A ZONE CLASSIFICATION SYSTEM FOR RISK ASSESSMENT OF IDIOSYNCRATIC DRUG TOXICITY USING DAILY DOSE AND COVALENT BINDING

Shintaro Nakayama, Ryo Atsumi, Hideo Takakusa, Yoshimasa Kobayashi, Atsushi Kurihara, Yoko Nagai, Daisuke Nakai and Osamu Okazaki
Drug Metabolism and Pharmacokinetics Research Laboratories, R&D Division, Daiichi Sankyo Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140-8710, JAPAN

The risk of idiosyncratic drug toxicity (IDT) is of great concern to the pharmaceutical industry. Current hypotheses based on retrospective studies suggest that the occurrence of IDT is related to covalent binding and daily dose. We determined the covalent binding of 42 radiolabeled drugs in three test systems-human liver microsomes and hepatocytes in vitro and rat liver in vivo-to assess the risk of IDT. On the basis of safety profiles given in official documentation, tested drugs were classified into the safety categories of safe, warning, black box warning, and withdrawn. The covalent binding in each of the three test systems did not distinguish the safety categories clearly. However, when the log-normalized covalent binding was plotted against the log-normalized daily dose, the distribution of the plot in the safety categories became clear. An ordinal logistic regression analysis indicated that both covalent binding and daily dose were significantly correlated with safety category, and that covalent binding in hepatocytes was the best predictor among the three systems. When two separation lines were drawn on the correlation graph between covalent binding in human hepatocytes and daily dose by a regression analysis in order to create three zones, 30 of 37 tested drugs were located in zones corresponding to their respective classified safety categories. In conclusion, we established a zone classification system using covalent binding in human hepatocytes and daily dose for the risk assessment of IDT.

References:

Biography
Shintaro Nakayama, a research scientist in DMPK Research Laboratory, Daiichi Sankyo Co., Ltd. He graduated from Graduate School of Pharmaceutical Sciences, Chiba University in 2001. He worked on clinical pharmacology in clinical development department from 2001 to 2003. Then he moved to the DMPK laboratory in 2003, and has been working on PK & ADME for drug discovery and development. Current researches have focused on reactive metabolites and idiosyncratic drug toxicity.