Clinical pharmacologists (kinetists) are charged with the obligation to quantify dose-response relationships (pharmacokinetics and pharmacodynamics) of clinically useful drugs. Clinical pharmacokinetic studies are performed to determine the rational use of medicines according to patient characteristics, such as disease and genotype of drug metabolizing enzymes (transporters), and predict the influence of pharmacokinetic drug interactions.\(^1\)

There are two basic approaches for performing pharmacokinetic evaluations in the drug development stage, the standard pharmacokinetic approach and population pharmacokinetic approach. Frequent blood sampling is required in the standard pharmacokinetic approach to determine pharmacokinetic parameters in individual subjects. In contrast, the population pharmacokinetic approach relies on infrequent (sparse) blood sampling from a larger population to obtain information on typical values (means and variance) for variability of pharmacokinetic parameters. However, it is often impossible for physicians and pharmacists in a hospital to design and perform these standard and population pharmacokinetic trials. That is, the number of blood samplings is limited in routinely treated patients because of ethical reasons. Moreover, high investment and long time period can be required to recruit a large number of appropriate patients.

There is another popular and useful approach, which is often used to predict pharmacokinetic parameters in a subject from a limited number of blood samples. That is, Bayesian analysis uses the statistical theory of Bayes’ theorem to predict pharmacokinetic parameters from 1–2 drug concentration data in individual patients. It should be noted that so-called prior information on typical values for variability of pharmacokinetic parameters in the population may be obtained not only from previous reports,\(^3\) but also from ongoing pharmacokinetic trials.\(^3\) The area under the curve (AUC) of drug concentration versus time can be associated with therapeutic or toxic effects of a drug. Therefore, AUC or oral clearance (CL/F) of orally administered drugs is a key pharmacokinetic parameter to evaluate drug exposure in patients. Clinical pharmacokinetists may focus attention on estimating CL/F and then select a simpler pharmacokinetic model for a target drug and should determine optimal limited sampling design for patients.\(^2,3\)

We have recently proposed an alternative design/analysis approach for patient-oriented clinical pharmacokinetic trials.\(^1,4,5\) Routinely treated patients often take drugs once or twice daily repetitively. Clinical practice-resembling pharmacokinetic trials may have less ethical problems and its feasibility can be relatively high.\(^3\) We have performed simulation for exploratory clinical pharmacokinetic trials, in which blood is sampled at two time points corresponding to peak and trough concentrations following repetitive oral drug administrations to 10–30 subjects.\(^1,4\) The simulation study indicated that AUC (or CL/F) is estimated accurately by the naive trapezoidal method and/or by the simple mono-exponential model.\(^1,4\) We were surprised that the pharmacokinetics of carvedilol in routinely treated patients with heart failure significantly differ from those in healthy subjects and the precise mechanism remains to be resolved.\(^5\)

Indeed, the pharmacokinetics of drugs in pediatric, elderly, and middle-aged patients with disease are often and unexpectedly different from those in young healthy volunteers. I think that pharmacokinetic evaluations for the patient population will be indispensable at least in the near future we must thus develop a limited sampling design and analysis method for each target drug and a new limited sampling strategy should be evaluated carefully by computer simulation prior to real clinical trials for best performance.

References

5) Horiuchi, I., Nozawa, T., Fujii, N., Inoue, H., Honda, M., Shimizu, T., Taguchi, M. and Hashimoto, Y.: Pharmacokinetics of...

Yukiya HASHIMOTO  
DMPK Associate Editor