Evaluation of PhysioTel™ Digital M11 Cardiovascular Telemetry Implant in Socially Housed Cynomolgus Monkeys Using Etilefrine and Moxifloxacin

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Abstract

The DSI JET/BP system is currently used to collect cardiovascular endpoints on toxicology studies. This technology enables continuous evaluation of electrocardiogram (ECG) as well as systemic blood pressure (BP), and is most often used in the development of large molecules (e.g., mAb). In contrast to the analog JET/BP system, the M11 PhysioTel™ system transmits a fully digital signal that eliminates cross talk between animals (Cordes et al. 2016). In addition, the M series ECG and BP components are internal, therefore animals do not need to wear a jacket, which is a significant advantage of the M series over the JET/BP system. Four female cynomolgus monkeys (3.0 to 3.8 kg) were implanted with the M11 implants and received single oral doses of reference compound etilefrine (sympathomimetic; binding to both α- and β-adrenoceptor) at 0, 3 and 10 mg/kg and or moxifloxacin (fluoroquinolone; inhibits DNA gyrase) at 0, 30 and 100 mg/kg. Telemetric data were continuously collected for 24 hours after each dose. Upon completion of the telemetry phase, a single dose of either 10 mg/kg etilefrine or 100 mg/kg moxifloxacin was administered followed by snapshot high definition oscillometry (HDO) BP, or restrained multi lead electrocardiogram measurements. Using the M11 technology, there was a dose-dependent increase in systolic (18 mmHg) and diastolic (9 mmHg) blood pressure as well as pulse pressure (9 mmHg) from 1 to 3 hours postdose, which was not detected by snapshot HDO BP in restrained animals. Moxifloxacin was associated with a dose-dependent QT and QT_{cl} (up to 14 msec) prolongation that was evident until 19 hours postdose, and also detected in restrained animals by snapshot multi lead ECG. PhysioTel™ digital M11 implants are considered a valid tool to evaluate drugs for potential cardiovascular (CV) liabilities in repeated dose toxicity studies. This technology also supports 3R improvements by eliminating jacket wearing and allowing group housing during data collection (Andersen et al. 2017).

Introduction

Currently, the minimally invasive jacketed external telemetry (JET/BP) is a commonly used approach to examine CV endpoints in nonhuman primate (NHP) toxicology studies, particularly for evaluating large molecule (e.g., mAbs) drug candidates. The JET/BP system requires minor surgery, acclimatization of the animals to the jacketing procedure, and staggered starts to avoid any crosstalk between implants, with the consequence of prolonged experimental periods. Moreover, JET /BP cannot be used in combination with continuous infusion; studies with juvenile NHP; if route of administration does not allow jacket wearing (e.g., intrathecal administration); or if the drug induces any kind of skin toxicity that would be amplified by the jacket wearing.

The purpose of this study was to evaluate the M11 implant with PhysioTel™ technology as a potential successor of JET/BP, avoiding the prescribed caveats.

Methods

Four healthy female cynomolgus monkeys of Asian origin (body weight range: 3.0 to 3.8 kg), were implanted with an M11 PhysioTel™ digital implant (size: 11 cm³; weight: 13.7g). The implant comprised one pressure catheter for measurement of systemic blood pressure that was inserted into the femoral artery; biopotential leads for ECG collections that were placed subcutaneously in a Lead II configuration, and temperature and activity sensors. The implant body was placed in between the abdominal muscle layers. Following a 21-day post-operative period, the animals were dosed according to the following study design with either etilefrine or moxifloxacin.

Drug 1 (Etilefrine)

Animal No.	Day of Dosing[a] Day 1	Day 4	Day 7
P0001	0 mg/kg	3 mg/kg	10 mg/kg
P0002	3 mg/kg	0 mg/kg	10 mg/kg
P0003	10 mg/kg	0 mg/kg	3 mg/kg
P0004	3 mg/kg	10 mg/kg	0 mg/kg

a For cardiovascular investigations.

Animal No.	Day of Dosing[b] Day 11
P0001, P0002, P0003, P0004	10 mg/kg

b For HDO BP.

Drug 2 (Moxifloxacin)

Animal No.	Day of Dosing[a] Day 15	Day 18	Day 21
P0001	0 mg/kg	30 mg/kg	100 mg/kg
P0002	30 mg/kg	0 mg/kg	100 mg/kg
P0003	100 mg/kg	0 mg/kg	30 mg/kg
P0004	30 mg/kg	100 mg/kg	0 mg/kg

a For cardiovascular investigations.

Animal No.	Day of Dosing[b] Day 24
P0001, P0002, P0003, P0004	100 mg/kg

b For Multi Lead ECG.

