ELUCIDATION ON UNIQUE PHARMACOKINETIC PROFILE OF FINASTERIDE BY A MODEL ANALYSIS INCLUDING ITS BINDING TO TESTOSTERONE 5-ALPHA-REDUCTASE

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Finasteride is a potent inhibitor of testosterone 5-alpha-reductase and it has been launched as a drug for the treatment of androgenetic alopecia (AGA) in Japan. In this study, pharmacokinetics of finasteride after single and multiple dosing were investigated in consideration of binding affinity of finasteride to 5-alpha-reductase. Healthy Japanese male adults received a tablet containing 0.2 or 1 mg of finasteride once daily for 17 days. Plasma concentrations of finasteride were determined at designated time points after the 1st and 17th day of dosing as well as before each dosing in the subjects. Compared AUC and Cmax of finasteride on the 1st day at 0.2 mg dose with those at 1 mg dose, their increases were much greater than dose proportional. However, trough plasma concentrations indicated the steady state was almost reached on the 2nd or 3rd day at both doses and dose-proportional increases in AUC and Cmax for the 0.2 and 1 mg dose were observed on the 17th day. In order to investigate the unique profiles of plasma concentrations at the 0.2 and 1 mg dose, the model analysis was conducted. The binding/dissociation kinetics to the target enzyme were incorporated into the model since the dissociation rate of finasteride from 5-alpha-reductase was observed to be slow in vitro. As a result, plasma concentration-time profiles at both doses were reasonably simulated and the effect of binding on plasma clearance was demonstrated on the 1st day at the 0.2 mg dose. These results indicate that the binding/dissociation kinetics to the target enzyme would contribute to plasma clearance of a drug, when the drug is dosed singly with a small dosage and the dissociation rate of the drug from the target enzyme is slow.

QUANTITATIVE PREDICTION OF HUMAN INTESTINAL AVAILABILITY OF CYP3A4 SUBSTRATES BASED ON UNBOUND CONCENTRATION

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We previously reported a method to predict human intestinal availability (Fg) of CYP3A4 substrates based on an in vitro metabolic study with human intestinal microsomes (HIM) and a transport or efflux study with Caco-2 cells. The Fg values that were predicted based on the total concentration were similar to those calculated from the reported human administration studies. When the Fg values were predicted based on the unbound concentration, the predicted values were much greater than the reported values. In this study, estimation methods of several parameters were modified, and the prediction based on the unbound concentration was improved. In our previous reports, the hepatic availability (Fh) values were obtained from the reported plasma concentration profiles following intravenous administration. The Fg values were then calculated using the Fh values and the reported plasma concentration profiles following oral administration. In the present study, the blood-to-plasma concentration ratio was measured, and the Fh and Fg values were obtained based on the blood concentration. Moreover, the efflux clearance from Caco-2 cells was calculated from the transcellular transport data, not from the flux data. As previously reported, the unbound fraction in the presence of HIM was measured to calculate the unbound metabolic clearance (CLm,u). The unbound fraction in Caco-2 cells was also estimated from an accumulation study, and the unbound efflux clearance (CLeff,u) was calculated from the transcellular transport data. CLm,u, CLeff,u and the reported Fg values of several CYP3A4 substrates were fit to the following equation: Fg = CLeff,u / (CLeff,u + α × CLm,u), and the scaling factor (α) of approximately 20 was obtained. Introduction of this scaling factor made the unbound concentration based prediction much improved.