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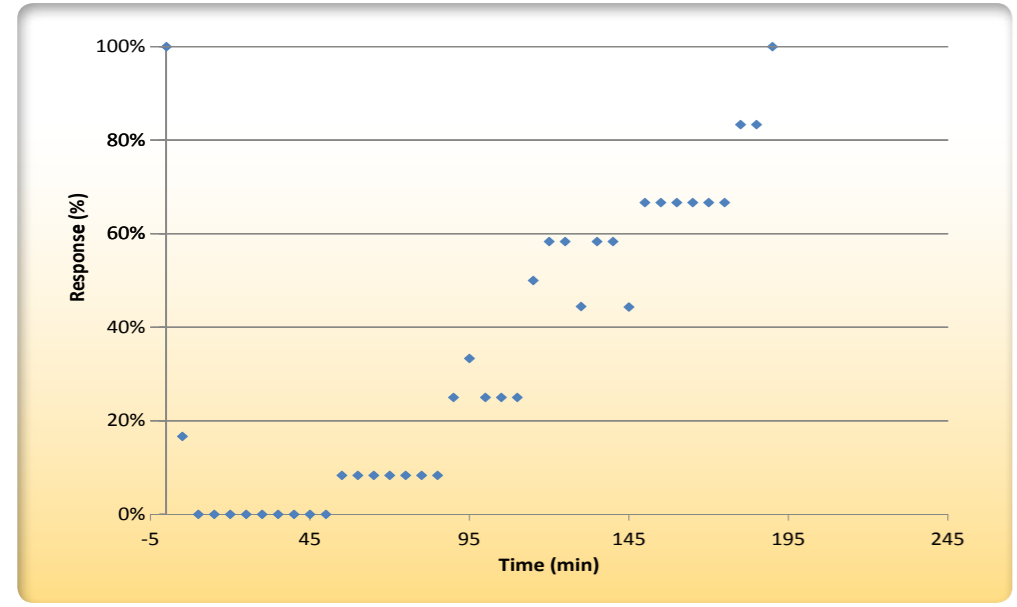
Introduction

The Göttingen minipig has become a routinely used species in regulatory toxicology. Many similarities between humans and minipigs justify the use of this species for non-clinical safety assessments. In the context of safety pharmacology core battery, cardiovascular (telemetry), respiratory (spirometry) and neurological (functional observation battery) investigations were conducted in Göttingen minipigs with various positive control drugs.

