Effect of green tea catechins on pharmacokinetics of simvastatin in healthy Japanese volunteers

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Green tea has been reported to have various health benefits including cancer prevention and antioxidative effect. Catechins, the main flavonoids in green tea, are considered to be potential components of these effects. Recently, a case report suggested that the consumption of catechin-rich green tea is associated with simvastatin intolerance. The present study aimed to evaluate the effect of catechin-rich green tea consumption on the pharmacokinetics of simvastatin lactone (SIM) and simvastatin acid (SVA), which are a prodrug and an active metabolite of simvastatin, respectively.

In an open-label, two-way crossover study with 14 days washout, a single oral dose of 10 mg SIM was administered to 12 healthy Japanese male volunteers (23-26 years old; body weight, 65.1±2.4 kg) after drinking of green tea (700 mL/day, total catechins of 640 mg) or water for 2 weeks. Blood samples were collected up to 24 hrs after the administration. Plasma concentrations of SIM and SVA were determined using LC/MS/MS. We also investigated the effect of green tea catechins on the metabolism of Cytochrome P450 (CYP) 3A which is the main metabolic enzyme of SIM and SVA, using human liver or intestinal microsomes.

Chronic consumption of catechin-rich green tea led to increases in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) and maximum concentration (C_{max}) of SIM by 1.6- and 1.3-folds, respectively, as compared to water. No change was observed in the elimination half-life of SIM between green tea and water, indicating that catechins mainly may inhibit SIM metabolism in the intestine. In addition, green tea consumption significantly increased $AUC_{0-\infty}$ and C_{max} of SVA by 1.5- and 1.6-folds, respectively. Green tea catechins showed inhibitory effects on the metabolism of CYP subtypes in *in vitro*. Furthermore, we predicted that epigallocatechin gallate, the main component of green tea catechins greatly contributes to inhibition of intestinal CYP3A in *in vivo* situation.

The chronic consumption of catechin-rich green tea may cause the clinically relevant interaction with simvastatin.