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Validation and utility of the PhysioTel™ Digital M11 telemetry implant for cardiovascular data evaluation in cynomolgus monkeys and Beagle dogs

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ABSTRACT

Introduction: The cardiovascular liability of candidate compounds can be evaluated by a number of methods including implanted telemetry, jacketed telemetry and surface lead electrocardiogram (ECG). The utility of the new PhysioTel™ Digital M11 cardiovascular telemetry implant was evaluated in monkeys and dogs.
Methods: Eight monkeys and dogs (4 males and 4 females per species) were implanted with the M11 device utilizing a femoral blood pressure catheter and periosteal ECG leads. The signal quality of the ECGs was determined as a percentage of software-matched waveforms and as a percentage of signal loss during the recording periods. To investigate sensitivity for detecting changes in QT/QTc and HR/BP, moxifloxacin and doxazosin were administered to monkeys and dogs implanted with the M11 device. Additionally, histopathological evaluation of the implant site was completed.
Results: For both monkey and dog, the percentage of recognizable waveforms was high (65% and 85%, respectively), while the average amount of signal loss was low (1% and 3%, respectively), indicating that the M11 implants delivered data of sufficient quality. In monkeys, moxifloxacin (90 mg/kg) induced QT and QTc prolongation up to 22 and 12 ms, respectively, while at 30 mg/kg in dogs, the maximal increases in QT and QTc were 13 and 16 ms, respectively. Doxazosin (1.5 and 1.0 mg/kg) produced HR increases up to 35 and 29 bpm with decreases in blood pressure up to −14 and −26 mm Hg in monkeys and dogs, respectively. The histopathological impact of the implant, catheter and biopotential leads was limited to expected minor local inflammatory changes as assessed at necropsy and with microscopic examination.
Discussion: Based upon the results of this study, the PhysioTel™ Digital M11 is a suitable technology for assessing cardiovascular parameters in monkeys and dogs, and because of the size and limited invasiveness of the implant, is well positioned for use on toxicology studies.

1. Introduction

Evaluation of cardiovascular (CV) endpoints on toxicology studies is typically performed using surface lead electrocardiograms (ECG), and on occasion, with a tail cuff measurement for blood pressure (BP). However, with the advent of jacketed external telemetry (JET) with a BP add-on, more robust cardiovascular evaluation can be implemented on toxicology studies to better characterize the CV liability of candidate compounds. Collecting CV data as an add-on, and potentially replacing a standalone study, is in alignment with The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines (ICH, 2000, 2009) and further promotes the principles of the 3Rs (Replacement, Reduction, Refinement) for animal use. JET has been successfully implemented and is widely used by the pharmaceutical industry, and is especially useful for testing CV risk for biologics for which the use of telemetry colony animals is not an efficient option. However, JET does have challenges primarily associated with jacketing and ECG surface lead placement that make alternative technologies attractive.

The purpose of this investigation was to evaluate the newly released M11 implant with PhysioTel™ technology [Data Sciences International (DSI)] as a potential alternative to JET. Several features of the implant make it suitable for use on toxicology studies, while offering advantages over JET. Like the PA-C40 or PA-C10 implants (DSI) used with JET, the

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M11 is small and only requires a minor surgery for implantation. However, the M11 does not require the use of jackets for collection of CV data which is an added animal welfare benefit. Wearing the jackets can induce animal stress and has been shown to elevate hemodynamic parameters in monkeys (Cordes, Harris, Holloway, Foote, & Steidl-Nichols, 2011) and dogs (data unpublished). Furthermore, the M11 implants provide surgically implantable bipolar leads for collection of ECGs in addition to the single pressure catheter for blood pressure monitoring. These advancements present a clear advantage in terms of consistency and reliability, over JET, which requires surface lead ECG collection. Therefore, the M11 technology offers potential improvements to animal welfare and data quality, as well as significant time and resource savings that can be realized through the elimination of jackets while maintaining the use of minor surgery to implant.

Prior to adoption of any new implanted telemetry technology for pharmaceutical testing, it is important to assess the reliability of the hardware, data quality and assay sensitivity, as well as the impact of the implant on animal health and pathology (especially for toxicology studies). In these studies with the M11 implant, data quality, detection of hemodynamic and ECG changes with administration of positive control agents (moxifloxacin and doxazosin), and impact to the histopathological examination were evaluated.

2. Methods

2.1. Study design

This study encompassed method validation for the M11 implant and positive control testing in a cohort of monkeys and dogs at two different test sites. Animals surgically implanted with the transmitter were given vehicle and positive control compound in crossover designed studies (n = 8 animals/group). Based upon the pharmacokinetic profiles of each compound, at least 5 days (>7 half lives) were permitted between dose administrations to ensure clearance of the compounds from systemic circulation. The alpha-1 adrenergic receptor antagonist doxazosin (Pfizer, Inc.) was administered as a single oral dose to monkeys (1.5 mg/kg in 20% PEG and water) and dogs (1 mg/kg in 0.5% methylcellulose and water). The fluoroquinolone antibiotic moxifloxacin (Sequoia Research Products, Ltd.) was administered as a single oral dose to monkeys (90 mg/kg) and dogs (30 mg/kg) in a vehicle of 0.5% methylcellulose, 0.1% polysorbate 80 and water.