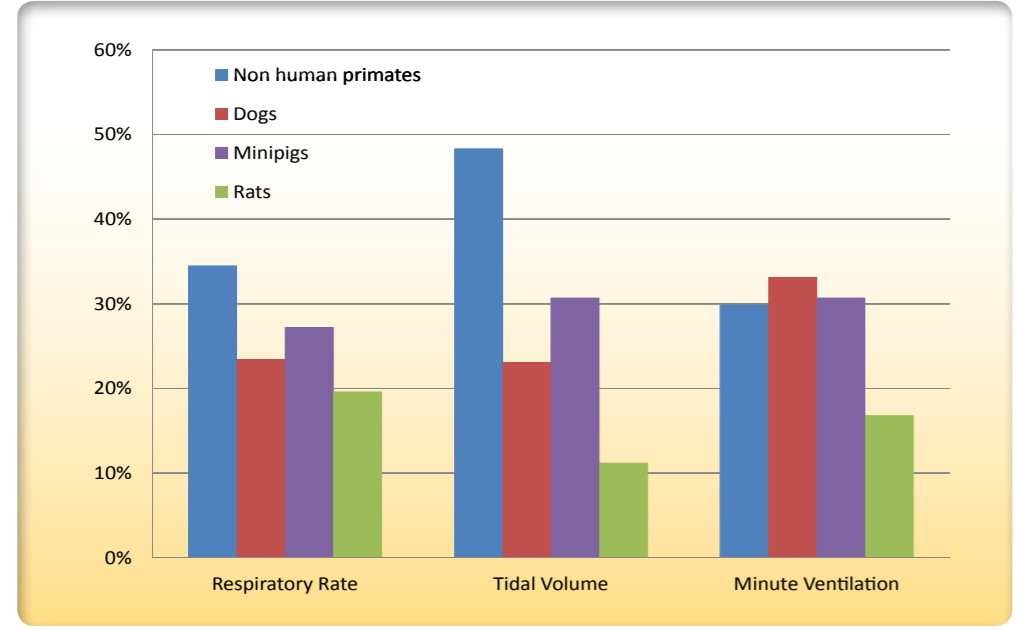
Materials and methods

Cardiovascular modulators (dopamine, remifentanyl, esmolol, medetomidine and sotalol) were administered to freely moving animals monitored by telemetry (Data Science International). Intravenous methacholine was used as a respiratory modulator and respiratory function was monitored with a pneumotachometer (SCIREQ Respiratory Equipment). Ketamine, propofol, amphetamine and xylazine were used as positive control drugs for neurological evaluations.

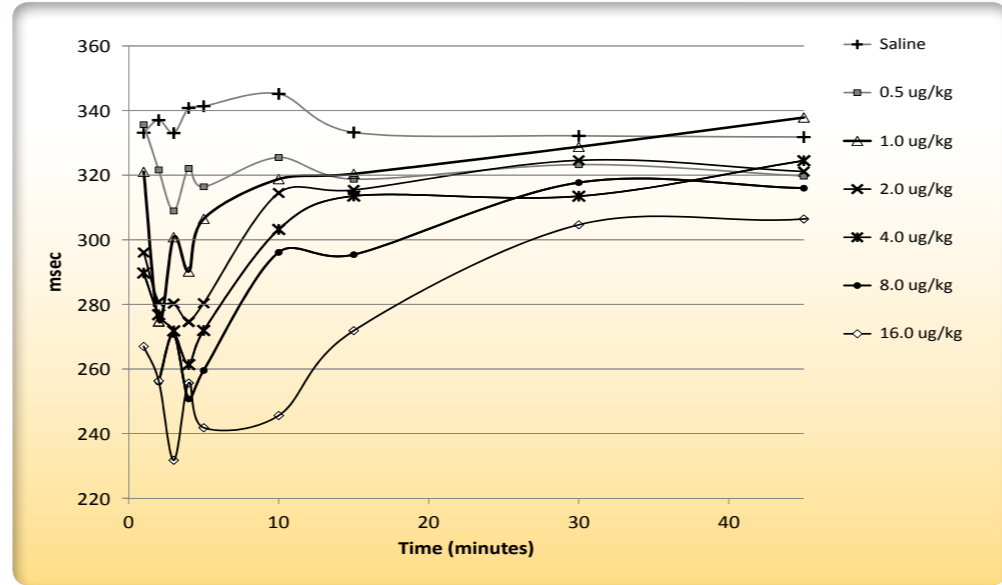
Results



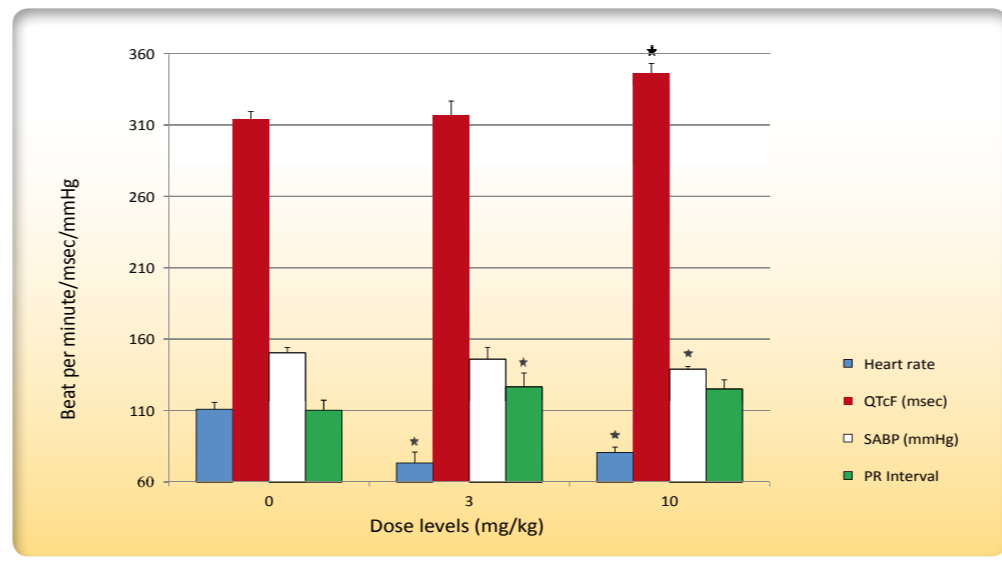
Spinal Segmental Reflex (Withdrawal) after ketamine (10 mg/kg, IM) Göttingen Minipigs (n=4)



