Original article

A cardiovascular monitoring system in conscious cynomolgus monkeys for regulatory safety pharmacology
Part 1: Non-pharmacological validation

Simon Authier [a,b,*], Jean-Francois Tanguay [c], Dominique Gauvin [b], Rocky Di Fruscia [b], Sebastien Fournier [a], Fernando Chaurand [a], Eric Troncy [b]

[a] *LAB Research Inc., 445 Armand Frappier, Laval, QC, Canada H7V 4B3*
[b] *Faculté de médecine vétérinaire, Université de Montréal, P.O. Box 5000, St-Hyacinthe, QC, Canada J2S 7C6*
[c] *Montreal Heart Institute-Research Center, 5000 Belanger Street, Montreal, QC, Canada H1T 1C8*

Abstract

Introduction: This project addresses the validation study design of a test system using a telemetered non-human primate model for cardiovascular safety pharmacology evaluation. **Methods:** The validation provided by the supplier evaluated installation (IQ) and operation (OQ) qualifications. This protocol was completed with tests evaluating electronic data management and accuracy and precision of transmitter ($n=4$) measurements for temperature and pressure criteria with a series of tested values. As part of performance qualification, physical activity (for 24 h) as well as cardiovascular, ECG (20 complexes for each animal) and systemic arterial blood pressure (SAP, 10 different measures), data were recorded simultaneously from the same animals ($n=4$) using certified equipment and the telemetry system. Reliability was evaluated over 60 days. **Results:** The IQ and OQ were completed successfully. The electronic data management was performed successfully. The *ex-vivo* evaluation for temperature and pressure showed high correlation ($R^2 > 0.99$) but with a slight pressure shift, as expected, with this transmitter model. For physical activity, the correlation coefficients were good to excellent with high activity counts but the comparison demonstrated a limited sensitivity of the telemetry system with animal presenting low activity levels. ECG interval measurement using the telemetry software was considered at least equivalent to manual measurement, but with some limitations in the reading of the ECG. The comparison between both methods of SAP measurement showed adequate precision ($R^2 = 0.969$) but no accuracy. **Discussion:** Reference monitoring methods are important to ensure proper test system validation. Monitoring with a reference methodology and the telemetry system is important in order to evaluate precision and accuracy of the test system. Computerized analysis may lack the capability to analyze ECG complexes with abnormal morphologies. This reinforces the need to have ECG evaluation prior to telemetry implantation along with visual evaluation of ECG tracing at standard speed (*e.g.* 50 mm/s) at all time points.

1. Introduction

The importance of telemetric monitoring in biomedical research involving laboratory animals has grown significantly

---

* Corresponding author. LAB Research Inc., 445 Armand Frappier, Laval, QC, Canada H7V 4B3. Tel.: +1 450 973 2240x1403; fax: +1 450 973 2259.

E-mail addresses: authiers@labresearch.com (S. Authier), Jean-Francois.Tanguay@icm-mhi.org (J.-F. Tanguay), d.gauvin@umontreal.ca (D. Gauvin), rocky.di.fruscia@umontreal.ca (R. Di Fruscia), fourniers@labresearch.com (S. Fournier), chaurandf@labresearch.com (F. Chaurand), eric.troncy@umontreal.ca (E. Troncy).

over the past years. This technology is an important tool for collection of a considerable number of physiological parameters including electrocardiograms, electroencephalograms, electromyograms, arterial blood pressures, ventricular blood pressures, locomotor activity, core body temperature and pleural pressures (Brockway, Mills, & Kramer, 1998). For researchers, especially those in the fields of pharmacology and toxicology, telemetry provides a valuable tool to define the physiological and pathophysiological consequences derived from advanced molecular, cellular, and tissue biology and to predict new compound effectiveness and safety in humans. Particularly, systemic arterial

pressure (SAP), heart rate (HR) and electrocardiography (ECG) should be evaluated as part of preclinical safety pharmacology (US FDA — ICH S7A, 2001, 2004).

