Preclinical Research and Development Specialists

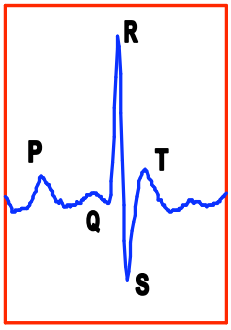
ECG: A tool for assessing drug safety and action

Background

An important part of preclinical safety profiling of a pharmacological agent involves screening for cardiac effects. Many toxic drug effects are reflected in changes to the rhythm of the heart, these include slowing (bradycardia) or quickening (tachycardia) of the heart rate, heart rate variability and/or alterations in the length of the interval of sinus waves that are reflected in electrocardiogram (ECG) traces. Used in conjunction with clinical observations, an ECG can detect potentially fatal drug-induced cardiac arrhythmias. One example is torsades de pointes, a polymorphic ventricular tachycardia caused by acquired or hereditary Long-QT syndrome, that can be triggered or exacerbated by pharmacological agents[1].

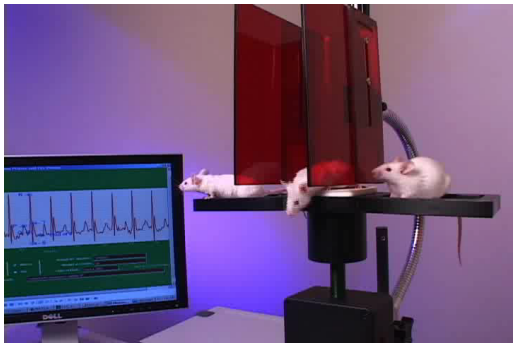
Examples of what intervals in ECG traces may reveal:

Interval	Interpretation
RR	bradycardia/tachycardia, heart rate variability
PR/PQ	heart block, arrhythmias
QRS	tissue properties
QT	Long QT-syndrome, drug effects on K^+, Na^+ and $Ca2^+$ ion channels (Different classes of drugs impact different ion channels)



ECGenie: Non-invasive electrocardiogram ideal for preclinical screening

Unlike telemetry, the ECGenie is a non-invasive electrocardiogram instrument, making it an ideal system for preclinical screening of novel compounds. After an initial acclimation period, a conscious rodent (rat or mouse) is placed on a platform equipped with a snap-in-place disposable footplate. The size and positioning of the electrodes on the footplate facilitate contact between the electrodes and the paws to provide a lead II ECG. Below are some of the features:



ECGenie

-ECGenie records the cardiac electrical signals at 2 kHz to provide optimal fidelity in describing the rapid ECG interval durations in mice (e.g., a QRS interval duration of ~8 ms).

-ECGs can be measured in approximately 10 subjects an hour.

-The ECGenie has been validated in the experimental literature. (See References)

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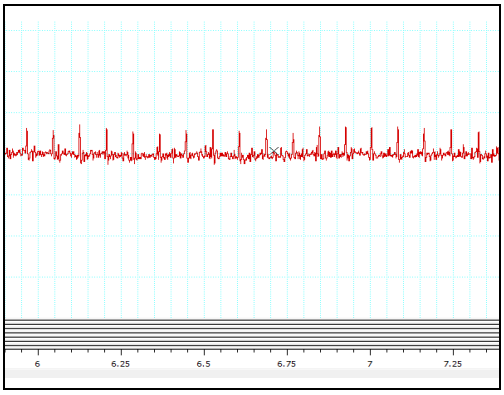
Data Acquired with the ECGenie

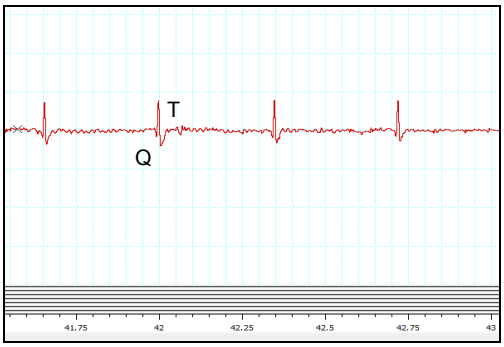
Below is data acquired with the ECGenie before, and then at 10, 20, and 30-minutes post-dosing with a compound.

Mouse ECG- Baseline – Mouse heart rate is approximately 668 bpm, close to the average normal heart rate (~700 bpm) for a laboratory mouse. Heart rate variability is minimal.

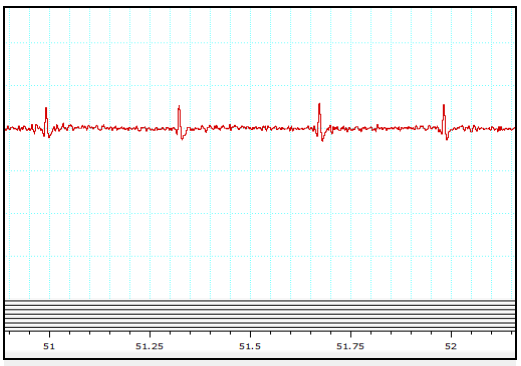


Mouse ECG- 10-minutes post-dosing - Mouse heart rate is approximately 398 bpm, demonstrating that this compound causes substantial bradycardia. The heart rate is now also clearly variable.

