Adaptive experimental design in early clinical trials

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Abstract

Phase I clinical trials are the first studies to test new drug candidates in humans. The main objectives of these trials are to estimate pharmacokinetic (PK) parameters and to determine an optimal dose for further exploration in Phase II. Although both these experimental issues have attained a lot of attention in the relevant literature, majority of the contributions treat the dose-finding and the PK studies as separate experimental tasks. There are some attempts to incorporate the PK data into the dose escalation clinical trial designs, cf. Piantadosi and Liu (1996), but only in order to increase the quality of a dose-response model.

Estimation of the PK parameters is usually assumed not to depend on the dose of a drug and any clinically reasonable dose is regarded as appropriate for the PK studies. However, under such assumption it may be impossible to achieve high accuracy of the parameter estimation. Therefore, the main concept here is to treat the dose as an additional design factor and to optimize the design with respect to both the dose level selection and PK parameter estimation. This is a complex multi-criteria optimization problem.

In the proposed method we use the ethical approach for dose selection developed in Zhang et al. (2006) and based on a continuation-ratio model as in Fan and Chaloner (2004). A Biologically Optimum Dose level is searched for in an adaptive experiment with simultaneous design optimization for the PK parameter estimation.

Keywords

Biologically optimum dose, Pharmacokinetic parameters, Continuation-ratio model.

References

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