The telemetry data were continuously collected for 22 hours continuously (at least 2 hours predose and 20 hours postdose) at a sampling rate of 500Hz.

Following completion of the telemetric data collection, a single snapshot, restraint HDO BP was collected at predose, 1 and 24 hours after etilefrine dosing, and a snapshot multi lead electrocardiogram was collected at predose, 4 and 24 hours after moxifloxacin dosing. The study was performed in an AAALAC-accredited facility with protocols approved by IACUC.

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Results

In general, the M series ECG, the BP as well as the body temperature signals were of good quality as evidenced by the very low percentage of data loss (around 5%). After treatment with etilefrine, a clear dose-dependent increase in systolic, diastolic, and mean arterial pressures and pulse pressure was noted, indicating a maximum increase around 1 hour postdose, with the effect lasting until approximately 3 hours postdose, without any effect on heart rate. No changes in ECG parameters or body temperature were observed after treatment with etilefrine.

Systolic pressure was increased by 9 mmHg in animals administered 3 mg/kg and by **18 mmHg** in animals administered 10 mg/kg. Diastolic pressure was increased by 4 mmHg in animals administered 3 mg/kg and by 9 mmHg in animals administered 10 mg/kg. Mean arterial pressure was increased by 7 mmHg in animals administered 3 mg/kg and to **14 mmHg** in animals administered 10 mg/kg. Pulse pressure was increased by 5 mmHg in animals administered 3 mg/kg and by **9 mmHg** in animals administered 10 mg/kg (Tables 1 and 2, Figure 1; number in bold = significant at 5% level).

The increase in blood pressure could not be confirmed by the restrained snapshot HDO BP measurement, collected at 1 and 24 hours postdose (Figure 2). This further demonstrates the limitations of restraint procedures for cardiovascular measurements in NHP since the procedure curtains potential adverse effects.

A dose-dependent QT and QT_c prolongation was noted starting approximately 1 hour postdose and lasting until 19 hours postdose following oral moxifloxacin treatment, without any effect on BP or any other ECG endpoint. In addition, the heart rate was slightly decreased from 10 hours postdose (dark cycle). No effect was noted on body temperature.

The increase for the QT interval was 0 msec (0.5 to 3 hours postdose); 10 msec (3 to 7 hours postdose), 11 msec (9 to 13 hours postdose) and 8 msec (13 to 19 hours postdose after 30 mg/kg, and 14 msec (0.5 to 3 hours postdose); 23 msec (3 to 7 hours postdose), 32 msec (9 to 13 hours postdose) and 22 msec (13 to 19 hours postdose after 100 mg/kg. For the QT_{cl} interval, the increases were 4 msec (0.5 to 3 hours postdose); **9 msec** (3 to 7 hours postdose), **8 msec** (9 to 13 hours postdose) and 10 msec (13 to 19 hours postdose after 30 mg/kg, and **12 msec** (0.5 to 3 hours postdose); **14 msec** (3 to 7 hours postdose), 5 msec (9 to 13 hours postdose) and 1 msec (13 to 19 hours postdose after 100 mg/kg (Tables 3 and 4, Figure 3; number in bold = significant at 5% level).

Table 3. Summary of QT and Corrected QT (QT_{cl}) Intervals, Fitted Means (% Change from Control)

QT Interval Treatment	0.5 to 3hr	3 to 7hr	9 to 13hr	13 to 19hr
Control	228	248	278	287
30 mg/kg	228 (0.0%)	258 (4.1%)	289 (3.9%)	296 (2.9%)
100 mg/kg	242 (6.0%)	271 (9.2%)	310 (11.5%)	310 (7.7%)
QT_{cl} Interval Treatment	**0.5 to 3hr**	**3 to 7hr**	**9 to 13hr**	**13 to 19hr**
Control	259	258	267	265
30 mg/kg	263 (1.6%)	267 (3.5%)	274 (2.8%)	275 (3.6%)
100 mg/kg	271 (4.5%)	272 (5.4%)	271 (1.7%)	266 (0.3%)

hr = hours; QT_{cl} = Corrected QT Shading = Significant at 5% level.

Table 4. Summary of QT and Corrected QT (QT_{cl}) Intervals, Treatment Differences (from Control 95% Confidence Interval)

QT Interval Treatment	0.5 to 3hr	3 to 7hr	9 to 13hr	13 to 19hr
30 mg/kg	0 (-25, 25)	10 (-27, 47)	11 (-26, 48)	8 (-23, 40)
100 mg/kg	14 (-12, 39)	23 (-14, 60)	32 (-5, 69)	22 (-9, 54)
QT_{cl} Interval Treatment	**0.5 to 3hr**	**3 to 7hr**	**9 to 13hr**	**13 to 19hr**
30 mg/kg	4 (-3, 12)	9 (1, 18)	8 (1, 14)	10 (-10, 29)
100 mg/kg	12 (4, 19)	14 (5, 23)	5 (-2, 11)	1 (-18, 20)

hr = hours; QT_{cl} = Corrected QT Shading = Significant at 5% level.

