Effective Use of Microdosing and Positron Emission Tomography (PET) Studies on New Drug Discovery and Development

The new FDA guidance contains details about a new investigational drug application process, the “Exploratory IND (eIND) that will enhance post-discovery drug development. As the FDA guidance says, eIND studies may help identify promising candidates early in the drug development process. eIND studies may ultimately reduce the number of human subjects and resources, which will be required to select promising drugs. Microdosing is one of the methods included in eIND. Microdose clinical trials can be used to obtain pharmacokinetic information on a tentative drug candidate in humans using labelled compound(s) and AMS or imaging technology using Positron Emission Tomography (PET), or non-labelled compound(s) and LC/MS/MS, and select drug candidates by ensuring adequate properties at an early stage. The Ministry of Health, Labor and Welfare in Japan formally issued guidance on microdosing clinical trials in June 2008. A “microdose” is defined as dosage less than 1/100 of the test substance calculated to yield a pharmacologic effect, with a maximum dose of $\leq 100 \mu g$. Because of such limited dosage, the risk to a human subject is regarded as minimal. Regulatory authorities in all regions of world have clarified in each of their guidance documents non-clinical safety studies to support such microdose clinical trials.

In October 2008, the NEDO (New Energy and Industrial Technology Development Organization) project entitled “Establishment of Evolutional Drug Development...
with the Use of Microdosing Clinical Trial: Based on the Quantitative Prediction Technology of ADME” was adopted in the field of Drug Discovery & Development (Translational Research), where I serve as leader. NEDO is Japan’s largest public R&D management organization for promoting the development of advanced industrial, environmental, new energy and energy conservation technologies. In this project, the quantitative prediction method1–3) for drug absorption, distribution, metabolism and excretion using mathematical modeling and simulation developed over the last 30 years by the author and many other scientists around the world will be applied to humans to validate this methodology (Fig. 1). That is, based on in vitro data on metabolism, transport and binding using animal and human tissues, the drug concentration-time profiles in the plasma and target tissues such as brain, tumor, liver and kidney will be predicted and the validity of the predictions will be investigated using clinical studies under microdose and therapeutic dose conditions (Fig. 2). The tissue concentration-time profiles of drugs will be measured by PET. The plasma concentration and urinary excretion of drugs and their metabolites will be determined either by AMS or highly sensitive LC/MS/MS methods. PET is a noninvasive imaging method useful in humans and animals to accurately measure pharmacodynamic endpoints (receptor occupancy), or the amount of tracer accumulation in a tissue over time to quantify transporter activity. For example, 11C-verapamil has been used to assess P-glycoprotein activity.4) PET is thus a promising approach to determine the functional change in transporters associated with genetic polymorphisms or drug-drug interactions. PET probes are also being developed for specific transporters in this NEDO project. For example, the effects of changes in OATP1B1 and MRP2 activity on pravastatin systemic and hepatic exposure were simulated using a physiologically-based pharmacokinetic (PBPK) model incorporating blood, liver (clearance and pharmacological target organ), and peripheral organs. The relative roles of OATP1B1 and MRP2 in drug exposure in the circulating blood and liver were clearly defined using such model-based analysis.5) The validity of this prediction will be confirmed in the future using 11C pravastatin PET label.

The following studies will be performed in the NEDO project.

1) Using PBPK modeling based on the microdose clinical tests and in vitro data on metabolism, transport and binding involving animal and human tissues, ADME properties of drugs in humans at the therapeutic dose will be accurately predicted.

2) The tissue distribution of drugs will be measured by molecular imaging technology, such as PET, in the microdose clinical tests. However, since information acquired is distribution on a microdose level, the results do not directly verify neither pharmacological effects nor safety properties. Then, the amount and rate of drugs distributed to the tissues at a therapeutic dose will be quantitatively predicted using the method described above.

3) Thus, the predicted time profiles of drug distribution to target tissue at the therapeutic dose will be integrated with the pharmacodynamic potency of the drugs in question (concentration-effect relationship) using mathematical modeling. Such an approach will
provide time profiles of pharmacological response of drugs in humans at therapeutic doses. A similar approach will also be applicable for predicting side effects (toxicities) caused by drugs.

The outcome of this NEDO project will be presented in the future to the consortium of pharmaceutical industries as a “package tool” which can be used for new drug development with a much higher success rate. I firmly believe this research project will revolutionize the strategy of new drug development around the world and not just in Japan.

References


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