

DEFERIPRONE DOSING RECOMMENDATION IN RENALLY IMPAIRED PATIENTS UNDERGOING CHELATION THERAPY

Francesco Bellanti¹, Meindert Danhof¹, Oscar Della Pasqua^{1,2}

¹ Division of Pharmacology, Leiden Academic Centre for Drug Research, the Netherlands

² Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Stockley Park, UK
Contact: bellantif@lacdr.leidenuniv.nl

Introduction and objectives

Patients affected by transfusion-dependent diseases undergo a life-long blood transfusion therapy to survive, which results into a series of complications, among which iron overload is the most relevant one. Chelation therapy is therefore required for the removal of iron excess. The objectives of this analysis are 1) to characterise the pharmacokinetics of the chelating agent deferiprone [1, 2] using a model-based approach and 2) to assess the effect of demographic and physiological factors on drug exposure in renally impaired patients.

Methods and Data

Data from 55 adult healthy subjects receiving deferiprone (solution 100 mg/ml) were used for model building purposes. A population pharmacokinetic analysis was performed using NONMEM VII. The contribution of gender, age, weight, and creatinine clearance on drug disposition was evaluated according to standard forward inclusion, backward deletion procedures. Model selection criteria were based on graphical and statistical summaries.

Table 1. Model parameters.

Parameters	Estimate	Median	CV (%)
CL/F (L/h)	30.8	30.9	3.1
V/F males (L)	78.4	78.5	2.4
Ka (h ⁻¹)	8.2	8.7	29.2
Lagtime (h ⁻¹)	0.146	0.145	3.9
Error: weighting factor	2.4	2.41	15.2
V/F females (L)	65.3	65.3	3.8
Eta CL/F (%)	23.87	23.6	17.6
Eta V/F (%)	16.67	16.34	20.2
Block CL-V	0.0345	0.0335	20
Eta Ka (%)	99.54	100	23.8
Sigma (%)	7.52	7.53	25.8

Model Validation - Healthy Subjects vs. Patients

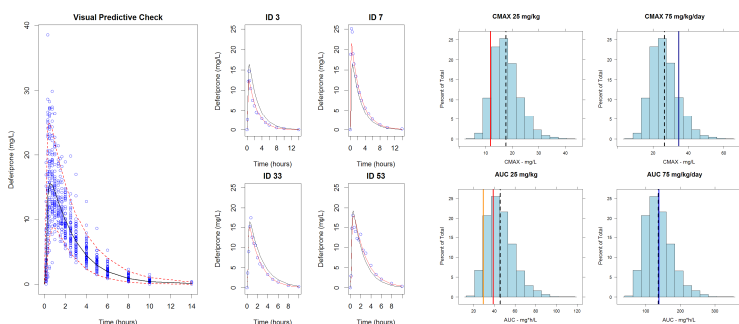


Figure 1. Visual predictive check, and predicted pharmacokinetic profiles in a random selection of subjects

Figure 2. Predicted AUC and Cmax distribution after administration of XX mg/kg. Vertical line depicts reference values from [3, 4, 5].

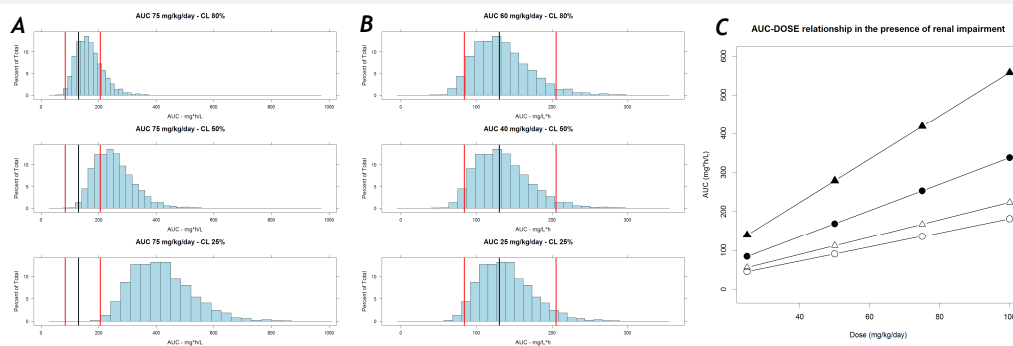
A one-compartment model with first order oral absorption was found to best describe the pharmacokinetics of deferiprone. Goodness-of-fit plots, and visual predictive check (VPC) indicated that the model provides an unbiased description of the data (figure 1).

As shown in figure 2, predicted AUC and Cmax were comparable with reported estimates in thalassaemic patients. In addition, gender differences in the apparent volume of distribution (20% difference) have been identified, which may contribute to an increase in peak concentrations in females. The expected changes in Cmax at the recommended dosing regimen though, are unlikely to have clinical implications.

Renal Impairment - Dosing Recommendation

Simulation scenarios revealed that dose adjustment is required for patients with reduced creatinine clearance (figure 3A). Doses of 60, 40 and 25 mg/kg for patients showing mild, moderate and severe renal impairment are proposed based on creatinine clearance values of 60-89, 30-59 and 15-29 ml/min, respectively (figure 3B). Changes in the AUC-Dose relationship at different degrees of renal impairment are shown in figure 3C.

Figure 3. Predicted AUC distributions in adult patients receiving the standard 75 mg/kg/day regimen (A) and the adjusted dosing regimen (B) stratified by level of renal impairment. Upper, mid and lower panel summarise findings based on patients showing 80, 50, and 25% of the normal clearance, respectively. Black and red lines represent the median, 5th and 95th percentiles of the reference population with normal renal function. (C) Impact of varying degrees of renal impairment on systemic exposure. Open circles and triangles, closed circles and triangles represent normal renal function, and reductions of 20, 50 and 75% in deferiprone clearance, respectively.



Conclusions

Our analysis has provided evidence of the impact of gender and creatinine clearance on the pharmacokinetics of deferiprone. Moreover, it supports the need for dose adjustment in renally impaired patients. The effect of these covariates on systemic exposure is currently not described in the prescribing information of deferiprone.

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