Concomitant evaluation of cardiovascular, respiratory and central nervous system functions following a single administration of a candidate drug in the cynomolgus monkey

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INTRODUCTION

Evaluation of the potential effects of new drug candidates on cardiovascular (CV), respiratory (Res) and central nervous system (CNS) functions is a part of the safety pharmacology core battery (ICH S7). These investigations are usually conducted separately in conscious non-restrained rodents (for Res and CNS) and non-rodents (for CV). A combination of implanted and jacketed external telemetry enables investigation of all safety pharmacology core battery parameters within a single study. Using a minimum number of animals, this approach allows collection of a maximum amount of relevant scientific data and simultaneous investigation of any possible interaction between different vital functions in the same animal. Therefore, this approach may improve the safety pharmacology assessment bringing scientific, economic and ethical benefits.

The purpose of the present study was to evaluate the feasibility of this approach and to investigate the effect of one single administration of a test item (a biological drug candidate, TI) simultaneously on CV, Res and CNS functions in the conscious non-restrained cynomolgus monkey using implanted (IT) and jacketed external telemetry (JET).

MATERIALS AND METHODS

Twelve cynomolgus monkeys in total (Le Tamarinier, Mauritius) implanted with telemetry transmitters (TL11m2-D70-PCT), Data Sciences International, Saint Paul, USA) were equipped with JET devices including Respiratory Inductive Phlebomography (RIP). Implanted telemetry data were recorded and analyzed with HEIM, Notocord software. JET data were recorded and analyzed with DSI Ponomah software. After a randomization, animals were allocated to three groups of six males and 2 females: Vehicle group, TI dose 1 and TI dose 2. After an acclimation period, animals were monitored by IT and JET, for 2 hours before and 24h after dosing. Each animal received one single intravenous administration of TI or vehicle over a period of 45 sec.

Parameters:
- Cardiovascular parameters: implanted telemetry
- Heart Rate: HR, Arterial blood pressure parameters: DAP, SAP and MAP, Body temperature, ECG parameters: PQ, QRS, QT, QTcB, Arrhythmia monitoring.
- Respiratory parameters: Jacket external telemetry (JET) & Respiratory Inductive Phlebomography (RIP), Respiration rate, Tidal volume and Minute volume.
- CNS - Functional observation battery (FOB) including 33 parameters covering the following domains: Neuologic, Autonomic and Behavioral

Study Design

RESULTS

Plasma exposure (PK) and circulating biomarker (BM):
TI was quantified in plasma samples at pre-dose, 4, 24, 72 and 168 hours after treatment. Cmax was reached at 4 hours after administration of TI and increased dose-dependently (see figure 1). Single intravenous administration of TI produced sustained and dose-dependent increases in plasma biomarker (BM, see figure 2).

Cardiovascular function

When compared to controls, no noticeable changes in heart rate, mean, systolic and diastolic arterial blood pressure, ECG parameters (PQ, QRS, QT, QTcB and QTcF) or body temperature were observed on Day 1 or Day 7 after single intravenous administration of TI (see figures 3 and 4). No treatment-related arrhythmias were reported at the observation time-points in this study on Day 1 or Day 7.

Respiratory function

With the exception of slight and isolated changes which were mainly related to individual variations on day 7, TI (at dose 1 and dose 2) had no effect on respiratory parameters up to 7 days after treatment (see figure 5).

CONCLUSION

In this study we have demonstrated the feasibility of combining implanted and jacketed external telemetry to investigate the effect of one single administration of a test item simultaneously on CV, Res and CNS functions in the conscious non-restrained cynomolgus monkey. The results confirm the efficacy of combining implanted and external telemetry in one single investigation in safety pharmacology assessment.

This combination approach can be recommended for the evaluation of potential adverse effects of drug candidates. It is a convenient approach for drugs with long lasting systemic exposure, and it brings scientific, economical and ethical benefits.

BIBLIOGRAPHIC REFERENCES


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