Mouse ECG- 20-minutes post-dosing - Mouse heart rate has slowed down further to184 bpm. Heart rate variability has decreased. The QT interval has lengthened.



Mouse ECG- 40-minutes post-dosing - Mouse heart rate has slowed down even further to 100 bpm. The QT interval is still elongated.



Data Analyzed with Emouse software: Analysis software designed to be used in conjunction with the ECGenie

Below is data analyzed with Emouse software. Displayed below is data for Heart Rate, Heart Rate Variability, and the QT interval across time points. Additional analysis parameters include: RR, PQ, CV, PR, QRS, ST, QTC, along with some additional heart rate variability metrics including MSSD and pNN50.

Figure 1. Heart Rate after compound dosing

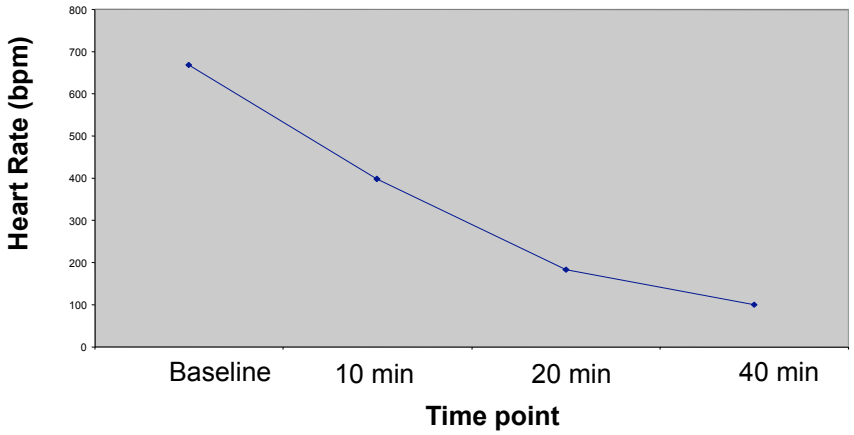


Figure 2. Heart Rate Variability after compound dosing

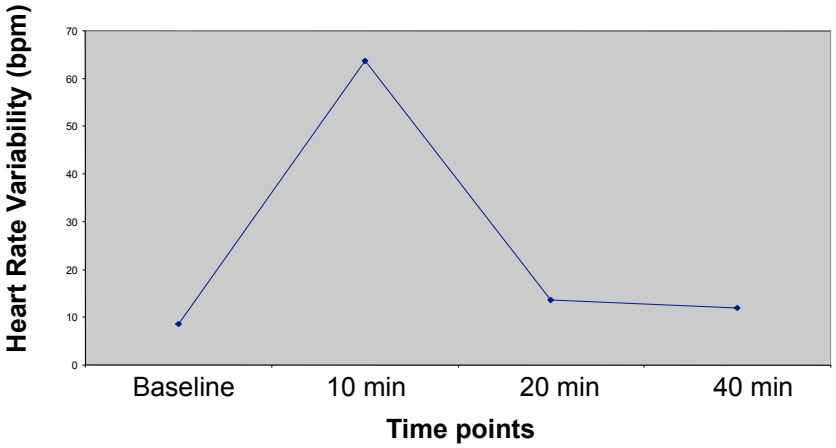
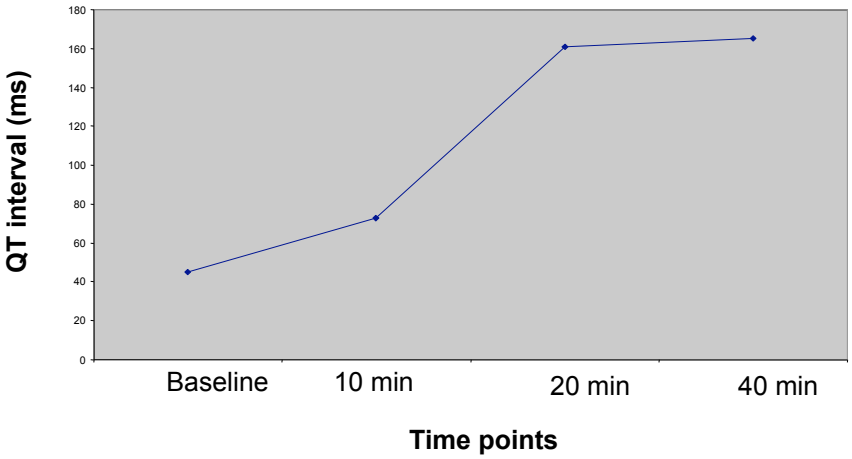


Figure 3. QT interval after compound dosing



References

1. *Drug-induced prolongation of the QT interval.* New England Journal of Medicine. 350(10): 1013-1022.

(Published studies validating the use of the ECGenie)

2. *Cardiac anomalies in b-glucuronidase (GUSB) null mice are corrected by non-ablative neonatal marrow transplantation.* PNAS 101:603-8; 2004.

3. *Metabolic and cardiovascular effects of hyperthyroidism are largely independent of beta-adrenergic stimulation.* Endocrinology 145:2767-2774; 2004.

4. *Identifying new mouse models of cardiovascular disease: a review of high-throughput screens of mutagenized and inbred strains.* J Appl Physiol. 94:1650-9; 2003.