If continuous measurement of cardiovascular parameters in experimental animals is essential for cardiovascular research, species selection for safety pharmacology and drug toxicity testing is important in order to develop new clinically useful pharmaceuticals. Historically, canine models were most frequently used for cardiovascular safety pharmacology studies when large laboratory animals were required. Some considerations for selection of relevant preclinical models have justified sensitivity evaluation and validation of telemetered non-human primate models (Chaves et al., 2006). New methods for correcting QT interval for HR have been recently evaluated in cynomolgus monkey (Holzgrefe et al., in press). Data obtained in conscious cynomolgus monkeys have also been published recently (Ando et al., 2005; Gauvin, Tilley, Smith, & Baird, 2006). The pharmacokinetics of xenobiotics in humans is closer to non-human primates than to dogs for a number of drugs (Ward & Smith, 2004). *In-vivo* metabolism also supports the use of non-human primate models for various drugs as metabolites may be responsible for adverse cardiovascular effects (Fermini & Fossa, 2003). Metabolism in non-human primates is closer to human than dog for some drugs (Zuber, Anzenbacherova, & Anzenbacher, 2002). Reducing the use of non-human primates in research is an important overall objective from both an ethical and resource perspective. However, the high degree of relevance of monkeys for some drugs makes it a judicious model for cardiovascular safety pharmacology evaluation, when justified.

In light of studies described in the literature (Akita, Kuwahara, Nishibata, Mikami, & Tsubone, 2004; Kramer et al., 2000; Harkin, O'Donnell, & Kelly, 2002; Schierok, Market, Pairet, & Guth, 2000; Schlatter & Zbinden, 1982), it was concluded that the use of radiotelemetry to measure SAP, ECG, HR, body temperature and locomotor activity in rodents has been sufficiently validated (Kramer et al., 2001; Kramer & Remie, 2005; Shiotani, Harada, Abe, Hamada, & Horii, 2007). Data on circadian rhythms of SAP (Gauvin et al., 2006; Gerber, Schnell, & Anzenberger, 2000; Schnell & Wood, 1993), HR (Gauvin et al., 2006; Gerber et al., 2000; Schnell & Wood, 1993), and body temperature (Cilia, Piper, Upton, & Hagan, 1998; Gauvin et al., 2006; Palkova, Sigmund, & Erkert, 1999) in marmoset and cynomolgus monkeys have been reported in the literature. For the latter, most of the data have only been reported in abstracts of annual meetings (Kamenosono, Hamada, Fukuzaki, Nagayama, & Kito, 1999; Kito, Kamenosono, Akune, Fukuzaki, & Nagata, 1999), or using a simple Holter monitor (Macallum & Houston, 1993). Even if non-human primates are used routinely for regulatory cardiovascular safety pharmacology, validation study results are rarely reported in the scientific literature and data available is often limited (Ando et al., 2005; Omata, Kasai, Hashimoto, Hombo, & Yamamoto, 2005). Validation of electronic technologies to generate electronic records and electronic signatures has been the subject of significant discussions among interested parties following issuance of the final Code of Federal Regulation 21

Part 11 (US FDA — CFR 21 Part 11, 1997). As a result of these concerns, FDA issued a guidance document providing insights on FDA interpretation of Part 11 requirements (US FDA — CFR 21 Part 11, 2003). This guidance emphasizes the importance of using a documented risk assessment to determine the extent of system validation.

The aim of the current project is to evaluate, similarly to what was done with rodents, the installation, operation and performance qualification of a telemetry system using a telemetered non-human primate model.

2. Methods

2.1. Hardware and software

This study evaluated the following components of the Data Science International (DSI, St-Paul, MN, USA) telemetric system:

Temperature and physical activity transmitters (Model TA10TAD70)
Pressure, biopotential, temperature and physical activity monitoring transmitters (Model D70-PCT)
Telemetry receivers (Model RMC-1)
Telemetry Data Exchange Matrix (Data Exchange Matrix™)
Ambient Pressure Reference (Model APR1)
Data acquisition and analysis software (Dataquest A.R.T.™ Gold Version 3.01)
Electrocardiogram analysis software (Physiostat™ ECG Analysis 4.01)

The system was installed by the DSI technical staff on a desktop computer (Optiplex GX270™, Dell, North York, ON, Canada). The study was conducted in accordance with the Good Laboratory Practice (GLP) regulations of the United States Food and Drug Administration (21 CFR Part 58 and subsequent amendments). The test plan consisted of the four phases presented below.

2.2. DSI validation protocol

First, the supplier (DSI) performed a series of tests (GLP Large Animal Validation Protocol) developed for the validation of the system based on 21 CFR Part 11 and Part 58. The validation protocol performed on-site by the supplier included installation and operation qualifications. Tests performed by the supplier evaluated all recording and analysis functions of the software in the absence of animals. Security checks and audit trails were also tested. Lastly, a transmitter simulator (TSS-1™, DSI) producing a signal with known characteristics was used to validate accuracy of radiowave signal capture.

2.3. Electronic data management

The ability to generate accurate and complete copies of electronic records is critical to allow proper interpretation of experimental results and is a requirement of 21 CFR Part 11.