

Evaluation of an Integrated Telemetry System (ITS) for Measurement of Cardiovascular and Respiratory Parameters in Cynomolgus Monkeys

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Introduction

The telemetric measurement of cardiovascular and respiratory parameters in conscious, freely moving animals is a pivotal component of safety pharmacology studies. Nonhuman primates are—among other species—one of the suggested species for *in-vivo* cardiovascular studies.¹ It is well known that heart rates as well as blood pressure values are different when measured in freely moving versus restrained and/or in anaesthetized animals. Hence, data obtained by telemetry are considered to reflect the physiological condition.² Although it is well known that monkeys in particular are promptly excited when restrained for any examination (e.g., ECG measurement) that may cause numerous physiological reactions and preclude the collection of scientifically reliable data,³ very little is known about the impact of the different housing conditions in terms of cardiovascular or respiratory values. The ITS system allows measurement of biopotential signals with full analysis including QTc in even group-housed animals due to advantages of multiple transmitter frequencies.⁴ Therefore, the aim of this study was twofold: first, to evaluate the ITS system for the measurement of aortic blood pressure, ECG waveforms, body temperature and intrathoracic pressure (ITP) using different reference compounds, and second, to compare the effects of individual and pair housing on cardiovascular and respiratory parameters.

Material and Methods

Two mature male cynomolgus monkeys (>6.0 kg) were dosed with the reference compounds (dl sotalol, chlorpromazine and theophylline given orally; ketamine given intramuscularly) on two consecutive days after saline administration acting as the corresponding vehicle (Table 1). Data were collected 2 hours at predose and 15, 30, 45, 60, 90 and 120 minutes post-dose, and then in hourly intervals for a total post-dose data collecting period of 6 hours using a 60-seconds data logging rate. In addition, the heart rate, mean arterial blood pressure and respiratory rate were measured when the animals were single-housed without (session 1) or with (session 2) visual contact, pair-housed (session 3) and isolated again (session 4). Each session consisted of a 3-day period and data were collected for 22 hours on each day.

Results and Discussion

Ketamine (20 mg/kg/day) when given intramuscularly caused a marked decrease in body temperature with a maximum (app. 5%) decrease at 60 minutes post-dosing on both occasions (Figure 1). Maximum ITP was also reduced in both animals whilst the animals were asleep (Figure 2), whereas the heart rate and blood pressure were not affected. Heart rates were markedly reduced, coupled with prolonged QT_c intervals in both animals and on both occasions after oral Sotalol (10 mg/kg/day) administration showing a maximum peak at 120 minutes post-dosing (Figures 3 and 4). Furthermore, there was a decrease in mean arterial blood pressure (MAP), but no changes in body temperature and ITP were observed (Figure 5). Chlorpromazine given orally at 25 mg/kg/day induced a moderate decrease in respiratory rates in combination with an increase in min. and max. ITP indicating an overall “tranquillized” breathing pattern (Figure 6). Oral theophylline treatment at 20 mg/kg/day elicited no effect that can be assumed as being drug related. However, in recently published studies theophylline was administered intravenously, which may have caused the difference to our unexpected results.⁵

The heart rates were lower when animals were allowed to have visual contact respectively pair-housed in comparison to animals that were isolated (Figure 7). There was also a trend toward reduced respiratory rates, indicating a “calmer” breathing pattern in pair-housed animals (Figure 8). Although there was no effect on MAP (Figure 9), the findings in heart rate as well as in the respiratory rate indicated an overall lower stress level in pair-housed animals rather than in singly housed animals.

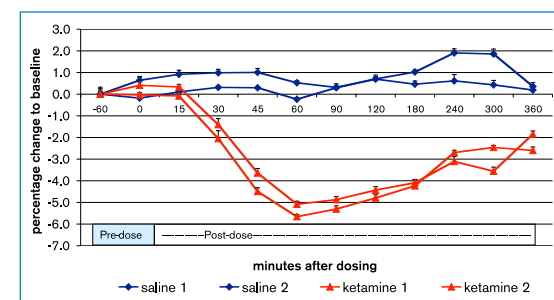


Figure 1. Body temperature of animal 20917 M following saline (blue) or ketamine (red) administration. Data are shown as mean +/- standard deviation.

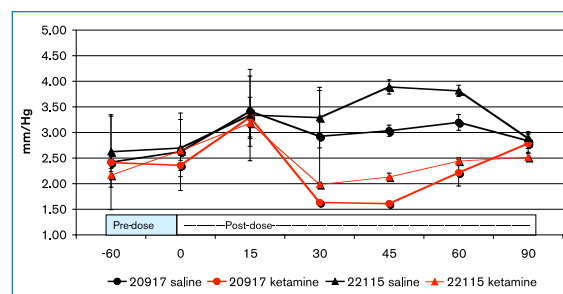


Figure 2. Maximum ITP following saline (black) or ketamine (red) administration. Data are shown as mean +/- standard error.

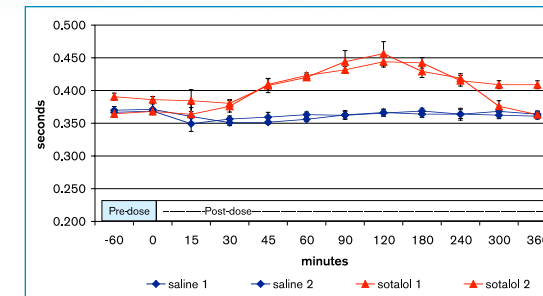


Figure 3. QT_{cB} interval for animal 20917 M after saline (blue) and sotalol (red) administration. Data are shown as mean +/- standard deviation.