The effects on QT and QT_{cb} were also confirmed by snapshot multi-lead ECGs collected at 4 hours postdose. The group mean QT interval was 153 msec before dosing, 172 msec at 4 hours postdose, and 157 msec at 24 hours postdose. The group QT_{cb} interval was 316 msec before dosing, 341 msec at 4 hours postdose, and 323 msec at 24 hours postdose. QT interval was increased by 19 msec, and QT_{cb} interval was increased by 25 msec at 4 hours postdose (Figure 4).

Discussion and Conclusion

For both reference compounds, the expected pharmacological activity was detected indicating either transient (etilefrine) or long lasting (moxifloxacin) effects.

Etilefrine, a potent sympathomimeticum, should induce vasoconstriction by binding to α-adrenoreceptor contributing to increased systemic blood pressure. In this study, the effect was recorded and was also comparable to recently completed study using JET/BP technology (Niehoff et al., 2014). However, it is currently unclear why heart rates were not increased, since etilefrine also should bind to β-adrenoreceptor causing increased heart rates and further contributing to increased blood pressure.

Moxifloxacin is a fluoroquinolone that inhibits DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication. The QT prolongation is most likely caused by blockage of the inward potassium rectifier (IKr) channel, also known as hERG. The magnitude of the QT and QT_{cl} prolongation following oral moxifloxacin administration in this project was as expected in cynomolgus monkeys and is comparable to previous studies (Holzgrefe et al., 2013).

In conclusion, the data suggested that the PhysioTel™ digital M11 system is capable of detecting potentially adverse or pharmacological effects on blood pressure, body temperature, and the electrocardiogram in conscious, freely moving cynomolgus monkeys, and also avoids some of the challenges of the JET/BP system, thus is considered a valuable successor.

Table 1. Summary of Blood Pressure Findings, Fitted Means (% Change from Control)

Treatment	Systolic 0.5 to 3hr	Diastolic 0.5 to 3hr	Mean 0.5 to 3hr	Pulse Pressure 0.5 to 3hr
Control	116	74	94	42
3 mg/kg	125 (7.3%)	78 (4.9%)	100 (7.2%)	47 (11.5%)
10 mg/kg	134 (15.7%)	83 (11.8%)	108 (15.3%)	52 (22.5%)

hr = hours. Shading = Significant at 5% level.

Table 2. Summary of Blood Pressure Findings, Treatment Differences (from Control 95% Confidence Interval)

Treatment	Systolic 0.5 to 3hr	Diastolic 0.5 to 3hr	Mean 0.5 to 3hr	Pulse Pressure 0.5 to 3hr
3 mg/kg	9 (-5, 22)	4 (-8, 15)	7 (-6, 19)	5 (-0, 10)
10 mg/kg	18 (5, 31)	9 (-3, 20)	14 (2, 27)	9 (4, 15)

hr = hours. Shading = Significant at 5% level.

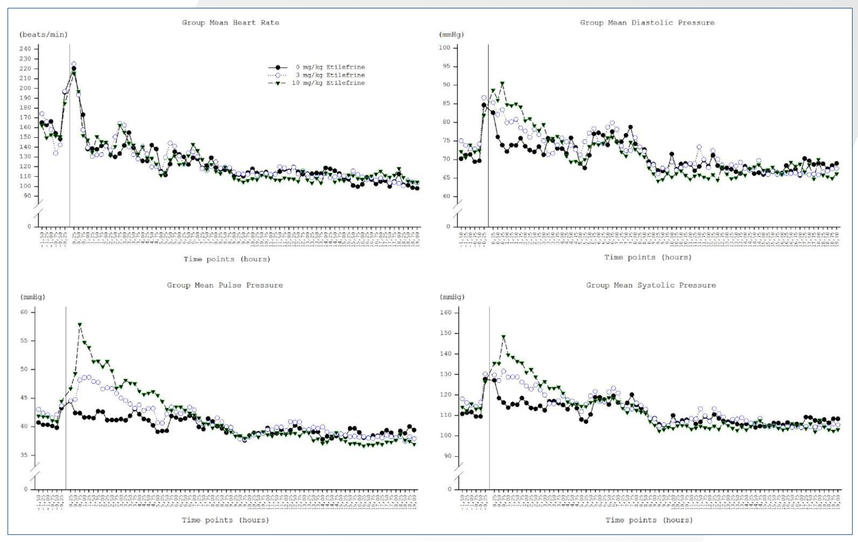

Figure 1. Group mean heart rate, systolic, diastolic and pulse pressure following oral etilefrine treatment. The vertical bar indicates the time of dosing.

