PHARMACOKINETIC ANALYSIS OF GASTRO-INTESTINAL TRANSIT AND ABSORPTION PROFILES IN PATIENTS BEFORE AND AFTER GASTROSTOMY

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The Gastrointestinal-Transit-Absorption (GITA) model is useful for the analysis and prediction of the transit and absorption behavior of drugs orally administered in rats and humans. In the present study, we attempted to assess the effect of gastrostomy on GI transit kinetics of drugs orally administered by using gamma-scintigraphy, a non-invasive technique to evaluate GI transit. We also attempted to predict the serum concentration-time curve of orally administered famotidine in the same subjects. To estimate GI transit, GI tract was divided into four segments, stomach, jejunum, ileum, and colon. 99mTc-labeled diethylenetriamine-pentaacetic acid (DTPA), an unabsorbable marker, was administered orally or via gastric fistula concomitantly with famotidine. The absorption rate constant of famotidine in each segment was extrapolated from the values obtained in rats. Pharmacokinetic parameters after intravenous administration cited from literature were used as weight function for predicting the serum concentration profile after oral administration. No significant change was observed in GI transit kinetics before and after gastrostomy. Based on GITA model, the serum concentration-time curves of famotidine were well predicted using obtained individual GI transit parameters.

A COMPREHENSIVE ANALYSIS ON THE SPECIES DIFFERENCE OF ORAL DRUG ABSORPTION IN DOGS, MONKEYS AND HUMANS

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Pharmacokinetic (PK) studies in experimental animals such as rats, dogs and monkeys are quite important at the preclinical stage to predict human PK. However, large species differences sometimes lead to the inaccurate prediction of human PK and may cause the serious problems in the clinical study. In this study, we investigated the PK of several commercial drugs in beagle dogs and cynomolgus monkeys to make clear the reason of the species differences. Drugs are administered to dogs and monkeys (IV and oral) and the total bioavailability (BA), Fa*Fg and Fh were calculated. Human data were obtained from the literature. We also conducted the in vitro metabolic stability assay in hepatic microsomes and the results were compared with the in vivo PK properties. From the result of in vivo PK analysis, most drugs tested showed lower BA in dogs and monkeys than that in humans, but only poorly permeable drugs showed the higher BA in dogs. CYP substrates showed quite low BA in both animals than that in humans. For those drugs, both Fh and Fa*Fg tended to be lower in dogs and monkeys than in humans and Fh values calculated from the in vitro study showed relatively good correlation with those obtained from in vivo PK analysis. Since in vitro permeability of CYP substrates were high, it seems that Fg is the main factor of low Fa*Fg. From these results, it was suggested that low oral BA in dogs and monkeys was attributed by not only the hepatic metabolism but also the intestinal first-pass metabolism.