Editorial

How Far Should We Go? Perspective of Drug-Drug Interaction Studies in Drug Development

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Pharmacokinetic drug-drug interactions (DDIs), affecting the systemic exposure of drugs, may result in a lack of efficacy, or increase in severe adverse reactions. Sometimes, because of the unexpected lethal adverse reactions caused by DDI, drugs are withdrawn from the market. To avoid such serious DDIs in the patients, it is now strongly recommended that the magnitude of DDIs with new chemical entities that act as victims (substrates) or perpetrators (inhibitors) be evaluated before drugs are marketed. Indeed, the regulatory guidelines/guidance in US, EU and Japan encourages pharmaceutical companies to conduct clinical drug-drug interaction studies with the probe drugs whose disposition is predominantly determined by the specific drug metabolizing enzymes and transporters when the predicted magnitude of interaction is greater than the thresholds.

Regarding drug transporters, drugs that can be probes of the specific transporters, are now being selected for regulatory guidelines. In addition to non-radio labeled compounds, the probe drugs are now expanding to radiolabeled or endogenous ones. Radiolabeled probes applicable to scintigraphy, SPECT and PET studies enable non-invasive measurement of tissue concentrations of the radioactivity in the brain and other non-clearance organs as well as clearance organs, and provide an insight into the interactions in the local drug concentrations determined by transporters. Indeed, rifampicin, which can inhibit the activities of various OATP isoforms in the liver at its therapeutic single dose, significantly inhibited the hepatic uptake of (15R)-16-m-toly-17,18,19,20-tetranorisocarbacyclin (15R-TIC), and furthermore, the study also suggests that the interaction mechanism of rifampicin involves the efflux into the bile.

Some endogenous, food-derived or microbiome-generating metabolites are known to be substrates of drug metabolizing enzymes and transporters. They may serve as probes for DDI study. It is obvious that the advantage of using endogenous metabolites is that there is no need to administer probe compounds for evaluating the activities of enzymes and transporters. This helps assessment of DDI risk even during phase I study where the pharmacokinetics of the drug candidate are evaluated at multiple doses, and consequently saves cost and time for conducting additional clinical DDI studies in the process of drug development. It also contributes to monitoring the activity of drug metabolizing enzymes and transporters in patients for whom injection of exogenous probe drugs that are not related to the therapy is not appropriate. On the other hand, it is also obvious that there are some disadvantages: circadian rhythm in the plasma concentrations of the metabolites, inter-individual difference in their absolute value, and sometimes, a lack of information on the elimination pathways and specificity of metabolizing enzymes and transporters, particularly in humans. The positive association of the magnitude of the changes in concentration of the metabolites with probe drugs supports the hypothesis that the metabolites can be used as metrics. To use metabolites for quantitative analysis of DDIs requires careful investigation of the contribution of target enzymes and transporters to the disposition of the metabolites.

Metabolites have been used for DDI studies in the research area of drug-metabolizing enzymes. For instance, CYP3A4 catalyzes 6β-hydroxylation of cortisol in the liver, and 6β-hydroxycortisol as well as cortisol is found in the urine. Thus, the ratio of 6β-hydroxycortisol and cortisol in the plasma and urine, or apparent 6β-hydroxycortisol formation clearance, defined by the amount of urinary excretion of 6β-hydroxycortisol by the area under the plasma concentration time profiles of cortisol, is used as an index for the magnitude of CYP3A4 induction or inhibition in the liver. This approach has also been applied to drug transporter research. Serum level and renal clearance of creatinine, a creatine metabolite, are well known biomarkers for renal failure. Some clinical reports have indicated that administration of some drugs, such as cimetidine, pyrimethamine and trimethoprim, cause a reversible increase in the serum creatinine level without, however, affecting the glomerular filtration rate (GFR). Creatinine undergoes tubular secretion in the kidney, which is a potential interaction site with drugs, although the contribution is small. Creatinine is a substrate of renal organic cation transporters such as organic cation transporter 2 (OCT2/SLC22A2), and multidrug and endotoxin extrusion 1 (MATE1/SLC47A1) and MATE2-K/SLC47A2 in their cDNA transfected cells. To date, cimetidine, pyrimethamine and trimethoprim have turned out to be pan MATE inhibitors at their therapeutic dose; cimetidine and pyrimethamine and trimethoprim show similar inhibition profiles to MATE1 and MATE2-K, and trimethoprim shows higher inhibition potency against MATE2-K than MATE1. DX-619 is also a potent inhibitor of OCT2 as well as MATEs in the kidney. Monitoring serum creatinine together with GFR enables detection of the significant inhibition of either or both OCT2 and MATEs. Because of the small contribution of the tubular secretion to the urinary excretion of creatinine, other metabolites with a large contribution to the tubular secretion are expected to prove useful for quantitative analysis of the DDI involving these transporters. N-methylnicotinamide (NMN), a metabolite of nicotinamide, is a typical cationic metabolite that is extensively excreted into the urine by tubular secretion as well as glomerular filtration. NMN is also a substrate of OCT2 and MATEs in their cDNA-transfected cells. Pyrimethamine administration significantly decreased the urinary excretion rates of NMN, but did not affect its plasma concentration, and thus, the renal clearance was significantly decreased in humans. Because the magnitude of interaction with pyrimethamine on the renal clearance is higher for NMN than for metformin, a typical MATE substrate, in humans, NMN will be a...
better substrate for the evaluation of DDIs involving MATEs. In addition to the organic cation transport system, the metabolite can be used for evaluation of DDIs involving the organic anion transport system in the kidney. The renal clearance of one of the cortisol metabolites, 6β-hydroxycortisol, is greater than the GFR, whereas that of cortisol is below the GFR. 6β-Hydroxycortisol is found to be a substrate of OAT3 and OCT2 in vitro in cDNA-transfected cells. Probenecid, a potent OAT inhibitor, significantly inhibited the uptake of 6β-hydroxycortisol by human kidney slices, and decreased the renal clearance of 6β-hydroxycortisol, accompanied by a significant elevation in the plasma level of 6β-hydroxycortisol in healthy subjects.5) Although 6β-hydroxycortisol is a MATE substrate in vitro, pyrimethamine administration did not affect its renal clearance in healthy subjects.

A great step forward in analytical too has been realized by the comprehensive analysis of metabolites in biological fluids, the so-called metabolomic analysis using GCMS, LC-NMR, LC-MS or LC-MS/MS. This approach has been already been applied to genetically modified animals that lack transporter genes and has identified the substrates in the biological fluids. For instance, sulfo and glucuronide conjugates are accumulated in the animal knockouts of ABC transporters such as MRP2, MRP3 and BCRP.6) This approach provides an insight into the physiological roles of drug transporters in the body. Metabolomic analysis has also identified the metabolites whose urinary excretion is altered by the administration of inhibitors in humans. Oral pyrimethamine caused a marked reduction in the urinary excretion of thiamine, carnitine and some acylcarnitines, although their urinary excretion rate is below the GFR.7) Of these metabolites, thiamine was confirmed as an OCT2 and MATEs substrate in their cDNA-transfected cells. In particular, metabolomics analysis of biological fluids will help unveil the interaction of drugs with drug-metabolizing enzymes and transporters before the approval or marketing of drugs, although that may require reverse translational analysis to figure out the mechanism causing the changes in the disposition of the metabolites. Technically, we are already here. What we need to do is to take up the challenge.

References

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