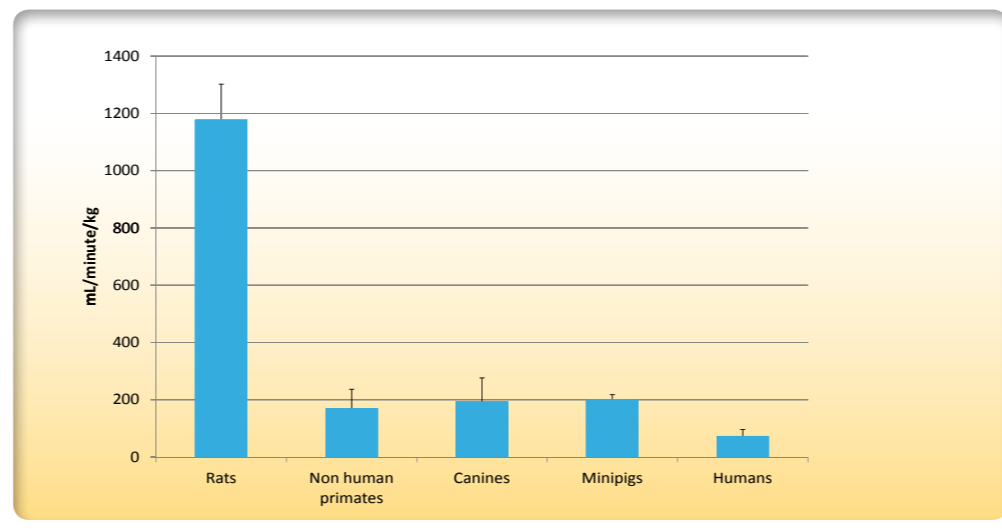
Minimum detectable difference with 5 min average (n=8)



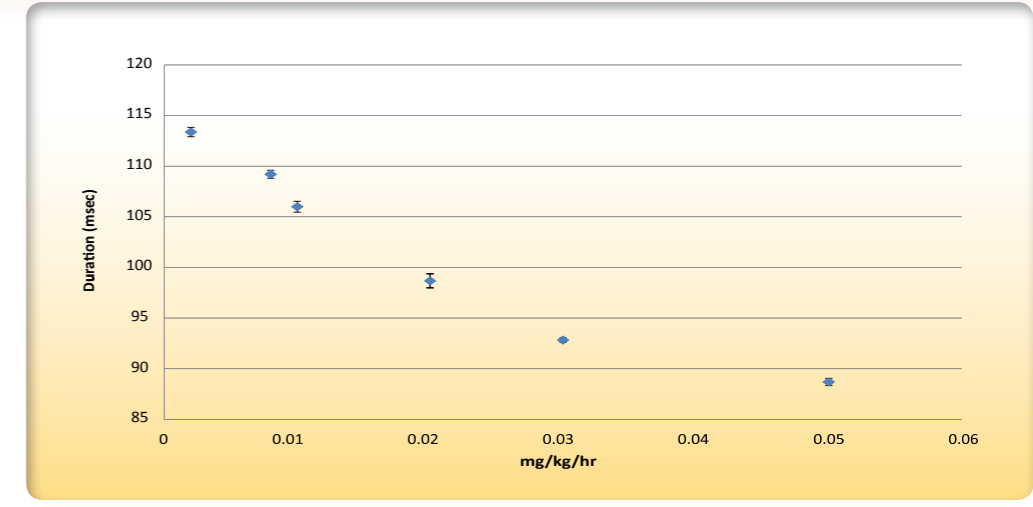
QTcF in Göttingen minipigs after remifentanyl administration (n=4)



