Abstract

A pharmacokinetic study of deferiprone

Single oral dose pharmacokinetics of an iron chelator, deferiprone (L1) and its metabolite, were studied in 20 normal healthy volunteers and 25 β-thalassemia hemoglobin E patients (β-thal/Hb E; 11 mild-moderate and 14 severe). After an overnight fasting, the subjects received a 25 mg/kg deferiprone. Blood samples were corrected pre-dose and 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 after dosing. Urine output was collected at 0, 0-2, 2-4, 4-8, 8-12, 12-24 hours. Deferiprone (L1) and glucuronide deferiprone (L1-G) concentrations in serum and urine were determined using a validated HPLC method. Non transferrin bound iron (NTBI) and urinary iron excretion (UIE) were also determined using colorimetric methods.

Absorption of L1 was rapid with time for the maximum serum concentration (Tmax) of 50 min both normal subjects and patients. The significant lower in maximum serum drug concentration (Cmax) and area under serum concentration time curve ($AUC_{0\text{-}inf}$) of L1 and L1G were observed in patients and depended on disease severity. The significant longer elimination half-life ($t_{1/2}$) of L1 was also found in severe patients (mean±SD; 127.1±17.7, 173.9±62.8 and 196.5±105.4 min for normal, mild-moderate and severe, respectively). The changes in pharmacokinetic parameters showed good correlations with iron loading status of the patients.

L1-iron complexes were increased simultaneously with L1 in blood circulation. The concentration of serum L1:iron complexes and UIE were found to be related with disease severity. There were good correlations between UIE and NTBI ($r=0.513$; $p=0.004$), serum iron ($r=0.585$; $p=0.001$) and ferritin ($r=0.667$; $p<0.001$). Moreover the lower molar ratio of L1:iron (<3) in serum and urine could be found in patients with heavy iron overload. It can be concluded that iron loading status of the patients was a major factor determining pharmacokinetics of L1. Thus, for the highest effectiveness with the lowest toxicity, dosage-regiment of L1 should be considered and monitored according to individual iron status of the patients.

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