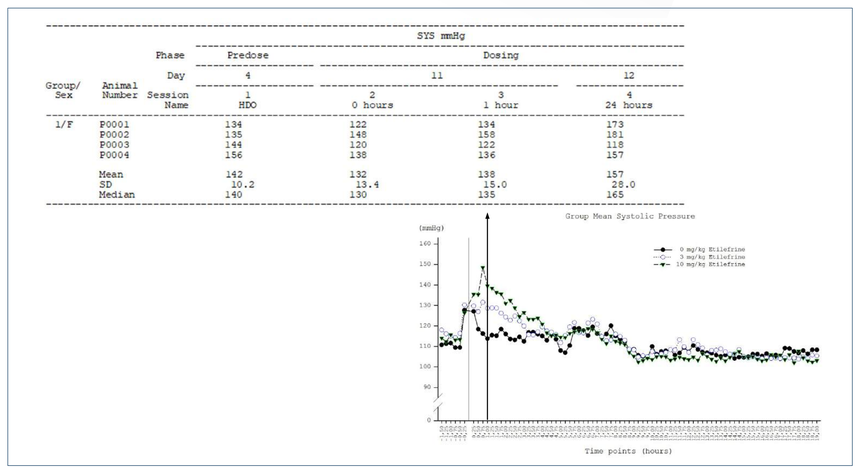

Figure 2. Group mean systolic blood pressure following oral etilefrine treatment. The vertical arrow indicates the time of HDO measurement.

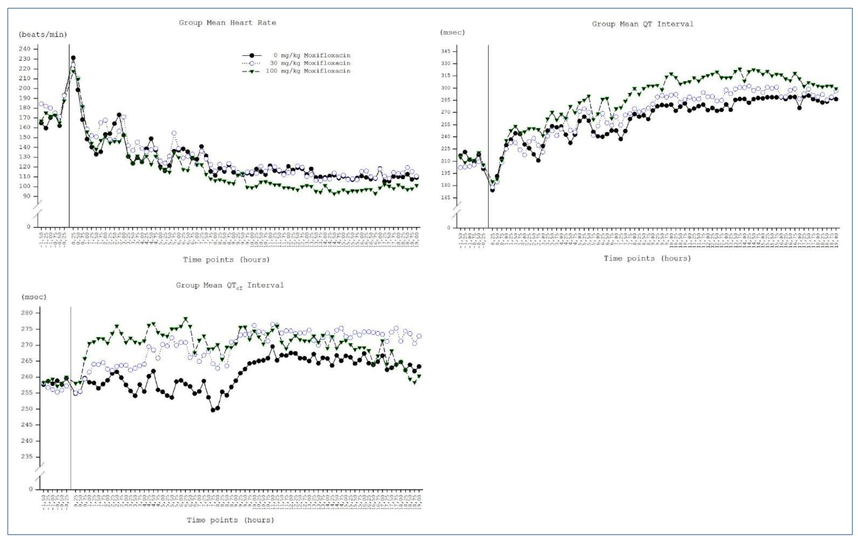

Figure 3. Group mean heart rate, QT and QT_{cl} interval following oral moxifloxacin treatment.

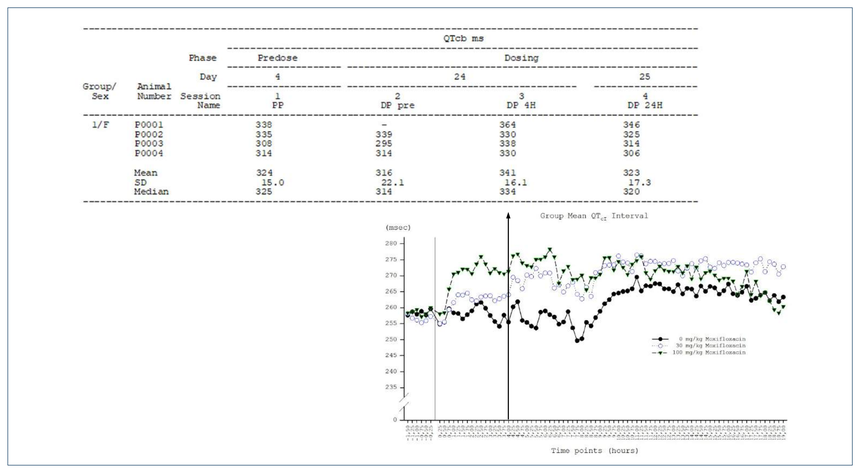

Figure 4. Group mean QT_c following oral moxifloxacin treatment. The vertical arrow indicates the time of multi lead ECG measurement.

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