stability and fidelity of the signals were excellent over time. When rats were resting quietly, a strong respiratory rhythm was seen in both signals. At the end of the study, the rats were lightly anesthetised with isoflurane and subjected to a head up and head down tilt tests to 45° resulting in reversible decreases and increases of ICP as expected. No visible damage from the ICP catheter was found on the brain surface at post-mortem.

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0102

Evaluation of cardiac electrophysiology (ECG), heart rate and index of cardiac electrophysiological balance (iCEB) during basal condition in awake telemetered and anesthetized guinea pigs

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The guinea pig in general is a sensitive but predictive species for investigating electrophysiological effects of a compound, as it possess specific ion channel expression profile similar to a human (except maybe for I_{to}). Therefore, anesthetized and awake guinea pig models are frequently used for cardiovascular safety assessment. ICHS7A guideline recommends the use of awake animals; however, revised ICHS7B guideline valued the use of anesthetized animals use. The aim of the present study was to evaluate ECG, heart rate and iCEB (a new biomarker to predict cardiac arrhythmia) during basal condition in awake and anesthetized guinea pigs to distinct the effect of anesthesia in these parameters. In pentobarbital-anesthetized female guinea pigs needle electrodes were attached for the recording of the surface ECG and heart rate. Another set of female guinea pigs were chronically implanted with telemetry transmitter (DSI-TA11CTA-F40) under ketamine, medetomidin anesthesia and after recovery period were used for subsequent recording of ECG and heart rate. New biomarker iCEB was calculated for both anesthetized and awake guinea pigs as a ratio of QT to QRS interval. Compared to awake guinea-pigs, QT/QTc-interval was significantly prolonged in pentobarbital anesthetized guinea pigs (281 ms versus 342 ms respectively; p < 0.05). It was observed that anesthesia displaces the QT-interval versus RR-interval curve upwards. Compared to awake guinea pigs heart rate and iCEB were significantly higher in anesthetized guinea pig (212 and 4.85 versus 237 and 6.04 respectively; p = 0.05). The present study demonstrates longer QT-intervals and increased iCEB in anesthetized rather than awake guinea pigs, and pentobarbital-mediated QT-prolongation displaces the QT and RR-interval logarithmic relationship without changing the slopes.

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0103

Quantified electroencephalography (QEEG) in safety pharmacology

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Quantified electroencephalography (QEEG) is a highly relevant translational technique able to measure the global effects of drugs on brain electrical activity. The aim of this study was to investigate the effects of four drugs with well-known side-effects, scopolamine, clozapine, ketamine and amphetamine on EEG in the conscious rat.

Fourteen telemetered rats were implanted with two surface electrodes over the frontal-parietal cortex. After post-surgical recovery, animals were administered with vehicle or a drug and EEG was recorded over 60 min, starting 15 or 30 min after systemic injection. The differences of the spectral power between vehicle and the different treatments were assessed for each frequency band.

Scopolamine (0.5 mg/kg) clearly increased theta and alpha frequencies over 60 min with similar effects on delta frequencies from 0 to 10 min. A significant increase of alpha and beta frequencies was observed with clozapine (2 mg/kg). Ketamine (30 mg/kg) globally increased total spectral power with marked effects on delta, beta and gamma frequencies. Amphetamine (4 mg/kg) tended to increase alpha frequencies but significantly decreased beta to gamma frequencies.

The increase of slow waves (delta to theta) potentially relates to the amnesic effects reported for scopolamine. Hyperactivity induced by amphetamine or ketamine potentially relates to the increase of theta to beta frequencies. An increase of intermediate frequencies is characteristic of a sedative-like effect, as observed with clozapine on beta frequencies.

These results suggest that QEEG is a sensitive and reliable translational tool to predict potential adverse effects induced by new compounds on the central nervous system.

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0104

A preload and lusitropy corrected dP/dt_{max}-derived index of contractility: Evaluation in telemetered beagle dogs treated with amrinone

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Assessment of inotropy for vaso-active compounds remains equivocal under current paradigms that employ left-ventricular pressure (LVP) derived indices as markers of contractility. For instance, the peak rate-of-rise of the LVP during systole (dP/dt_{max}) is known to be preload-dependent. This study aimed to develop an LVP-based index of contractility showing blunted sensitivity to compound-induced changes in myocardial loading.

Eight dogs (13 ± 2 kg) were chronically instrumented (via a left-thoracotomy) for the telemetered monitoring of an ECG and LVP. The animals received four doses of amrinone (0, 0.5, 2, and 5 mg/kg PO). Beat-to-beat LV hemodynamic/mechanical indices were derived at two 90-minute epochs taken before and 3-hours post-treatment. Four preload-adjusted indices were evaluated: the LV triple-product (TP) and dP/dt_{max} values normalized by either the absolute (TP/EDPc) or the lusitropy-corrected end-diastolic pressure (TP/EDPc and dP/dt_{max}/EDPc); for the purposes of this study, the time-constant of LV relaxation (tau) was used to correct EDP for changes in lusitropy (i.e., EDPc = EDP/tau).

Amrinone triggered dose-dependent reductions in LV filling pressures (EDP: 0 ± 6, −9 ± 4, and −24 ± 5 %) while dP/dt_{max} increased post-treatment at all doses (8 ± 2*, 12 ± 3*, and 14 ± 5 *%); however, a clear dP/dt_{max} dose-dependent change was not noted. Contrastingly, all preload-corrected indices, both lusitropy-adjusted (dP/dt_{max}/EDPc;
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