PREDICTION OF INTESTINAL FIRST-PASS EFFECT BASED ON A CAT MODEL.
Masataka Ishiji, Yumiko Iwase, Tomoo Itoh
School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

First-pass effect is one of the most important factors to limit the bioavailability of orally administered drugs. CYP3A4 is the most abundant among CYP isozymes both in the liver and the small intestine in humans, and the substrates of CYP3A4 are subject to significant first-pass metabolism in the small intestine as well as in the liver. Since there are no in vitro methods to predict the intestinal availability (Fg) quantitatively, we attempted to establish a model to predict Fg based on a CAT (Compartmental Absorption and Transit) model.

In our prediction model, the gastrointestinal tract is divided into nine compartments; the stomach, the small intestine which is evenly divided into seven segments, and the colon. Each segment of the small intestine is accompanied by the absorptive epithelia with metabolic function. Drug transport through the absorptive epithelia was estimated with Caco-2 cells. Metabolic clearance of the drug in the epithelia was estimated from the metabolic studies using human intestinal microsomes. The simulation was performed with the pharmacokinetic software, SAAM2.

Alprazolam (ALP), triazolam (TRZ), midazolam (MDZ), and testosterone (TST) were used as the model substrates of CYP3A4. None of these drugs is the substrate of P-gp. Fg values were calculated based on a CAT model with the metabolic and transport parameters obtained in vitro, and the predicted Fg values were compared with those obtained from reported human administration studies.

Fg values calculated from the human data were in the order of ALP > TRZ > MDZ > TST. Predicted Fg values were also in the same order, although the predicted values of TRZ and TST were greater than those in humans. The present method is capable of predicting Fg values fairly well at least for the compounds tested in this study.

VIRTUAL CLINICAL TRIALS (I): PREDICTION OF INTER-INDIVIDUAL DIFFERENCE IN BIOAVAILABILITY
Motohiro Kato,1 Takashi Ito,2 Toshiko Koue,3 Koji Chiba4 and Yuichi Sugiyama5
1Chugai Pharmaceutical Co.Ltd., 1-135 Komakado, Gotemba 412-8513 Japan, 2Daiichi Pharmaceutical Co.Ltd., 16-13 Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan, 3Otsuka Pharmaceutical Co.Ltd., 463-10 Kagasuno Kawauchi-cho, Tokusima 771-0192 Japan, 4Pfizer Japan Inc. 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589 and 5The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Factors such as the genetic polymorphism of metabolizing enzymes, body weight, sex, age, and smoking produce individual difference in the pharmacokinetics of some drugs. We have been constructing a method of prediction of individual difference in pharmacokinetics from a Monte Carlo simulation considering such factors and succeeded in the prediction of pharmacokinetics for CYP3A4 substrates. The simulation showed that drugs with low bioavailability (F) due to first pass metabolism exhibited large individual variability. Low F drugs in clinical also exhibit large individual variability. The simulation reproduced the same results as the actual results. For the simulation of individual differences of F, the fraction absorbed (Fa) was assumed to be 100%. The inter-individual difference in Fa may also contribute to the inter-individual difference in F. Next, the effect of inter-individual difference in Fa on F was investigated. We collected F data for drugs that are mainly excreted to urine to obtain data for individual difference in Fa. The coefficient of variation of F for low F drugs was approximately 50%. We simulated the inter-individual differences of Fa using various absorption rate constants with CV of 50%. The simulated CV values reflected actual CV values at all F values. This study suggests that absorption might contribute to the inter-individual differences in F similar to first pass metabolism.