OPTIMIZATION OF CYTOCHROME P450 INHIBITORS FOR CYP IDENTIFICATION: INVESTIGATION OF SELECTIVITY FOR PROBE SUBSTRATE REACTIONS IN HUMAN LIVER MICROSONES

Tomoko Inoue, Mizuki Horiuchi, Masashi Yabuki, Setsuko Komuro and Yoshiaki Terauchi
Pharmacokinetics Research Laboratory, Dainippon Sumitomo Pharma Co., Ltd., 1-98, Kasugade Naka 3-Chome, Konohana-ku, Osaka 554-0022, Japan

Chemical inhibitors for cytochrome P450 (CYP) are useful tools for identification of CYPs involved in drug metabolism. Isoform-selective inhibitors have been recommended by FDA document (Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling, FDA preliminary concept paper, October 1, 2004), but the exhaustive investigation of selectivity for probe substrate reactions of CYP isoforms had not been done well. The aim of the present study was to evaluate the selectivity of isoform-selective CYP inhibitors for representative probe substrate reactions in human liver microsomes. Furafylline (CYP1A2), tranylcypromine (CYP2A6 and CYP2C19), quercetin, paclitaxel and rosiglitazone (CYP2C8), sulfaphenazole (CYP2C9), (+)-N-3-benzylnirvanol (CYP2C19), quinidine (CYP2D6), diethyldithiocarbamate (CYP2E1), ketoconazole and azamulin (CYP3A4) were screened for their inhibitory selectivity towards 10 CYP-mediated reactions in human liver microsomes at two concentrations (low, concentration at which inhibitor is considered to inhibit probe substrate reactions specifically; high, tenfold of low concentration). As a result, although most of isoform-selective CYP inhibitors selectively inhibited specific probe substrate reactions at low concentration, we were less able to inhibit selectively at high concentration. In addition, some of them inhibited reactions of other CYP isoforms even at low concentration. The above information should help avoid misleading interpretations in CYP identification studies and be useful for designing rational protocols.

THE USE OF HIGH-TEMPERATURE TREATMENT TO ELIMINATE DRUG INTERACTIONS DUE TO GRAPEFRUIT JUICE

Yoshihiro Uesawa and Kiminori Mohri
Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan.

Grapefruit juice contains components that may increase the bioavailability of drugs; however, approaches to the removal of these components have been little investigated. It is known that furanocoumarin derivatives, such as bergamottin and 6', 7'-dihydroxybergamottin in grapefruit juice, induce such drug interactions. In the present study, it was found that the high-temperature treatment of grapefruit juice decreases concentrations of bergamottin and 6', 7'-dihydroxybergamottin. We incubated grapefruit juice for 10, 20, 30, 40, 50, and 60 min at 4, 37, 62, 72, and 95°C; furanocoumarin derivatives in each sample were then measured, using high-performance liquid chromatography equipped with photodiode array detector. The concentrations of bergamottin and 6', 7'-dihydroxybergamottin were decreased in a time- and temperature-dependent manner, 82.5 and 97.9% respectively, after incubation for 1 hr at 95°C. In contrast, the concentration of bergaptrol increased in a time- and temperature-dependent manner (27.7% after 60 min at 95°C). In addition, the effect of each grapefruit juice sample on testosterone 6β-oxidation in human liver microsomes was observed. The inhibitory effects of grapefruit juice heated to 95°C were decreased in a time-dependent manner, as in the case of bergamottin and 6', 7'-dihydroxybergamottin concentrations. These results suggest that the heat treatment of grapefruit juice reduces the concentrations of furanocoumarin derivatives, thus eliminating the potential for drug interactions.