Thesis Title Pharmacokinetics of Hydroxyurea in Thai Patients with Beta-thalassemia/HbE Disease

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ABSTRACT

Hydroxyurea (HU), an antitumor agent, is prone to be used in the treatment of thalassemia. As the disease is mostly found in Thais, HU's pharmacokinetic should be studied in order to provide additional data for drug use. The study was designed to study pharmacokinetics of HU after single administration at a dose of 20 mg/kg, and after single administration of HU at three different doses of 10, 20 and 30 mg/kg, and the evaluation of clinical outcome of HU treatment for 6 months.

Pharmacokinetic study of HU after single dose of 20 mg/kg was carried out in 14 beta-thalassemia/HbE patients, six men and eight women, with the mean (± SD) age and weight of 30.93 (± 8.39) years and 42.36 (± 5.18) kg, respectively. HU was administered as a single oral dose of 20 mg/kg after an overnight

fast. Breakfast was allowed 2 hours later. Blood samples were collected prior to drug administration and at 0.25, 0.50, 1, 2, 4, 6, 8, 10 and 24 hours after drug administration. Plasma were separated, kept at -20 ^{o}c until analysis which were performed within 2 days of collection. HU was analysed by colorimetric method that showed high precision with % CV of 4.29 and 4.06 at the concentration of 0.5 and 2.0 mg/l, respectively. The PCNONLIN one-compartment open model was used to determine the pharmacokinetic parameters. The mean $\pm$ SEM values of peak plasma concentration (C_{max}), time to reach peak plasma concentration (T_{max}), elimination half-life ($T_{1/2}$), absorption rate constant (K_a), area under the plasma concentration-time curve ($AUC_{0-\infty}$), the volume of distribution (Vd) and the total body clearance (Cl) were 26.43 $\pm$ 1.66 mg/l, 1.59 $\pm$ 0.09 hours, 1.33 $\pm$ 0.10 hours, 0.8056 $\pm$ 0.0974 hr^{-1} and 119.98 $\pm$ 9.83 mg.hr/l, 0.35 $\pm$ 0.03 l/kg and 133.72 $\pm$ 14.18 ml/min, respectively. Comparison of C_{max}, T_{max}, $T_{1/2}$, Vd and Cl between male and female, between splenectomized and nonsplenectomized patients and between patients with normal functions of hepatic and biliary tract and patients with impaired functions of hepatic and/or biliary tract were not significant difference.

The pharmacokinetic of HU after single administration of three different doses of 10, 20 and 30 mg/kg was studied in 4 beta-thalassemia/HbE patients, two males and two females, with the mean ($\pm$ SD) age and weight of 32.25 ($\pm$ 4.43) years and 44.73

(± 5.17) kg, respectively. Each patient administered each dose after an overnight fast and blood samples were collected and assayed. The results indicated linear pharmacokinetic as C_{max} (mean ± SEM) were 10.80 ± 0.76, 20.87 ± 1.10 and 31.55 ± 3.50 mg/l, $AUC_{0-\infty}$ were 53.04 ± 2.57, 96.60 ± 3.89 and 162.52 ± 8.73 mg.hr/l and Cl were 158.35 ± 7.94, 161.62 ± 8.29 and 142.67 ± 13.00 ml/min, following 10, 20 and 30 mg/kg dose of HU, respectively.

Treatment of beta-thalassemia/HbE patients with HU for 6 months was evaluated and presented in the last part of study. Each patient received 10 mg/kg/d as the first dose and dose adjustment was applied till the optimal dose was obtained which must not exceed 20 mg/kg/d. The results demonstrated significantly increased in total hemoglobin (Hb) and fetal Hb (HbF) concentrations by 13.66 and 38.89%, respectively and decreased in HbE by 4.55%. Chronic administration showed no accumulation of the drug. Adverse effects were found but reversible when the drug dose was reduced or discontinued.

The present study demonstrated that HU was rapidly absorbed from GI tract, extensively eliminated within 24 hours and there was no accumulation of the drug after chronic administration. In addition, HU induced Hb and HbF concentrations and decreased HbE concentration, the drug should be a potential candidate for the treatment of beta-thalassemia/HbE disease.