Editorial

Microdosing for Reduction of the Time and Resources for Drug Development

Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

During the past two decades of pharmaceutical development, a large number of promising drug candidates selected by safety and pharmacological programs using experimental animals and in vitro, have dropped out of following clinical developments. The ratio of successful candidates was extremely low. At present it is well recognized that preclinical studies using human tissues are essential for characterization of profiles of pharmacokinetics (PK) and pharmacodynamics (PD) of candidates. Unfortunately, it is very difficult to predict safety and efficacy of candidates in humans on the basis of accumulated preclinical information. Without clinical studies, it is impossible to assess characteristics of candidates as therapeutic drugs, for example the extent of individual and racial difference of PK/PD and drug-drug interaction in humans.

Therefore, for reduction of the time and resources for drug development, it has been emphasized that evaluation of efficacy and pharmacokinetic profile of candidates in clinical studies should be started in the early stage of drug development as soon as possible.

For the purpose of reforming the strategy of early clinical studies in Europe, the European regulators (EMEA) published a position paper in 2003. In the paper, the EMEA approved a single dose study using a microdose technique with a dose less than 1/100th of the dose calculated to yield a pharmacological effect and/or a maximum dose of 100 μg, under the condition of the minimal preclinical safety package. Following this announcement of microdose concepts by the EMEA, the FDA published a new guidance for exploratory IND studies in 2006, which had three samples of clinical study designs including microdosing. In Japan, Japanese Society for the Study of Xenobiotics (JSSX) had discussed the advantages of exploratory clinical study including microdose trials conducted in Japan. After devoted and scientific discussions by the members of JSSX and the government, a new organization was established in 2005 for acceleration of exploratory clinical studies in Japan. Under the current global stream of exploratory clinical studies, international discussion of ICH-M3 started in late 2006 to harmonized essential preclinical programs for the study.

Over the last decade, new drug candidates for gene or molecular target therapy of disease have been developed successively on the basis of revolutionary advances in gene and molecular biology. These candidates necessarily requires new concepts and tools for preclinical and clinical evaluations.

Thus, microdose study is expected as a very promising clinical tools. On the point of risk/benefit of microdose study using a very low actual dose, hot discussion has continued concerning the issue of linear pharmacokinetic correlation between the data of microdose and pharmacological dose, dealing with current Japanese regulations, and sensitive and reliable analytical techniques. Especially, as for drug analysis in microdose study, it is essential to improve detection limits of LC/MS/MS, special synthesis of radio-labeled candidates for positron emission tomography (PET) imaging, and contamination in accelerator mass spectrometry (AMS). Researchers working for drug metabolism and pharmacokinetics are expected, as specialists, to overcome existing technological hurdles in microdose study in collaboration with scientists in other research field, and to demonstrate a important role in the early drug development.

The DMPK Editorial Board desires and welcomes valuable information related to microdose study conducted around the world.

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