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DOSE SELECTION AND POPULATION PHARMACOKINETICS OF IMATINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA.

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Imatinib is the molecular target drug which selectively inhibits Bcr-Abl tyrosine kinase causing Philadelphia-positive chronic myeloid leukemia (CML) and KIT tyrosine kinase causing KIT-positive gastrointestinal stromal tumors. However, the population pharmacokinetics (PPK) of imatinib for Japanese patients remains unknown. Imatinib (200-600mg/day) was orally administered and blood samples were collected up to 45 month. We performed a PPK study of 33 CML patients(20 males, 13 females : 47.5 years old on the average) with 439 samples using Nonlinear mixed-effect model. Age, body surface area, creatinine clearance and ALT were found as a clearance covariates in the final model, especially age and body surface seemed to be essential for the dose selection based on the clearance value. The bootstrap method showed the robustness of this model. The present result demonstrated that the current administration method at a dose of 400 mg/day is appropriate and effective but some patients who was smaller body surface area developed side effects. Our results may prove to be useful as a basic reference for the clinical usage of imatinib.

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CYTOSOLIC SULFOTRANSFERASE-MEDIATED FORMATION OF NATRIURETIC SUBSTANCE, XANTHURENIC ACID SULFATE

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Natriuretic substances are a group of molecules affecting sodium homeostasis in the body. Recently two new molecules having natriuresis effects, xanthurenic acid 8-O-β-D-glucoside and xanthurenic acid 8-O-sulfate (XA-sulfate), have been purified from human urine. In the present study, we have investigated the sulfation of xanthurenic acid (XA) in mouse tissues to assess the contribution of specific sulfotransferases (STs) to the reaction. All tissue cytosols studied (liver, stomach, jejunum, colon and kidney) were capable of forming XA-sulfate with no significant differences in \( K_m \) values between tissues of both sexes. Jejunum showed the lowest \( K_m \) value (male: 0.7 ± 0.05; female: 0.6 ± 0.04 \( \mu \)M) and the value of \( V_{max}/K_m \) for the reaction was much greater than those of other tissues. The kinetic analyses with mouse STs (St1a4, St1b3, St1c9 and St1d1) showed the lowest \( K_m \) value for St1b3 (0.52 ± 0.02 \( \mu \)M), and the value was comparable with that of jejunum cytosol. The highest expression of St1b3 in small intestine was confirmed by reverse transcription-PCR and immunoblot analyses. Thus St1b3 is suggested as a major enzyme responsible for XA-sulfation in jejunum. Similar to mouse St1b3, human ST1B2 and rat ST1B1 mediated XA sulfation efficiently. These results indicate the functional role of ST1B subfamily of sulfotransferase on XA-sulfate formation in the body, which XA is likely to be an endogenous substrate for ST1B subfamily enzymes.