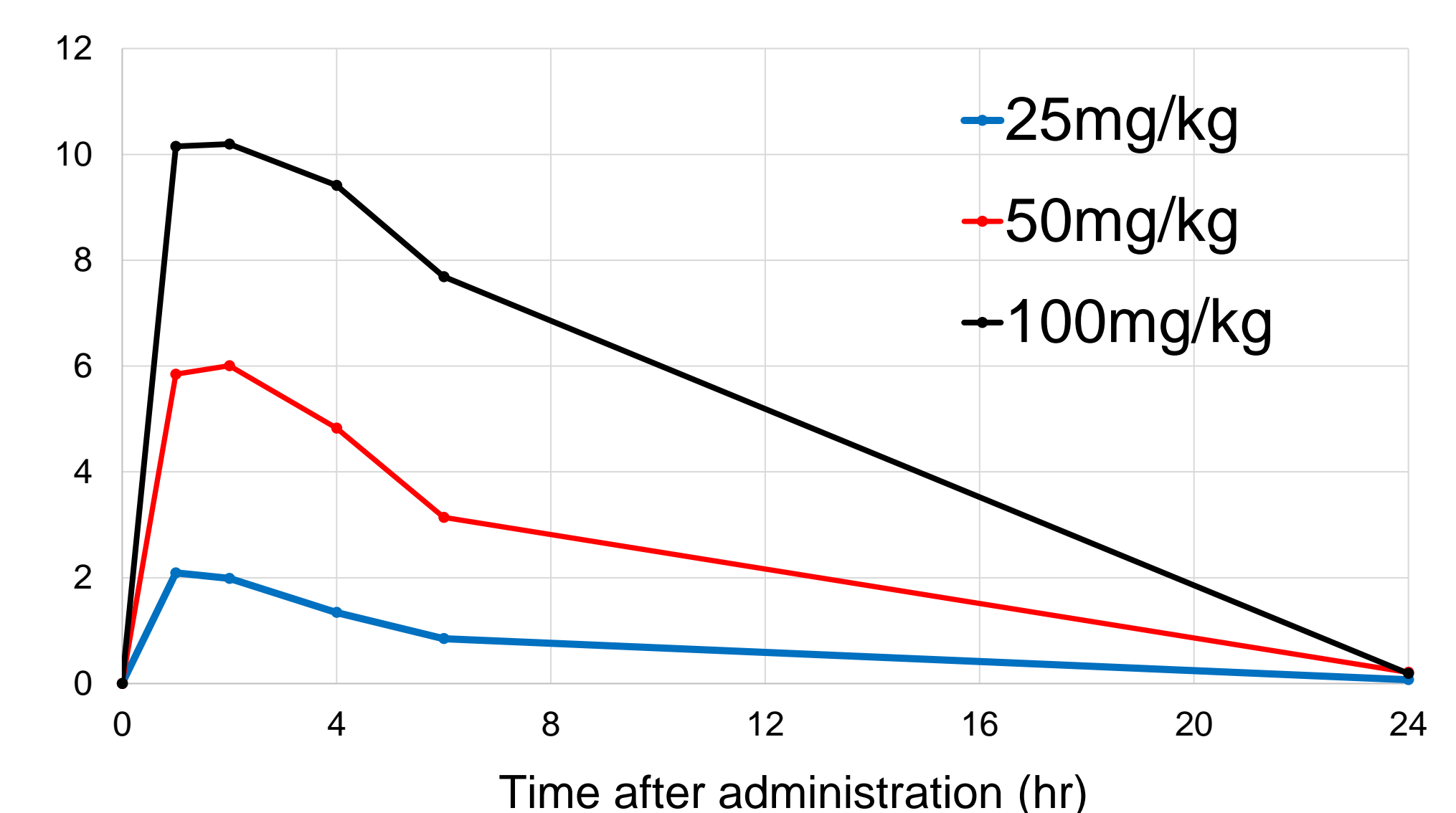
Probabilistic analysis of QTc



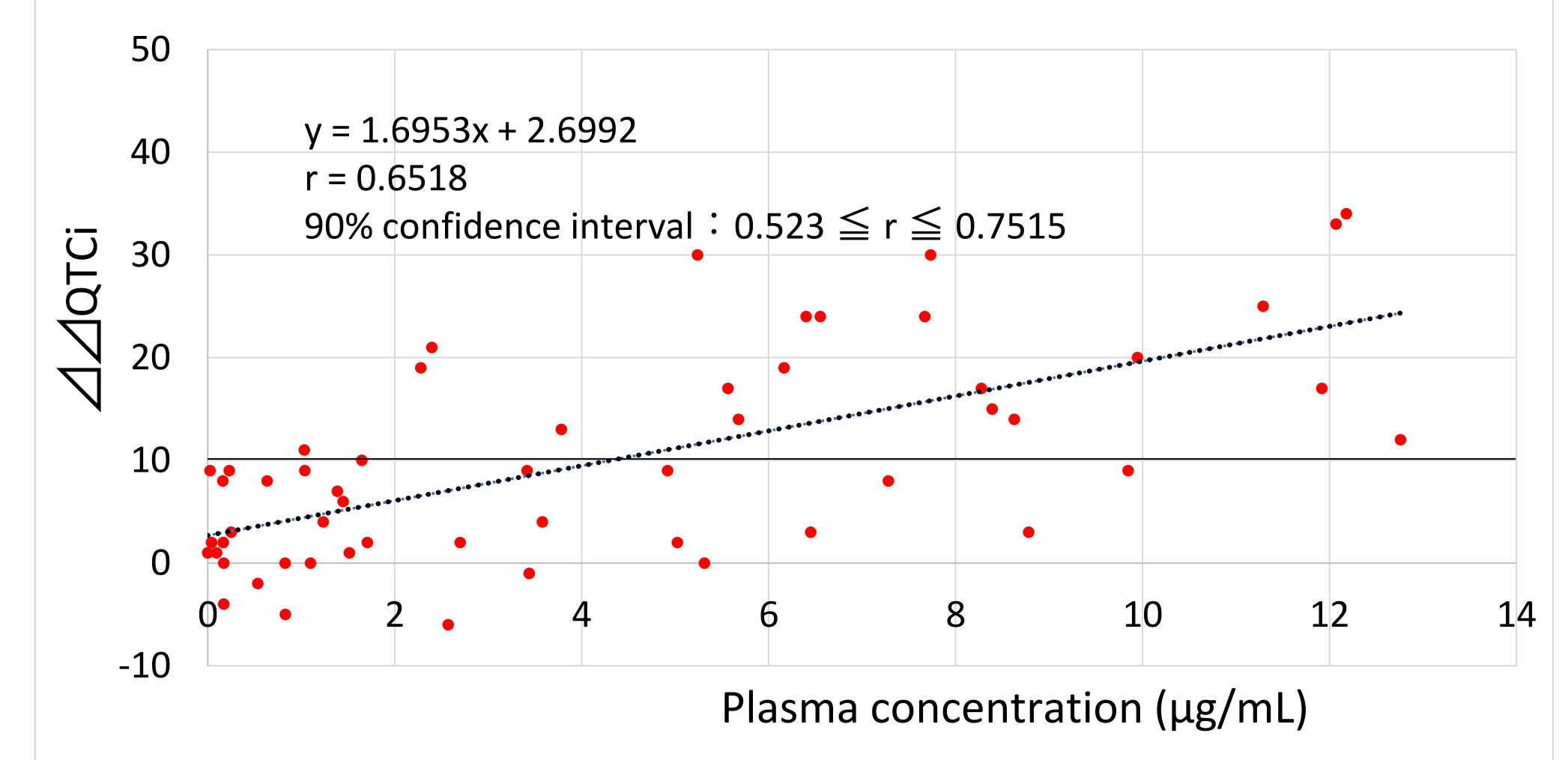
Animal No.	Slope of QTc-RR plot		
	Individual	Bazzet	Fridericia
No.1	-0.0024	-0.0622	0.0026
No.2	-0.0004	-0.1569	-0.0815
No.3	0.0097	-0.0491	0.0190
No.4	-0.0028	-0.0977	-0.0165
Mean	0.0010	-0.0915	-0.0191
S.D.	±0.0059	±0.0482	±0.0441

Probabilistic analysis of QTc

Plasma concentration (μg/mL)



E/R analysis



Conclusion

Ferrets weigh approximately 1.5 kg and are easily tamed. While they are bred as a family pet, they are useful as an experimental animal with highly crossable with humans and are used for development of influenza and COVID-19 vaccine, etc. In this study, we could assess the QT-prolonging effect by using telemetered ferrets according to the Q&A of "best practice considerations for in vivo studies". This result would be meaningful to contribute to expand the choice of experimental animal species, and save the amount of test article.



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