Title: Investigation of sparse clinical sampling in light of baseline oscillations and between-individual variability using pharmacokinetic/pharmacodynamic modelling

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Introduction: Cortisol exhibits a circadian rhythm in horses. It is a well-known biomarker that is suppressed by dexamethasone. A sampling protocol of cortisol with one pre- and one post drug administration sample is used in dexamethasone suppression tests. However, diurnal fluctuation and inter-individual variation may hamper the utility of test results. The aim of this study was to quantify the determinants of baseline fluctuation and between-individual and between-occasion variability for guidance of an improved test protocol.

Materials and methods: A meta-analysis was done on published dexamethasone and cortisol time series by means of non-linear mixed effects modelling. Cortisol response was described by a turnover model of oscillating behaviour coupled to an inhibiting function. Model parameters were average baseline (k_{avg}), amplitude (α), phase shift (t_0), fractional turnover rate (k_{out}), maximum suppression (I_{max}), potency (IC_{50}), and Hill coefficient (n). Random effects were introduced on all parameters except I_{max} and n, to model variability between individuals and k_{avg} was modelled to vary between occasions. To adjust for a transient pre-estimation period, initial model conditions were calculated analytically. The performance of the test-protocol was studied by calculation of the probability that cortisol is suppressed below a specific threshold. Probabilities were predicted by model simulations at i.v. dexamethasone doses between 0–60 µg/kg.

Results: Model accuracy was verified using posterior predictive checks. The model mimicked experimental data well. Parameter precision expressed as relative standard deviation was less than 25% except for IC_{50} (∼40%). Variance parameters were estimated with precision 22% for k_{avg} and between 30% and 72% for remaining variables. Variability and magnitude of average cortisol baseline and amplitude were both shown to be suppressed for increasing dexamethasone concentrations. Successful suppression of the cortisol response below the threshold was predicted to 0%, 50%, 80%, 90%, and 95% at 0, 12, 28, 43, and 60 µg/kg dexamethasone, respectively.

Conclusions: Increased cortisol suppression and lowered variability with higher doses increased the probability of a reliable test-result. However, the protocol result in false positive reports in a small fraction of healthy horses.