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M. Iftakhar Alam, Barbara Bogacka, D. Stephen Coad

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Pharmacokinetically guided optimum adaptive dose selection in early phase clinical trials

M. Iftakhar Alam[a,*], Barbara Bogacka[b], D. Stephen Coad[b]

[a] *Institute of Statistical Research and Training, University of Dhaka, Dhaka-1000, Bangladesh*
[b] *School of Mathematical Sciences, Queen Mary University of London, London E1 4NS, U.K.*

Abstract

A new statistical method is introduced for dose finding in phase IB/IIA trials, which, along with efficacy and toxicity as endpoints, also considers pharmacokinetic information in the dose-selection procedure. Following the assignment of a current best dose to a cohort of patients, the concentration of a drug in the blood is measured at the locally D-optimal time points. The dose-response outcomes are also observed for each patient. Based on the updated information, a new dose is selected for the next cohort so that the estimated probability of efficacy is maximum, subject to the condition that the estimated probability of toxicity is not more than a chosen constant. Another condition for the dose selection is related to the total exposure of the drug in the body, expressed by the area under the concentration curve over time, so that the curative purpose is likely to be achieved in the population without overdosing. Simultaneously to the maximisation of the estimated probability of efficacy, the mean area under the concentration curve for a chosen dose is not allowed to be more than a target value taking into account its inter-patient variability. The purpose is to investigate the gain in efficiency of using pharmacokinetic measures in the dose escalation. The proposed method is found to identify the optimal dose accurately without exposing many patients to toxic doses.

Keywords: Area under the concentration curve, Continuation ratio model, D-optimum sampling times, One-compartment pharmacokinetic model, Population pharmacokinetics.

1. Introduction

Interest has grown in recent years in the development of dose-finding methods incorporating both toxicity and efficacy as endpoints. The idea in these methods is to find a dose for further development which is both safe and efficacious. Thall and Russell (1998) developed a dose-finding method that satisfies both efficacy and safety requirements. The method treats a sufficient number of patients, like

*Corresponding author. Tel.: +8801716187606; fax: (880-2) 9667222.
Email address: iftakhar@isrt.ac.bd (M. Iftakhar Alam)