Prospective Optimisation of Screening Experiments for Pain Compounds

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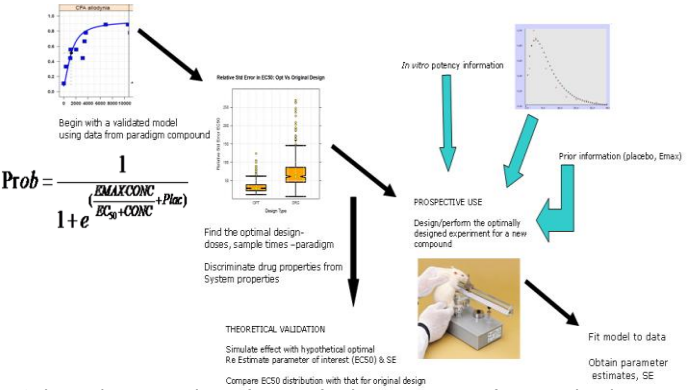
Introduction & Aim

Experimental protocols in pain research are usually based on empirical criteria. Screening of compounds relies on accurate ranking of their pharmacokinetic and pharmacodynamic properties. A model-based approach for the analysis of such experiments is desirable, but time consuming. In the current investigation, we apply robust ED-optimality in a prospective setting for a new chemical entity (NCE) wherein prior information from a paradigm compound is used to optimise the study design, and thereby accurately estimate the parameter of interest (EC50).

Materials and Methods

Fig1:The steps for experimental design optimisation are outlined in the flow chart below.



Gabapentin was used as reference for the assessment of prospective data on the effects of pregabalin. Pain response is dichotomised and a logistic regression model is applied under the assumption that EC50 is the only unknown parameter. Initial estimates for the NCE were based on an in vitro potency ratio of 2:1. The design variables for optimisation were PK sampling times and doses. Uncertainty of 50% was assumed for the between-subject variability as well as for the EC50. The designs were validated using stochastic simulations and estimations (SSE) (n=500). The precision (root mean squared error-RMSE) and bias (mean prediction error-MPE) of parameter estimates for standard and optimised protocol designs were then compared as were the simulated PK~TIME profiles of each design. A nonparametric bootstrap was performed using both designs to obtain the confidence intervals for EC50. POPED 2.10/ MATLAB 7.9 were used for the optimisations, and NONMEM 6 for simulation.

Results

Fig 2: Viusal predictive check of model according to the typical screening design. Doses tested include placebo, 10, 30 and 100 mg/kg pregabalin. For this diagnostic, a simulated probability of ≤0.5 was defined as a response to treatment and >0. 5 a treatment failure.

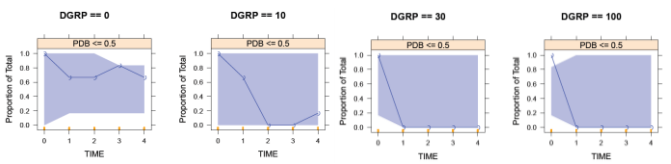
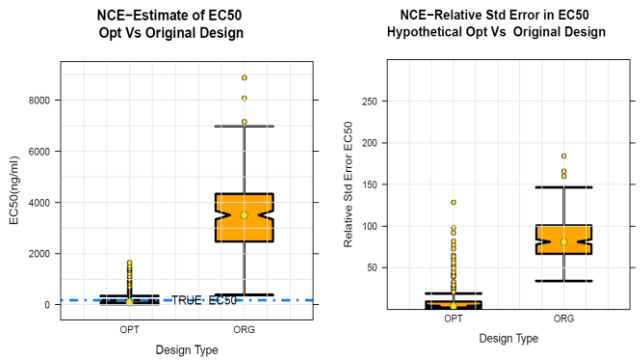
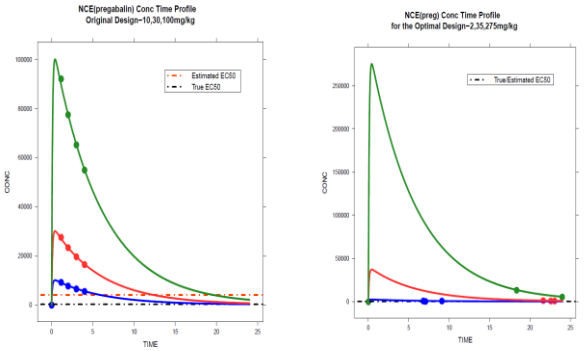


Fig. 3: Comparison of the parameter (EC50) estimate and the corresponding relative standard error (RSE) for the optimised and original designs.



The RMSE for the original vs. optimal design was 38.25 & 18.01% respectively. The MPE was 67.23 & 5.60% for the two designs. As can be seen from the simulated CONC~TIME profiles and the corresponding sampling times in Fig. 4, EC50 cannot be accurately estimated based on a typical protocol design .

Figure 4. Simulated PK profiles for the typical (left) and hypothetical optimal (right) design during the evaluation of a new compound. Information collected in a typical experiment does not take into account the concentration range corresponding to EC50.

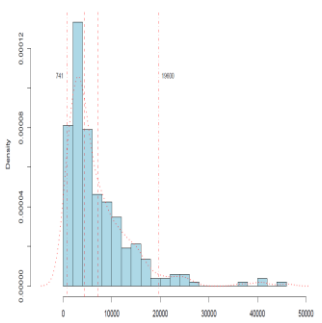


Sampling times for the original design are the same for each dose group, whilst for the optimal design these vary per dose group. EC50 estimate for the original design was 4000 ng/ml. In contrast, based on an optimised design, EC50 was found to be 80 ng/ml. The true (nominal) EC50, as determined by the differences in in vitro potency, was assumed to be 109 ng/ml.

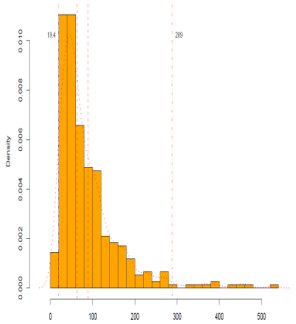
Figure 5 below shows the frequency distribution (2.5-97.5% Confidence Interval-CI) of the EC50 estimates for n=500 bootstrap runs. The EC50 (ng/ml) values are presented on the X axis and the Y axis represents the density of the frequency distribution. A wide range is observed for the original design (CI: 741,19600 ng/ml). Optimisation procedures clearly improve parameter precision and accuracy (CI: 19.4, 289 ng/ml) .

Fig 5: bootstrap of original vs. optimal design. Note wide differences in the x-axis.

EC_{50} density with original design



EC_{50} density with optimal design



Discussion

Empirical protocols can often lead to biased estimates and inaccurate ranking of candidate molecules. The high standard errors and wide confidence intervals are the consequence of arbitrarily chosen sampling times, which ignore the range of observations relevant for accurate estimation of the parameter of interest.

We assumed that the true EC50 was known from in vitro data and optimised the design with 50% uncertainty. Despite uncertainty, the optimal design performed better than a typical protocol. It should be noted that PD measurements were considered uncorrelated for the purposes of our analysis. Correlations could not be tested due to large noise and wide intervals between successive measurements.

Our analysis demonstrate the implications of empirical design in drug screening, when decisions about the progression of a molecule and subsequent dose selection rely on the accuracy of EC50 estimates. The use of ED-optimality concepts is critical to support the design of more informative experimental protocols in pain research, taking into account uncertainty.

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