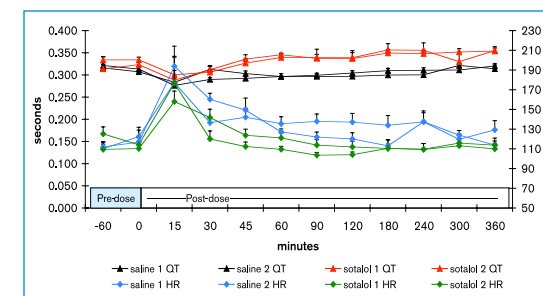


Figure 4. QT_{cF} interval and heart rate for animal 22115 M following saline (black/blue) and sotalol (red/green) administration. Data are shown as mean +/- standard deviation.

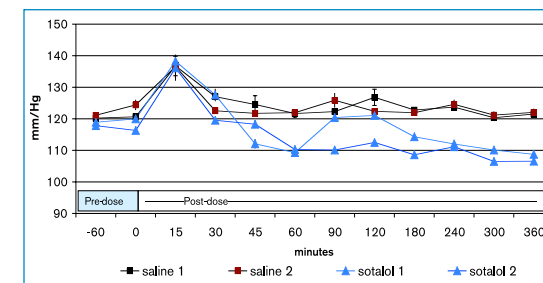


Figure 5. MAP for animal 20917 after saline (black) or sotalol (blue) administration. Data are shown as mean +/- standard error.

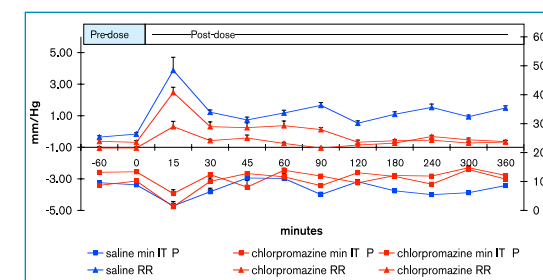


Figure 6. Mean ITP from animal 22115 after saline (blue) or chlorpromazine (red) administration. Data are shown as mean + standard error.

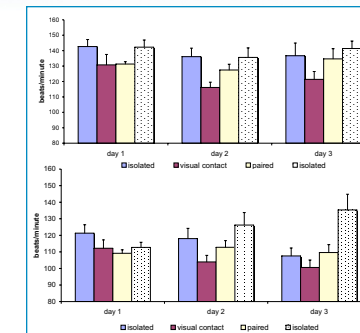


Figure 7. Mean heart rate from animal 20917 (above) and 22115 (below). Data are shown as mean + standard error.

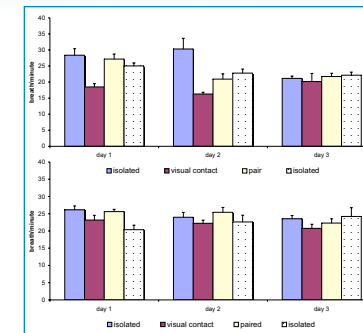


Figure 8. Mean respiratory rate from animal 20917 (above) and 22115 (below). Data are shown as mean + standard error.

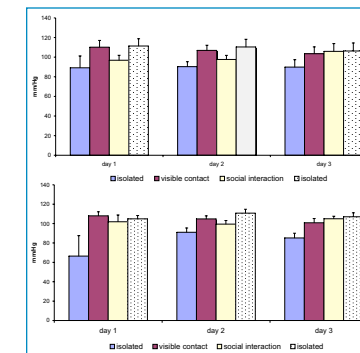


Figure 9. MAP from animal 20917 (above) and 22115 (below). Data are shown as mean + standard error.

Conclusion

The ITS system is a valid tool to monitor cardiovascular and respiratory parameters in conscious freely moving and group-housed cynomolgus monkeys. In addition, the data suggest that visual contact as well as pair-housing are linked to overall lower heart and respiratory rates in comparison to single-housed animals and thus providing scientifically more reliable results.

References

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Part	Number of Animals	Males	Compound	Route	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dosing Volume (mL/kg)
A	2		Saline	i.m.	0.0	0.0	0.2
A	2		Saline	i.m.	0.0	0.0	0.2
A	2		Ketamine	i.m.	20.0	100.0	0.2
A	2		Ketamine	i.m.	20.0	100.0	0.2
B+C+D	2		Saline	oral (gavage)	0.0	0.0	10.0
B+C+D	2		Saline	oral (gavage)	0.0	0.0	10.0
B	2		Sotalol	oral (gavage)	10.0	10.0	1.0
B	2		Sotalol	oral (gavage)	10.0	10.0	1.0
C	2		Chlorpromazine	oral (gavage)	25.0	2.5	10.0
C	2		Chlorpromazine	oral (gavage)	25.0	2.5	10.0
D	2		Theophylline	oral (gavage)	20.0	2.0	10.0
D	2		Theophylline	oral (gavage)	20.0	2.0	10.0



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