STRATEGY FOR PREDICTION OF DRUG-DRUG INTERACTIONS CAUSED BY MECHANISM-BASED INHIBITION IN THE DRUG DISCOVERY THROUGH DEVELOPMENT STAGES

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Reactive metabolites produced by metabolizing enzymes are known to induce hepatitis or idiosyncratic toxicities via binding to proteins or other components in the liver or other organs, whereas binding to metabolizing enzymes can cause drug-drug interactions (DDIs) by enzyme inactivation, so-called mechanism-based inhibition (MBI). Some drugs have been withdrawn from the market due to MBI, and thus evaluation of the potential for MBI and prediction of the degree of DDI are recognized as very important.

Many pharmaceutical companies conduct MBI evaluation in the early discovery stage. Although mechanism-based inhibitors are considered to be high risk for DDI, clear criteria for evaluating DDI risk have not been established for CYP inhibition screening. We developed a method of visually categorizing the DDI risk caused by MBI using the IC₅₀ data with and without preincubation.¹ This method will provide a simple assessment of DDI risk, especially in the early stages of drug development.

In the late development stages, estimation of the inactivation parameters (k_inact and K_I,app) and detailed DDI risk evaluation in clinic are necessary. Methods to predict the degree of DDI caused by MBI using in vitro inactivation parameters have been reported. One is a relatively simple method using a single inhibitor concentration, such as unbound blood concentration in the steady state, to predict the increase in AUC of a co-administered drug. If clinical data of the plasma concentration of an inhibitor and a substrate is available, then a method using a physiologically based pharmacokinetic (PBPK) model is recommended because it can predict DDI more precisely due to the use of the change in the inhibitor and substrate concentration over time. We attempted to predict the degree of DDI caused by a mechanism-based inhibitor, mibebradil, in humans using a PBPK model. The predicted increase in the plasma concentrations of a probe, midazolam, was close to the observed values.

The strategy we adopted to predict DDI caused by MBI according to the drug development stage described above can facilitate more efficient development of new safe medicines with reduced risk of DDI by reactive metabolites.

References:

Biography

Nobuo Sekiguchi is a research scientist of DMPK at Chugai Pharmaceutical Co., Ltd. He graduated from Chiba University and joined the pharmaceutical industry in 1996. He has been working on DMPK research in drug discovery and development. His current research is focused on DDI caused by MBI, and he has published and presented papers at conferences on MBI.