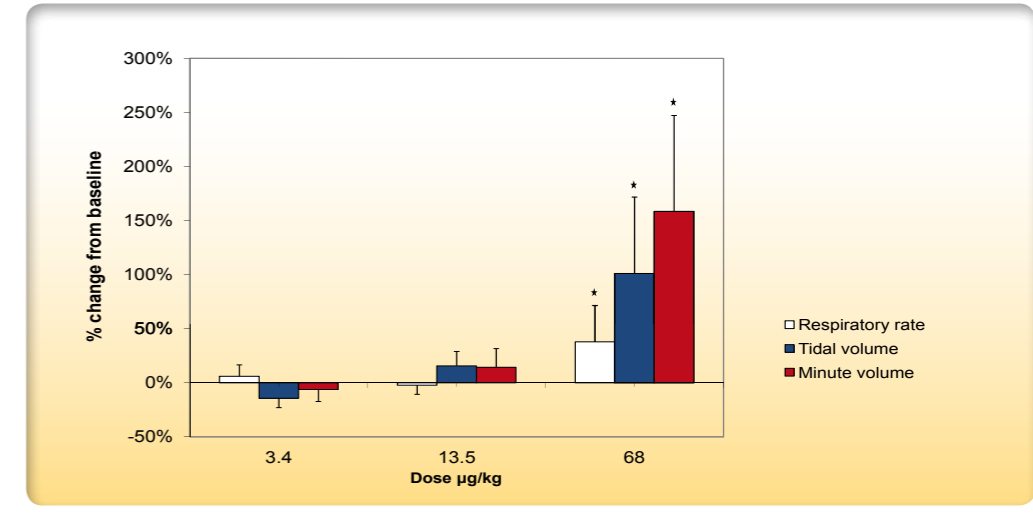
Effect of oral sotalol in Göttingen minipigs (n=4) * p<0.05



Baseline minute volume in various species



Effects of dopamine infusion on QA interval in conscious Göttingen minipigs (n=4)



Effects of methacholine (IV) in Göttingen minipigs (n=6) * p<0.05

Functional Observation Battery		Test of cranial nerve function	Cochlear nerve evaluation
Body temperature	General observation	Menace response	Olfactory nerve evaluation
Mental status	Mental status	Pupil light response direct	Jaw tone
Head posture	Head posture	Pupil light response consensual	Facial sensory examination
Motor activity	Motor activity	Pupil size and symmetry	Facial symmetry
Coordination	Coordination	Ocular position	Gag reflex
Stance	Stance	Ocular motility	Tongue function
Gait	Gait	Oculovestibular reflex	Spinal Segmental reflexes
Circling	Circling	Palpebral reflex	Perineal reflex
		Pathologic nystagmus	Withdrawal (interdigital skin)
			Triceps/Patellar

Discussion

The minipig has gained increasing acceptance as a non-rodent species for regulatory toxicology studies. Our results illustrate cardiovascular, respiratory and neurological evaluations which can be conducted to fulfill ICH S7A requirements as part of safety pharmacology core battery testing. The minipig is recognized as a valuable model for dermal administration but this species may also be justified for oral, subcutaneous, IV injection or infusion toxicology studies.

Conclusion

In conclusion, our results suggest that the Göttingen minipig is a suitable species to fulfill all aspects of the safety pharmacology core battery.