The Göttingen Minipig in Cardiovascular Safety Pharmacology

– The Anaesthetised Minipig Model at Nycomed

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Minipigs are widely used in cardiovascular sciences as research and treatment models for cardiovascular diseases, but also for cardiovascular safety investigations of potential new drugs.

The most important guidelines for non-clinical safety pharmacology studies, ICH S7A [1] and S7B [2], propose minipigs as a relevant laboratory animal species for *in vivo* cardiovascular studies. Although the use of conscious animals is preferred by the guideline S7A, the guideline S7B also mentions anaesthetised animal models as adequate or even useful in certain circumstances. The benefits of anaesthetised models include a reduction of heart rate variability and better signal quality with fewer artefacts caused by movement. Additionally, more precise and sophisticated safety margins can be determined by dosing high amounts of the test compound without any harm to the animals.

At Nycomed, an anaesthetised minipig model has been used for cardiovascular safety pharmacology investigations for several years. It is a highly standardised test system and is also accepted for GLP-compliant studies by the authorities. Therefore, it is routinely used in the candidate phase of potential new drugs just before the first human clinical trial is conducted, but it can also be useful for specific scientific questions in earlier drug-development phases.

Generally, six female Göttingen Minipigs weighing between 9 and 12 kg are used. Anaesthesia is induced by a facemask using isoflurane and maintained by continuous infusion of propofol. Buprenorphine serves as an analgesic. Animals which stop breathing spontaneously are mechanically ventilated with oxygen and compressed air.

The compound is administered as an intravenous infusion over a period of 15 minutes into the right femoral vein, followed by a wash-out period of 30 minutes. This enables the effect of different doses of the compound to be tested on just one animal. The investigation starts with an infusion of the vehicle and is followed by 4–6 different doses using an ascending dosing regimen.

Blood pressure is measured by a microtip catheter, which is placed in the abdominal aorta via the left femoral vein. The pressure in the left ventricle of the heart is measured by a microtip catheter placed in the left ventricle via the left carotid artery. Pulmonary arterial pressure is measured by a balloon catheter positioned in the pulmonary artery through the left external jugular vein and via the right heart. For acquisition of a surface ECG (6 leads corresponding to the triangular Nehb-Spörri and modified Goldberger leads), three needle electrodes and one adhesive electrode pad on the back of the animal were used. The arterial blood pressure signal, left ventricular pressure signal, pulmonary arterial pressure signal and ECG are continuously recorded using a validated computerised system for cardiovascular studies.

At predetermined time points, values for systolic and diastolic blood pressure (SAP, DAP), heart rate (HR), left ventricular pressure (LVP), maximum rate of left ventricular pressure rise (dp/dtmax) and pulmonary arterial pressure (PAP) are derived from the respective pressure signals and an average of 1 minute is calculated for each parameter.

ECG intervals are measured in the axial lead of the Nehb-Spörri leads and average values of 10 beats are calculated at predetermined time points. Furthermore, the ECG is examined visually over the entire acquisition period to monitor the number of extrasystoles, arrhythmias and other changes.

The physiological variation of cardiovascular parameters within a study design as described above was illustrated by repeated intravenous infusion of 0.9% (w/v) aqueous NaCl solution. For instance, when compared to the pre-dose value, changes in mean heart (HR) rate did not exceed ±21%; changes in mean systolic arterial blood pressure (SAP) did not exceed ±13%; and changes of ECG-intervals did not exceed ±10% over the entire acquisition period.

Several reference compounds with known effects on the cardiovascular system were used to validate the anaesthetised minipig model. As a consequence of its b-adrenoceptor agonistic properties, isoprenaline caused a rapid, infusion-dependent stimulation of heart rate (figure 1) and contractility as well as a drop in blood pressure (figure 2). Sotalol, an antiarrhythmic drug known to prolong the QT-interval and to potentially cause torsade de pointes, prolonged the QT-interval in a dose-dependent manner. This prolongation could also be verified after correction for the heart rate by the formulas according to Bazett (QTc-B, figure 3) and Fridericia (QTc-F, figure 4).

