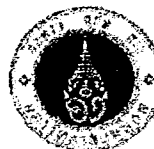


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Pharmacokinetics of deferiprone in patients with β -thalassaemia: impact of splenectomy and iron status.

Abstract

BACKGROUND AND OBJECTIVE: Iron-rich transfusions and/or a compensatory increase in iron absorption ultimately result in iron loading in patients with β -thalassaemia. Hence, without iron chelation, iron accumulates relentlessly. Deferiprone has been shown to be capable of reducing the iron burden in patients with β -thalassaemia. However, there is wide interpatient variation in deferiprone-induced urinary iron excretion (UIE). We hypothesized that splenectomy and iron status might influence the pharmacokinetic profiles of deferiprone in patients with β -thalassaemia/haemoglobin E, and the present study was aimed at examining this hypothesis. **STUDY PARTICIPANTS AND METHODS:** Thirty-one patients with β -thalassaemia/haemoglobin E (20 splenectomized and 11 non-splenectomized patients) were enrolled in the study. After an overnight fast, the subjects received a single oral dose of deferiprone 25 mg/kg of bodyweight. Blood samples were collected pre-dosing and at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 480 minutes after dosing. Urine output was pooled and collected at 0-2, 2-4, 4-8, 8-12 and 12-24 hour intervals. Serum and urine concentrations of deferiprone and its metabolite deferiprone glucuronide were determined using a validated high-performance liquid chromatography method. Serum deferiprone-chelated iron and UIE were determined using a validated colourimetric method.

RESULTS: No significant difference in the pharmacokinetic parameters of non-conjugated deferiprone was observed between splenectomized and non-splenectomized patients. However, the maximum serum concentration (C_{max}) and the area under the serum concentration-time curve (AUC) from time zero to infinity (AUC_{∞}) values of deferiprone glucuronide were significantly lower (both $p < 0.05$) in splenectomized patients (median 53.2 $\mu\text{mol/L}$ and 12 634 $\mu\text{mol} \cdot \text{min/L}$, respectively) than in non-splenectomized patients (median 70.5 $\mu\text{mol/L}$ and 20 601 $\mu\text{mol} \cdot \text{min/L}$, respectively). The C_{max} and the AUC from time zero to the time of the last measurable concentration (AUC_{last}) values of serum deferiprone-chelated iron, as well as UIE, were significantly higher ($p < 0.001$) in splenectomized patients (median values 7.1 $\mu\text{mol/L}$, 1645 $\mu\text{mol} \cdot \text{min/L}$ and 77.1 μmol , respectively) than in non-splenectomized patients (median values 3.1 $\mu\text{mol/L}$, 545 $\mu\text{mol} \cdot \text{min/L}$ and 12.5 μmol , respectively). Urinary excretion of non-conjugated deferiprone and deferiprone glucuronide did not differ between the two groups. Further analyses using multiple linear regressions indicated that the iron profiles (non-transferrin-bound iron and ferritin) were significant predictors of the pharmacokinetic parameters of non-conjugated deferiprone, deferiprone-chelated iron and UIE. In addition, splenectomy status was identified as the strongest predictor of the AUC_{last} of deferiprone-chelated iron and UIE.

CONCLUSION: Both iron and splenectomy status have significant effects on the pharmacokinetics and iron chelation efficacy of deferiprone. A greater degree of iron overload in splenectomized patients results in alterations in pharmacokinetic parameters (the C_{max} and AUC) of deferiprone glucuronide and deferiprone-chelated iron, as well as a significant increase in UIE.

For More Information

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