Preface

Update on Prediction of Drug Metabolizing Enzyme- and Transporter-based Drug Interactions

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

DMPK started the Theme Issue in 2008 aiming at facilitating research, promoting drug development, and making DMPK more attractive. Previous Theme Issues focused on gene regulation of drug metabolizing enzymes and transporters (volume 23, number 1), pharmacological and toxicological aspects of transporters (volume 23, number 4), pharmacokinetics and pharmacodynamics projections in exploratory drug development (volume 24, number 1) and albums with new functions and clinical applications (volume 24, number 4). These issues attracted considerable attention from readers. As the fifth Theme Issue, we plan to compile reviews for the prediction of drug interactions because one of the missions of JSSX is the appropriate use of drugs in clinics. Theoretically, drug interactions take place in any pharmacokinetic process and have potential to cause serious adverse events and/or lack of expected pharmacological effects. Therefore, predicting the degree of drug interactions has always been an important issue in drug development.

Together with the increasing availability of human tissue samples such as human liver microsomes and human hepatocytes as well as recombinant human enzymes, the in vitro system for studying drug metabolism has been well established. Such systems allow evaluation of inhibition and/or induction potential of drugs against specific metabolic enzymes, and thus serve as useful information for predicting the degree of drug interactions in vivo. Appropriate mathematical models are required for describing pharmacokinetic alterations due to enzyme inhibition/induction observed in vitro. Quantitative prediction of drug interactions, particularly those caused by inhibition of metabolic enzymes, has thus attracted much attention in academia and pharmaceutical industries for many years, and some of research achievements have been reflected in regulatory guidelines after repeated discussion on the methodology for assessing drug interaction potential of new chemical entities. Important roles of drug transporters in pharmacokinetics and transporter-based drug interactions are being increasingly understood. The most recent draft drug interaction guidance released by US Food and Drug Administration (FDA) in 2006 includes how to study drug interactions mediated by transporters. An international working group is establishing standards for the in vitro evaluation of transporter-based interactions. The FDA White Paper on this issue is coming out soon in Nature Reviews Drug Discovery.

This Theme Issue invited six groups of authors, world-leading scientists, to update prediction of drug metabolizing enzyme- and transporter-based drug interactions. First, Dr. Naomi Nagai (Pharmaceuticals and Medical Devices Agency, Japan) states regulatory views and the situation of drug interaction studies in new drug applications for new molecular entities approved in Japan between 1997 and 2008. She discusses several areas that need to be updated in future guidelines.

For the prediction of in vivo interactions from in vitro metabolic studies, the selection of appropriate enzyme source is essential for accurately evaluating the effects of drugs on metabolic processes of other drugs. Dr. Andrew Parkinson (Xenotech LLC, USA) and co-workers compare the three commonly used in vitro systems, i.e. human hepatocytes, liver microsomes and recombinant enzymes, focusing on their applications to drug interaction studies. Compared with drug interactions taking place in the liver, predictions of those involving intestinal metabolism have not yet been established due to lack of appropriate mathematical models describing first-pass metabolism in the intestine. Dr. Aleksandra Galetin (University of Manchester, UK) and co-workers describe the importance and methodology of incorporating the intestinal metabolism in the prediction of drug interactions. Dr. Akihiro Hisaka (The University of Tokyo, Japan) and co-workers address this issue as one of their points on the quantitative prediction of drug interactions. They propose a prediction strategy based on the contribution of elimination pathways and unbound drug concentrations in the liver, both estimated based on the clearance concept.

Substrate and inhibitor specificities extensively overlap between drug metabolizing enzymes and transporters, forming a network that can efficiently eliminate xenobiotics. The complex drug metabolizing enzyme-transporter interplay involved in the disposition of drugs makes it very challenging to predict clinical drug interactions. In light of this issue, Dr. Jane P. F. Bai (US FDA) provides her insight into the prediction of the safety margin for the worst drug interactions based on intravenous drug interaction studies, as well as the need for integrating those with pharmacogenetics. Finally, Dr. Toshihisa Ishikawa (Tokyo Institute of Technology, Japan) and co-workers address recent advances in the strategy of trans-
port mechanism-based drug design, presenting examples of predicting transporter-drug interactions by quantitative structure-activity relationship analysis.

Drug interactions are one of the critical safety issues in the management and treatment of disease. We hope that the reviews in this Theme Issue will be useful to the industry, government and academia in research on the prediction of drug interactions. We sincerely thank all authors for their generous cooperation.

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