Editorial

Drug-induced Liver Toxicity Studies: Research into Human Metabolites Clarifies Their Role in Drug Development

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

On January 1, 2014, Professor Hiroshi Yamazaki became the fourth Editor-in-Chief of Drug Metabolism and Pharmacokinetics (DMPK), the official journal of the Japanese Society for the Study of Xenobiotics (JSSX). The former Editors-in-Chief, Professors Masahiro Hayashi, Kan Chiba, and Ikumi Tamai, and their editorial teams did a tremendous job in setting up and developing DMPK into the successful international journal that it is today. To make your research available to a worldwide audience, the Editorial Office would like to invite you to submit your manuscripts to DMPK, which is included in the Thomson Reuters Scholarly & Scientific Research platform.

One of the themes recently emphasized by DMPK Editors is drug-induced toxicity, which is among the most important research topics for academic, industrial, and clinical researchers. Drug-induced liver toxicity is the single most prominent adverse event causing non-approval of a drug or its withdrawal from the market by a regulatory agency. Many drug-induced toxicity events are associated with immune-mediated hypersensitivity reactions, which are idiosyncratic in nature and therefore difficult to predict. In the United States, more than 50% of cases of acute liver failure in adults are caused by drugs.1) It is, therefore, not surprising that many drug regulatory authorities require evaluation of the potential for metabolic activation prior to market approval as well as during the post-marketing period. Both in vitro and in vivo studies play roles in the safe development and effective use of medicines. Chimeric mice with humanized liver or human cytochrome P450 genes are used as animal models to investigate human metabolites during drug development, and this approach was covered in a recent editorial in DMPK. The editorial team believes that DMPK is one of the best international journals for disseminating the findings of a wide variety of such drug metabolite-related toxicity studies.

From 2002 to 2010, considerable discussion centered on the importance of drug metabolites as potential determinants of drug safety.2) This debate led to a guidance note for the drug-development industry issued in 2008 by the United States Food and Drug Administration, namely “Guidance for Industry Safety Testing of Drug Metabolites” and ultimately culminated in recommendations from the International Conference on Harmonization M3(R2) in 2010. These guidance documents laid out criteria establishing when human metabolites need to be measured in laboratory animal species and defined the circumstances under which direct testing of a metabolite in animal toxicology studies is needed to provide a reliable risk assessment. Recent developments in bioanalytical methodology have yielded several strategies to provide robust data that can inform critical decisions related to metabolite quantification and monitoring in plasma. On behalf of the DMPK Editors, I would like to invite submission of Original Articles, Notes, and Letters to the Editor specifically dealing with the issues discussed above.

The National Institutes of Health LiverTox database was developed by the Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Library of Medicine to promote basic and clinical research on drug-induced liver toxicity. This is a free on-line source of textual documents on liver injury caused by prescription and nonprescription drugs, herbal medicines, and dietary supplements collected from various databases, the scientific literature, and the interpretations of the curators.3) Recently, systematic research into metabolic drug activation has become more comprehensive and more complex. DMPK welcomes the development and application of new methodologies for investigations of the interaction of toxic agents and living systems.

Based on the current increasing trend for the mechanistic evaluation of drug toxicity, the detailed analysis of human metabolites, and the increasing potential for reliable predictions, the DMPK Editorial Board recognizes the global importance of these hot topics and welcomes your contributions as reports or discussions to be published in the journal, thereby ensuring that your views and findings will be seen by the drug metabolism community worldwide.

References

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