Inhibitory effect of the CYP typical inhibitors under long term incubation in human liver microsomes

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CYP450 (CYP) isoforms are responsible for the metabolism of the majority of drugs in human. In case of the metabolic enzyme identification of CYP isoforms for the low intrinsic clearance (CLINT) candidate compounds, it is necessary to perform metabolic reaction with long term incubation. In addition, when performing the metabolic enzyme identification with long term incubation, the specificity and sustainability of a typical inhibitor is important. In this research, we evaluated the inhibitory effect of typical CYP isoforms in human liver microsomes (HLM) using long term incubation (incubation time of CYP typical inhibitors was 60 min). The final concentration of HLM was 1 mg protein/mL to clarify the inhibitory effect of CYP typical inhibitors under long term incubation.

Discussion

This study characterized the specificity of each CYP typical inhibitor under long term incubation in HLM. At 1 µM, α-naphthoflavone (CYP1A2 inhibitor) showed specific inhibition to CYP1A2. However, at 25 µM, it inhibited other CYP isoforms (CYP2B, CYP2C9, and CYP3A). By contrast, furafylline (CYP1A2 inhibitor) showed specific inhibition to CYP1A2 at the maximum concentration (25 µM) (Table 1 and Figure 1). As for the typical inhibitors of which the inhibitory effects were weaker, as the concentration increased, the inhibitory effects might be weakened by the metabolism of the typical inhibitors themselves. As for the typical inhibitors of which the IC50 values were the highest, the inhibitory effects were not observed under long term incubation.

Table 5 and Figure 5 Inhibitory effect of Sulphinaphthene for each CYP isoform in HLM

Table 6 and Figure 6 Inhibitory effect of Benzamidinate for each CYP isoform in HLM

Table 7 and Figure 7 Inhibitory effect of Montelukast for each CYP isoform in HLM

Table 8 and Figure 8 Inhibitory effect of Ketocazole for each CYP isoform in HLM