Pimobendan, Etilefrine, Moxifloxacine and Esketamine as Reference Compounds to Validate the DSI PhysioTel® System in Cynomolgus Monkeys

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Introduction

Determination of cardiovascular endpoints still is a pivotal requirement to protect healthy volunteers in Phase 1 clinical trials. Since most recent European guidelines for the care and housing of laboratory animals require increased cage sizes and encourage group housing, telemetric data recording becomes challenging (ETS 123, 2007). The PhysioTel® digital system is capable to handle these requirements by offering significantly increased transmission ranges as well as individual signal frequencies. The goal of this study was to evaluate the feasibility of the system to detect changes in left ventricular pressure (LVP), systemic blood pressure (SBP), electrocardiography (ECG), body temperature (Temp.) and activity (Act.) after administration of different reference compounds applying a standard Latin square design study.

Method

Four male cynomolgus monkeys were surgically implanted with a PhysioTel®L21 full implant for measurement of LVP, AOP, ECG, temperature and activity. Following a recovery period of at least 6 weeks, Penomah Open Art® was used to collect and analyse all telemetric data recordings. The animals received all reference compounds according to a Latin square design (Table 1) except pimobendan where a 5th dose was added. Another set of four male cynomolgus monkeys (non implanted) received the same reference compounds on the same dosing days and blood samples were taken at 0 (predose), 1, 4, 6, and 24 hours postdose into lithium heparin tubes and the plasma stored frozen until analysis (data not included in the poster). For statics, the telemetric data were analysed by a modified Latin square design analysis of covariance, with repeated measures (time) embedded within each treatment period. The covariate was the mean baseline observation for each subject on each dosing day. The variance-covariance structure used in the analysis was the one providing the smallest Akaike Information criterion out of the four: Compound symmetry, heterogeneous compound symmetry, autoregressive (1), and heterogeneous autoregressive (1).

Results

Pimobendan (Figure 1) induced an increase in the dP/dt max and heart rate value, being evident for up to 4 hours postdose at a dose level of 10 mg/kg. Furthermore, there was a slight decrease in the left ventricular end diastolic pressure (LVEDP). A marked (5 and 10 mg/kg) and slight (2 mg/kg) increase in mean, systolic, diastolic blood pressure and pulse height as well as dP/dt max for up to 5 hours (5 and 10 mg/kg) or 2 hours (2 mg/kg) postdose was found after oral etilefrine (Figure 2). A marked QT and QTc prolongation (around 20 to 40 ms) at 60 and 160 mg/kg being evident from 2 until 22 hours postdose was measured after oral moxifloxacine (Figure 3). Esketamine (Figures 4 and 5) injections caused a mild increase in dP/dt max and mean, systolic, and diastolic blood pressure and pulse height as well as dP/dt max for up to 5 hours (5 and 10 mg/kg) or 2 hours (2 mg/kg) postdose at a dose level of 10 mg/kg. Furthermore, there was a slight decrease in the left ventricular end diastolic pressure (LVEDP) and QTcF interval was markedly prolonged (up to 40 ms) until 16 hours postdose (5 and 10 mg/kg). Furthermore, activity and temperature was markedly decreased at 1 mg (until 3 hours postdose) and 2.5 and 5 mg/kg (until 5 hours postdose). QT and QTcF interval was markedly prolonged (up to 40 ms) until 40 hours postdose (5 and 10 mg/kg). Furthermore, there was a slight decrease in the left ventricular end diastolic pressure (LVEDP) and QTcF interval was markedly prolonged (up to 40 ms) until 16 hours postdose (5 and 10 mg/kg). Furthermore, activity and temperature was markedly decreased at 1 mg (until 3 hours postdose) and 2.5 and 5 mg/kg (until 5 hours postdose).

Discussion and Conclusion

For all reference compounds the expected pharmacological activity could be detected as either transient (pimobendan, etilefrine, esketamine) or longlasting (moxifloxacine) effects. The calcium sensitizer pimobendan as expected increased the dP/dt max and heart rate. However, the left ventricular end diastolic values decreased and systemic blood pressure also remained unchanged. Furthermore, it has to be noted that pimobendan in the cynomolgus monkey induced effects at much higher dose levels than in the dog (Markert et al., 2007). Etilefrine induced the expected increase in systemic blood pressure as well as contractility and these effects are comparable to a recently completed study using JET/5P technology (Niehoff et al., 2011). The magnitude of the QT and QTc prolongation following moxifloxacine administration was as expected in cynomolgus monkeys and is comparable to previous studies (Holzgrefe et al., 2013). Esketamine as an anaesthetic affected nearly every biopotential tested including body temperature and activity. However, taking into account that an increased activity pattern is usually considered adverse, some kind of activity stimulating reference compound (e.g., amphetamine) should be considered for potential future studies (Rose et al., 2011). In conclusion, the data suggest that the PhysioTel® system is capable to detect potentially adverse or pharmacological effects on contractility, blood pressure, electrocardiogram, temperature and activity in conscious, freely moving cynomolgus monkeys.

References

Council of Europe. Appendix A of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes (ETS no. 123) – Guidelines for the accommodation and care of animals (article 5 of the convention). Cons 2006;123, effective from July 15, 2007.


Cynomolgus Monkeys

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