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An evaluation of endpoint variability and implications for study statistical power and sample size in conscious instrumented dogs

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Introduction: The sensitivity of a given test to detect a treatment-induced effect is intrinsically related to the variability of that parameter observed without treatment and the number of observations made in the study (e.g., the number of animals). To evaluate test sensitivity to detect drug-induced changes in myocardial contractility using the maximal rate of pressure increase in the left ventricle during systole, $LVdP/dt_{max}$, a Health and Environmental Sciences Institute (HESI) supported consortium designed and conducted studies in chronically instrumented, conscious dogs using telemetry systems (1). This study evaluated the inherent variability of the primary endpoint, $LVdP/dt_{max}$, over time in individual animals as well as the variability between animals for a given laboratory. An approach is described to evaluate test system variability and thereby test sensitivity which may be used to support the selection of the number of animals for a given study, based on the desired test sensitivity.

Methods: A double 4x4 Latin square study design using Beagle dogs (N=8) was conducted across six independent laboratories. $LVdP/dt_{max}$ was assessed via implanted telemetry systems using the same protocol and each of the six laboratories conducted between two and four studies (1). Vehicle data from each study was used to evaluate the between- and within-animal variability in different time averaging windows. Simulations were conducted to evaluate statistical power and type I error for $LVdP/dt_{max}$ based on the estimated variability and assumed treatment effects in hourly or bi-hourly intervals, or super intervals.

Results: The within-animal variability can be reduced by 30% through the use of a larger time averaging window. Between-animal variability is laboratory-dependent and is less impacted by the use of different time averaging windows. The statistical power analysis shows that with N=8, the double Latin square study design has over 90% power to detect a maximum change of up to 15% or approximately 450 mmHg/sec in $LVdP/dt_{max}$. With N=4, the single Latin square design has over 80% power to detect a maximum change of up to 20% or approximately 600 mmHg/sec in $LVdP/dt_{max}$.

Discussion: A statistical procedure is described to quantitatively evaluate the acute cardiac effects from studies conducted across six sites and objectively examines the variability and sensitivity that were difficult to calculate consistently. This assessment focuses on the evaluation of $LVdP/dt_{max}$, but is appropriate for other parameters such as blood pressure, or ECG parameters.

References:

(1) Guth B *et al.* (2015) *J Pharm Tox Meth* **75**: 70-90.