EFFECT OF S-1 ON PHARMACOKINETICS OF IRINOTECAN AND ITS METABOLITES IN COLORECTAL CANCER PATIENTS AND RATS

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The usefulness of combination therapy with irinotecan (CPT-11) and 5-fluorouracil (5-FU) for the treatment of colorectal cancer has been demonstrated. Previous reports suggested that 5-FU inhibits the enzymatic conversion of CPT-11 to the biologically active metabolite, SN-38 by carboxylesterase. Here we report the effect of coadministration of S-1, containing tegafur, a prodrug of 5-FU. This study was designed to evaluate the effect of S-1 administration on pharmacokinetics of CPT-11 and its metabolites in patients with advanced colorectal cancer and male SD rats. The concentrations of the carboxylate and lactone forms of CPT-11 and its metabolites were measured by HPLC. We found that the coadministration of S-1 decreased the plasma concentrations of CPT-11 and its metabolites in the patients and rats. In particular, Cmax and AUC of SN-38 carboxylate form and total (i.e., the sum of carboxylate and lactone forms) were markedly decreased. Furthermore, the coadministration of S-1 increased the biliary excretion of SN-38 carboxylate form and total in rats. In contrast, the in vitro study showed that S-1 and 5-FU did not inhibit the activity of carboxylesterase. In conclusions, coadministration of S-1 increased the biliary excretion of SN-38 carboxylate form and total, resulting in a corresponding decrease in the plasma concentrations of CPT-11 and its metabolites.

IN VITRO ASSESSMENT OF CYP2D6*10 ACTIVITIES ; PREDICTION OF INCREASE IN DRUG PLASMA CONCENTRATIONS IN ITS HOMOZYGOUS AND COMPARISON WITH POOR METABOLIZERS

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[Objective] CYP2D6*10 appears frequently in Asians (the allele frequency; 40–50%). Its homozygous are categorized in intermediate metabolizer, but comparable increases in plasma AUC with those in non-Asian poor metabolizers (PM) have been reported for drugs such as metoprolol, tropisetron, risperidone and propafenone. The objective of this study is to evaluate in vitro metabolizing activities of CYP2D6*1 and *10 for various substrates, and compare in vitro data with reported in vivo data in a pharmacokinetically quantitative manner. [Method] Each substrate was incubated with expressed CYP2D6*1/*10 enzymes or pooled human liver microsome. The metabolic rates were evaluated by measuring depletion of a substrate with an HPLC method. The contribution of CYP2D6 among total CYPs was evaluated from microsomal incubations in the presence of antibody of CYP2D6 or quinidine. We predicted in vivo oral clearance from the ratio of the metabolic rates (*10/*1) and the contribution ratio of CYP2D6. [Result] The in vitro activities of CYP2D6*10 were 50-fold less for metoprolol and 12-fold less for propafenone compared to CYP2D6*1. Similar extents of decrease, more than 10-fold, were observed for other CYP2D6 substrates in general. In vivo oral clearances in subjects carrying *10 homozygous were predicted to be 5.9-fold less for metoprolol and 3.7-fold less for propafenone, respectively. The predictions were similar to reported AUC ratio; 2.7-4.3 for metoprolol, and 2 for propafenone. Oral clearances in the PMs were predicted to be 6.6 and 4.8-fold less for metoprolol and propafenone, respectively. In conclusion, significant decreases in intrinsic activity of CYP2D6*10 (10^1-2 order) contributes greatly to apparent increases in plasma AUC comparable to those observed in PMs.