Editorial

Can Drug Interactions Be Evaluated by Monitoring Plasma Drug Concentrations?

If an OATP1B1/1B3 inhibitor is co-administered with a statin, then the plasma concentration of the latter can increase several-fold; however, the pharmacological activity will not change significantly. In fact, alteration of the pharmacological effect of pravastatin with its chronic administration has not been observed in subjects with OATP1B1 polymorphisms. This is considered to be caused by the absence of large variations in the drug concentration at the target sites. In addition, it is theoretically proven that the inhibition of uptake transporters results in smaller changes in the tissue concentration than in the plasma concentration. In contrast, when efflux transporters are inhibited, the tissue concentration is expected to increase to a markedly greater extent than the plasma concentration (“Calm on the surface, but a big fire in the core” in a Japanese idiom (Uchiwa-wa-hinokuruma), a statement of Dr. Yuichi Sugiyama, RIKEN). When a drug with more potent action to inhibit MRP2 than OATP1B1 is concurrently used, pravastatin is likely to exert its pharmacological effect at a lower dose; the concurrent use may result in a marked increase in the liver concentration compared with that in the plasma concentration, which makes it difficult to detect drug interactions in regular clinical studies or postmarketing therapeutic drug monitoring. This phenomenon is not limited to the liver and similarly applies to MATE inhibition in the kidney or P-gp inhibition in the gastrointestinal tract. Although there is little change in the plasma concentration, the drug concentration may markedly increase in the epithelial cells of the renal tubule and gastrointestinal tract, resulting in cellular toxicity.

As a noninvasive technique to monitor changes in the tissue drug concentration, positron emission tomography (PET) using [11C]-labeled compounds is well known. Because this technique requires synthesis of the [11C]-labeled target drug, it is not necessarily highly versatile; however, it is attractive because animals and humans can be evaluated across-the-board (“pure straight” in a mahjong hand (Ikki-tsukan), a statement of Dr. Yasuyoshi Watanabe, RIKEN). To prevent adverse reactions due to drug interactions, it is more important to properly evaluate the perpetrator drug than the victim drug and quantitatively evaluate its effect. In this respect, the PET scan using a selective substrate of individual transporters as a probe is very useful and is expected to become a standard clinical drug interaction test of the next generation. Takashima et al. have already reported a drug interaction test using [11C]-labeled telmisartan and [11C]-labeled dehydropravastatin as probes.

In nonclinical studies using model animals, it is possible to evaluate drug interactions at the tissue level by directly measuring drug concentrations in each tissue. However, because it is known that there are species differences in drug transporters similar to those in drug metabolic enzymes such as cytochrome P450, attention is required when interpreting their results. These days, transgenic (Tg) animals, in which animal-derived transporters are genetically modified to human transporters, are being developed. This presents a possibility that drug interactions at the tissue level, which have been difficult to evaluate in humans till date, may become evaluable by animal experiments.

In addition, as a technique to measure the drug concentration in tissues more locally, matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI imaging MS, also termed imaging MS) is attracting attention. Imaging MS initially came into practical use as a comprehensive search tool of biological components (biomarkers) used as markers of drug efficacy and toxicity, and after various phases of technical innovation, it is close to reaching the level where it can be utilized for the quantitation of low-molecular weight target drugs. There exists a report of the image of systemic distribution in rats similar to a systemic autoradiogram using [11C]-labeled compound using this technique. The use of this technique to perform drug interaction tests in Tg animals will enable the evaluation of variations in drug distribution along with that of metabolites in tissues at the time of concurrent drug use.

Similar to the plasma concentration, variations in the tissue concentration do not necessarily contribute to enhancement (reduction) of drug efficacy or toxicity accordingly. This point requires the most attention in drug interaction studies. It is vital to search for appropriate drug efficacy/toxicity biomarkers with nonclinical or clinical studies and clarify the association with variations in drug concentrations. Drug interaction studies using new technologies such as an imaging MS may bring about a dramatic development when simultaneous quantitation of drugs and biomarkers becomes possible.

References


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