

EVALUATION OF TEST ARTICLE-RELATED VENTRICULAR PREMATURE COMPLEXES IN CONSCIOUS TELEMETERED DOGS



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Introduction

Drug-induced arrhythmia is a serious cardiovascular liability in drug discovery and development. Although ECG waveforms are recorded continuously in most standard cardiovascular safety pharmacology studies, only part of the recorded ECG waveforms have been evaluated for arrhythmias in the past. With the assistance of available computer software, it is now practical to evaluate a continuous 24 hours ECG waveform for arrhythmias. This study provides an example which demonstrate the importance of a continuous analysis of ECG for detecting a test article-related ventricular arrhythmia in conscious telemetered dogs.

Methods

Telemetry (DSI) implanted beagle dogs with standard subcutaneous lead (base-apex) were used in the standard single oral and 2-hour intravenous infusion cardiovascular safety pharmacology studies using a balanced Latin-square crossover study design. The doses of compound x used in the single oral dose study were 10, 100 and 300 mg/kg, while the doses used in the iv infusion study were 20, 60 and 120 mg/kg. ECG and blood pressure waveforms were recorded continuously at 2 hours prior to dosing up to 24 hours after the start of dosing using PoNeMah (4.2). The recorded ECG waveforms were evaluated for ventricular arrhythmias using two methods. One method (periodic analysis) involved visual inspection of selected timepoints (2 timepoints prior to dosing and 15 timepoints postdose, 5-min segment for each timepoint). For the other method (continuous analysis), ventricular premature complexes (VPCs) were quantified by analyzing all recorded ECG waveforms beat by beat for approximately 26 hours assisted by a validated computer software (EMKA ECG -Auto).

Objectives

Optimizing arrhythmias detection using ECGs obtained in a cardiovascular safety pharmacology study by comparing periodic analysis and continuous analysis methods.

Results

The periodic method did not detect test-article related arrhythmias in the oral dose study. However, the continuous analysis method detected test article-related VPCs in 3 out of 4 dogs with total VPC episodes ranging from 11 to 1174 in the high dose group (300 mg/kg).

Results (Cont'd)

The periodic method detected test article-related VPCs in 2 out of 4 dogs in the high dose group (120 mg/kg) and no test article related VPCs in the mid dose group (60 mg/kg) in the iv infusion study. However, the continuous analysis detected test article-related VPCs in all 4 dogs with total VPC episodes ranging from 458 to 1753 in the high dose group and 3 out of 4 dogs with total episodes ranging from 13 to 48 in the mid dose group. Tmax for the oral study was between 1 to 2 hours postdose and Tmax was achieved immediately at the end of the 2

Table 1: Number of VPCs in Oral CV Dog Study (1 Hour Intervals)

| Time ^c (hours) | Animal D06M-6040 | | Animal D06M-6041 | | Animal D06M-6042 | | Animal D06M-6043 | |
|------------------------------|------------------|----------|------------------|----------|------------------|----------|------------------|----------|
| | Veh | 300mg/kg | Veh | 300mg/kg | Veh | 300mg/kg | Veh | 300mg/kg |
| -2--1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| -1-0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 0-1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 1-2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2-3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3-4 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| 4-5 | 0 | 0 | 0 | 261 | 0 | 0 | 0 | 0 |
| 5-6 | 0 | 0 | 0 | 92 | 0 | 0 | 0 | 0 |
| 6-7 | 0 | 0 | 0 | 236 | 0 | 0 | 0 | 0 |
| 7-8 | 0 | 0 | 0 | 363 | 0 | 0 | 0 | 0 |
| 8-9 | 0 | 0 | 0 | 179 | 0 | 0 | 0 | 0 |
| 9-10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10-11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11-12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12-13 | 0 | 0 | 0 | 95 | 0 | 0 | 0 | 0 |
| 13-14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14-15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15-16 | 0 | 0 | 0 | 0 | 0 | 11 | 0 | 0 |
| 16-17 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 17-18 | 0 | 18 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18-19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19-20 | 0 | 26 | 0 | 4 | 0 | 0 | 0 | 0 |
| 20-21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 21-22 | 0 | 16 | 0 | 0 | 0 | 0 | 0 | 0 |
| 22-23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 23-24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 0 | 60 | 1 | 1174 | 0 | 11 | 1 | 0 |

Figure 1: Bigeminy and Multifocal VPCs in Oral CV Dog Study



Figure 2: Bigeminy VPCs in Oral CV Dog Study



Figure 3: Number of VPCs in Oral CV Dog Study (5 Minute Intervals)

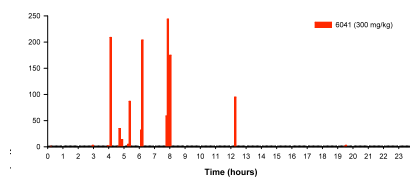


Figure 4: Number of VPCs in iv CV Dog Study (1 Hour Intervals)

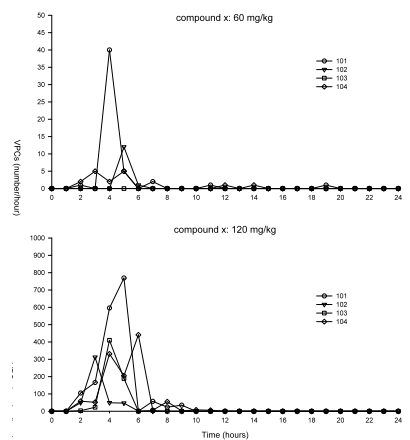


Figure 5: Number of VPCs in iv CV Dog Study (5 Minute Intervals)

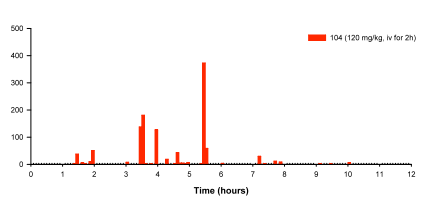
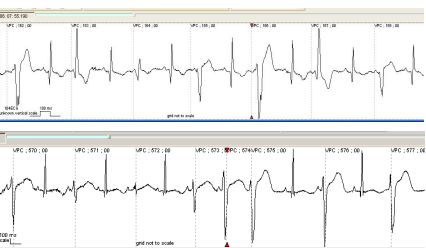


Figure 6: Multifocal VPCs and NSVT in iv CV Dog Study



Conclusions

- VPCs occurred intermittently and, thus, the probability of detecting VPCs is dependent on the timepoints selected and segment length used.
- The peak incidence of VPCs did not parallel the C_{max} by approximately 6-18 and 1-4 hours in the oral and iv studies, respectively.
- The results indicate that periodic analysis may fail to detect test article-related arrhythmias and that continuous analysis should be considered.

References

Ulloa HM, Houston BJ, ALTrogg DM. Arrhythmia prevalence during ambulatory electrocardiographic monitoring of Beagles. *Am. J. Vet. Res.* 1995;56:275-281.

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