All in all, the anaesthetised minipig model, as described in this article, provides reliable and reproducible results. It is an excellent, guideline-compliant animal model for cardiovascular safety pharmacology investigations.

FIGUR 1

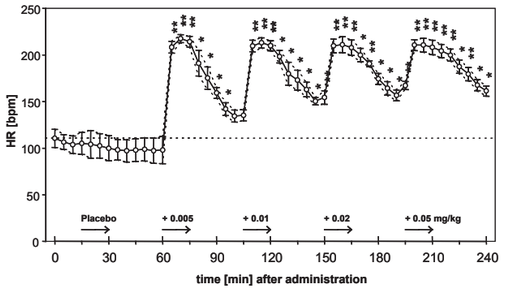

*Figure 01: Effects of isoprenaline on mean heart rate [bpm]: Mean ± SEM, pre-dose mean as bar, n= 4, paired t-test (two-sided), *, **, *** : p<=0.05, 0.01, 0.001 (changes to pre-dose values)*

FIGUR 2

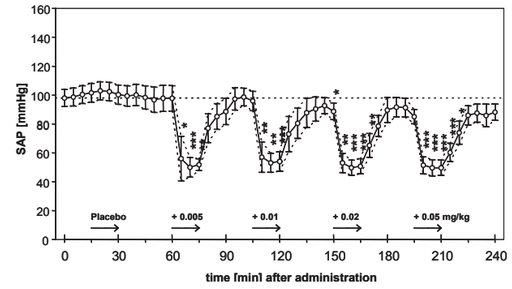

*Figure 02: Effects of isoprenaline on mean SAP [mmHg]: Mean ± SEM, pre-dose mean as bar, n= 4, paired t-test (two-sided), *, **, *** : p<=0.05, 0.01, 0.001 (changes to pre-dose values)*

FIGUR 3

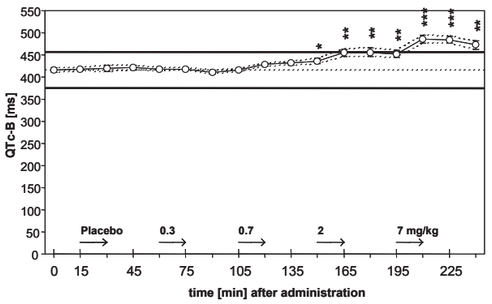

*Figure 03: Effects of sotalol on mean QTc-B [ms]: Mean ± SEM, pre-dose mean and ± 10% as bars, n= 5, paired t-test (two-sided), *, **, *** : p<=0.05, 0.01, 0.001 (changes to pre-dose values)*

FIGUR 4

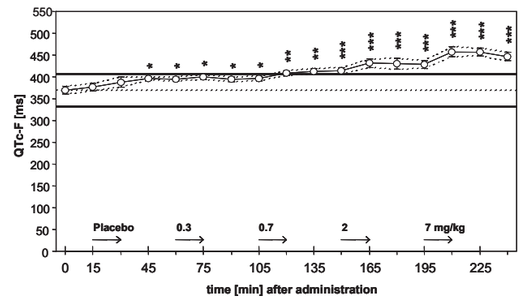

*Figure 04: Effects of sotalol on mean QTc-F [ms]: Mean ± SEM, pre-dose mean and ± 10% as bars, n= 5, paired t-test (two-sided), *, **, *** : p<=0.05, 0.01, 0.001 (changes to pre-dose values)*

REFERENCES

[1] **Guidance for Industry:** ICH S7A Step 4: Safety Pharmacology Studies for Human Pharmaceuticals. 8 November, 2000

[2] **Guidance for Industry:** ICH S7B Step 4: The nonclinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals. 12 May, 2005