INTRODUCTION

Purpose of toxicity study on pharmaceuticals is to characterize their toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility by animal experiments or by in vitro toxicity studies. From these toxicity data we estimate the effects of drugs on human in relation to its clinical use. However, it is well known that there are possibilities of large differences in the toxicity of chemicals among species, strains, and individuals. For example, LD50 of TCDD in guinea-pigs were about 1,000 times smaller than those in hamsters. Therefore, it is, sometimes, inappropriate to extrapolate animal data to human depending simply on the administered dose.

Physiological, pathological, environmental, pharmaceutical, experimental factors, may also affects toxic responses. Influences of these factors are represented mainly by the differences in drug concentration surrounding target tissues and by the differences in the sensitivity of target tissues to toxic insults. On the other hand, studies on the mechanism of toxicity and on drug metabolism made us understood that, in most cases, toxicity correlates better with the blood levels of the compounds than with their dose itself. Thus, we expected to overcome most of the species differences depending pharmacokinetics (PK) by comparing the toxicity based on blood levels.

Harmonization on Toxicokinetics (TK)

In the process of ICH, there was a proposal on the harmonization of the PK studies. However, it was difficult to harmonize all of PK issues. Thus, we tried to harmonize on two issues in PK. One was determination of blood levels in toxicity tests and the other was repeated dose tissue distribution studies. Harmonization of these issues were achieved in October, 1994 as Note for guidance on toxicokinetics: The assessment of systemic exposure in toxicity studies and Pharmacokinetics: Guidance for repeated dose tissue distribution studies. Regulatory authorities of three region had taken each necessary steps to implement the agreements. In Japan, those were notified on July 2, 1996 and asked pharmaceutical companies to incorporate TK to the toxicity tests which start after January 1, 1997.

Definition and objectives of TK

TK in ICH guidelines as defined as the "generation of pharmacokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, to assess systemic exposure." This definition of TK is different from the other's. For example, OECD used the term, toxicokinetics, as study of the absorption, distribution, excretion, and metabolism of substances (OECD, 417). The only difference from PK seems to be the difference in the category of test substances. Thus, definition of TK by ICH is limited to the field of drug development for human use and it does not apply to the other chemicals like agricultural drugs and food additives, etc.

Primary objective of TK was defined "to describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study." Data on the linearity of the exposure levels depending on the dose is important for the drug evaluation. Data on the changes during repetitive administration by drug- or age-related
induction or inhibition of ADME mechanism are also expected.

Secondary objectives were described as "to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in non-clinical toxicity studies, and to provide information that, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies."

As an outcome of harmonization of TK, doses which cause maximum exposure are now accepted as a maximum dose in toxicity studies. In the case of carcinogenicity studies, exposure level which exceed about 25 times of clinical exposure is also considered enough as a maximum dose.

Toxicity studies that were covered by TK guidance were single dose toxicity study, repeated dose toxicity study, reproductive and developmental toxicity studies, mutagenicity study, and carcinogenicity study.

**Principles of TK studies**

Now, toxicity study for pharmaceuticals without any support by TK data is not acceptable. However, we do not require TK to incorporate into all of those toxicity studies. Necessity and range of TK studies should be determined by step by step approach and case by case decision-making, depending on the results of preceding toxicity studies, TK studies, PK studies, and clinical studies.

Systemic exposures are estimated mainly by the determination of the test substance in blood, plasma, or serum. However, determination of the metabolites or determination in other biological matrix, instead, can be acceptable in specific circumstances where it is appropriate. Toxicity studies on metabolites may be...
CONCLUSION

By the introduction of TK we will be able to get information on the relationships of plasma concentration to the beneficial effects and the toxicity of pharmaceuticals. These data are important to extrapolate data from animal experiments to human and to assess the safety margin depending on the blood levels. TK data are also useful to estimate the impact of drug interactions and genetical polymorphism of drug metabolizing enzymes to drug therapy.