2.2. Animals

All experiments involving animals were conducted as per the guidelines and study protocols reviewed and approved by Pfizer Institutional Animal Care and Use Committee.

Four male and four female cynomolgus monkeys (*Macaca fascicularis*) of Mauritius origin (SNBL and Covance) were used for the study, were at least 2.5 years old and ranged in body weight between 4.3 and 9.0 kg. Monkeys were housed in stainless steel cages and pair-housed at all times with the exception of telemetry days. A standard diet of pelleted food (Certified Primate Diet 5K91) supplemented with vegetables and/or fruit was provided twice daily at approximately 7:00 AM (prior to dosing) and 1:00 PM (4 hours postdose (HPD)) and remained with the animals overnight. Water was provided ad libitum. Environmental conditions were maintained between 16 and 25 °C, 30–70% humidity, a minimum of 12 air changes/h and a 12-hour light/dark cycle (6 AM/6 PM lights on/off).

Four male and four female Beagle dogs (*Canis lupus familiaris*) of Marshall Farms origin were used for this study, were at least 1 year old and ranged in body weight between 8.2 and 10.2 kg. Dogs were housed in 4 ft. × 6 ft. runs and pair-housed at all times with the exception of telemetry days. A standard diet of dry food (Certified Purina Diet 5L66) was provided once daily at approximately 2:00 PM (5 HPD) and remained with the animals overnight. Water was provided ad libitum. Environmental conditions were maintained between 16 and 25 °C, 30–55% humidity, a minimum of 12 air changes/h and a 12-hour light/dark cycle (6:30 AM/6:30 PM lights on/off).

Eight (n = 8) animals of each species were chosen for these studies to provide a relevant comparison to internal historical data, as eight animals are commonly monitored as part of a toxicology CV add-on or a traditional standalone Safety Pharmacology telemetry study in our facility.

2.3. M11 implant

The M11 is a PhysioTel™ Digital implant (Fig. 1A) intended for use with large animals and is smaller (11 cm^3) and lighter (13.7 g) than the L11 or D70-PCTP transmitters from DSI, but slightly larger than the PA-C10 or PA-C40 BP implants used with JET. The M11 implants used on this study had 1 pressure catheter (which was 1.4 mm in diameter and 35 cm in length for monkeys, and 0.7 mm in diameter and 15 cm in length for dogs), biopotential leads for ECG collection, and temperature and activity sensors. A comparison of the PhysioTel™ Digital M11 implant, D70-PCTP and JET BP PA-C40 transmitter specifications can be found in Supplementary Table 2.

2.4. Surgical procedures

2.4.1. Monkey

Monkeys were anesthetized with isoflurane in oxygen following premedication with buprenorphine, meloxicam, glycopyrrolate and ketamine (sedation). Intra-operative administrations included intravenous (i.v.) fluids, cefazolin (i.v.), and an external heat source. Routine anesthetic monitoring was performed, which also included direct blood pressure measurement (via telemetry device). An intermuscular pocket was created between the muscles of the internal oblique and transversus abdominus muscles through aponeurosis incision. The transmitter was inserted and secured with nylon sutures with the antenna perpendicular to midline in the lower abdominal muscle fascia of the external oblique. The systemic blood pressure catheter was tunneled and inserted 10 cm into the left femoral artery with the tip into the external iliac artery. ECG biopotential leads were secured in a lead 2 configuration to the costal periosteum with nonabsorbable braided polyester sutures. Bupivicaine was used as a splash block in the surgical sites prior to three layer closure with absorbable polydioxanone in the fascia, and poliglecaprone 25 to appose muscle and dermis. Animals were placed on scheduled analgesics (buprenorphine and meloxicam) in the postoperative period and completed an uneventful recovery. A full physical examination and complete blood count (CBC)/blood chemistry analysis was performed prior to release for study use.

2.4.2. Dog

Dogs were anesthetized with isoflurane in oxygen following premedication with acepromazine, meloxicam, glycopyrrolate and buprenorphine. Intra-operative administrations included intravenous (i.v.) fluids, cefazolin (i.v.), and external heat source. Routine anesthetic monitoring was performed which also included direct blood pressure (via telemetry device). An intermuscular pocket was created for transmitter placement between the muscles of the external and internal abdominal oblique along the left lateral flank. The antenna was directed across cranially in the fascia layers following the body wall using blunt dissection for insertion. The systemic blood pressure catheter was tunneled and inserted 15 cm into the left femoral artery with the catheter tip residing in the illiac artery. ECG biopotential leads were secured in lead 2 configuration to the costal periosteum with nonabsorbable braided polyester sutures. Bupivicaine was used as a splash block in the surgical sites prior to three layer closure with absorbable Polydioxanone in the fascia, and poliglecaprone 25 to appose muscle and dermis. Animals were placed on scheduled analgesics (buprenorphine and meloxicam) in the postoperative period and