Editorial

Pharmacokinetics and Pharmacodynamics: Where are they going?

As can be easily understood from the journal name, pharmacokinetics is a major field covered by Drug Metabolism and Pharmacokinetics (DMPK). Pharmacokinetics in a broad sense is defined as the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body, and the kinetics of these processes. As a consequence of these pharmacokinetic processes, the plasma concentration-time profile of drug is determined. However, drug level in the plasma (or pharmacokinetics) itself is not important in clinical pharmacotherapy. Rather, clinical outcome of drug therapy such as desired effect and undesired adverse drug reaction is important and is the major concern in clinical pharmacotherapy. In other words, pharmacokinetics is important when the concentration of the drug in the plasma and/or at the site of action is known to be related to the magnitude of the effect produced. This is a basic tenet of clinical pharmacokinetics, and practically, it is a prerequisite condition for drugs subjected to Therapeutic Drug Monitoring (TDM). In TDM, dosage regimen is adjusted to achieve the proper plasma concentration of the drug in its therapeutic window, where desired effect of the drug can be expected and adverse drug reaction can be avoided in most, though not all, patients.

Pharmacodynamics is explained as the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body, the mechanisms of drug action, and the relationship between drug concentration and effect. Thus, the concept of pharmacodynamics would be fairly broad and different in different research fields. For example, the term “pharmacodynamics” seems to be used in a narrower sense in the field of biopharmaceutics. In various textbooks of biopharmaceutics in Japan, pharmacodynamic model is defined as the model with which to explain the relationship between the plasma concentration of drug and its pharmacological effect, such as Emax model based on the receptor theory. In addition, integrated model of pharmacokinetics and pharmacodynamics has been employed to express the effect of drug as a function of time after administration. The validity of these pharmacodynamic models and pharmacokinetic/pharmacodynamic combined models has been verified in various drugs in experimental animals and even in humans. However, generally speaking, in contrast to pharmacokinetic-based dosage adjustment (that is, TDM), such a concept or methodology for pharmacodynamics has not been directly utilized, nor commonly accepted, in clinical pharmacotherapy. The precise reason is not clear, but it may be still at an immature stage, or may be impractical.

Recently, it is attempted to utilize pharmacokinetic parameters or parameters derived from pharmacokinetics and pharmacodynamics as indices for the efficacy and safety of pharmacotherapy. A typical example is pharmacokinetic/pharmacodynamic approach for the treatment of infectious diseases with antibiotics. The minimum inhibitory concentration (MIC), which is the lowest concentration that completely inhibits visible growth of the bacterium, has been widely used as a main pharmacodynamic parameter to describe the susceptibility of bacteria to antibiotics. The evaluation of the relationships between efficacy parameters and pharmacokinetic/pharmacodynamic indices such as time above MIC (T > MIC), ratio of maximum concentration to MIC (Cmax/MIC), and ratio of area under the time-concentration curve to MIC (AUC/MIC) are assumed to be important to determine the possible effective dosage regimens in patients. For example, the efficacy of β-lactam antibiotics is known to be correlated with T > MIC. Once the information concerning MIC was obtained, antimicrobial efficacy of a certain drug can be managed by setting T > MIC at a proper percentage relative to the dosing interval using pharmacokinetics or population pharmacokinetics. Such an approach would be practically useful and applicable in clinical pharmacotherapy. Another example is pharmacokinetic/pharmacodynamic studies of anticancer drugs. Many studies have been carried out to examine whether certain pharmacokinetic estimates can be utilized as prognostic factors for clinical outcome including efficacy and safety of anticancer drugs. Once the relationship was found, pharmacokinetic estimates may be useful in controlling the efficacy and safety of the anticancer drug. For example, thrombocytopenia induced by carboplatin is known to be related to AUC of the drug. In addition, AUC of carboplatin would be inversely related to glomerular filtration rate (GFR). Based on these findings, Calvert’s formula utilizing target AUC and patient’s GFR is often employed to determine the dosage of carboplatin. Thus, in order to apply pharmacokinetic/pharmacodynamic concepts in clinical pharmacotherapy, it is important i) to find proper pharmacodynamic marker(s) reflecting the efficacy or safety of the drug (biomarkers/surrogate markers), ii) to find the relationship between pharmacokinetic estimates and these pharmacodynamic markers, and iii) to control the pharmacokinetics of the drug to obtain better clinical outcome. Pharmacodynamics may also be important for understanding the role of functional proteins such as drug transporters and metabolizing enzymes, which determine the macro- and/or micro-pharmacokinetics of drug, in clinical pharmacotherapy. Recently, there are some leading studies examining the relationship between pharmacodynamics
(clinical outcome) and the expression and function of drug transporters and metabolizing enzymes.

The above mentioned pharmacokinetic/pharmacodynamic research may still be under the development, but it is undoubtedly important research area not only for clinical pharmacotherapy but also for drug development. As described in DMPK Instruction to Authors, pharmacodynamics is an important and suitable research area in conjunction with pharmacokinetics for this journal. So far in DMPK, articles related to pharmacodynamics were fewer than those related to pharmacokinetics, but readers working on this important research area are encouraged to submit their accomplishments to this international journal. The development of the research area related to pharmacodynamics would be essential for further development of pharmacokinetics and therefore of DMPK and JSSX.

Mikihisa Takano, Ph.D.
DMPK Associate Editor