PHARMACOKINETICS

Effects of renal impairment on the pharmacokinetics of orally administered deferiprone

Correspondence Dr Fernando Tricta, MD, Medical Affairs, ApoPharma Inc., 200 Barmac Drive, Toronto, Ontario M9L 2Z7, Canada. Tel.: +1 416 401 7332; Fax: +1 416 401 3867; E-mail: ftricta@apopharma.com

Caroline Fradette[1], Vincent Pichette[2], Éric Sicard[3], Anne Stilman[1], Shalini Jayashankar[1], Yu Chung Tsang[1], Michael Spino[1,4] and Fernando Tricta[1]

[1]ApoPharma Inc., 200 Barmac Drive, Toronto, Ontario M9L 2Z7, Canada, [2]Hôpital Maisonneuve-Rosemont, 5415 Assomption Boulevard, Montreal, Quebec H1T 2M4, Canada, [3]Algorithme Pharma, 575 Armand-Frappier Blvd., Laval, Quebec H7V 4B3, Canada, and [4]Leslie Dan Faculty of Pharmacy, 144 College St, Toronto, Ontario M5S 3M2, Canada

AIMS

In light of the growing recognition of renal disease in thalassemia, it is important to understand the impact of renal impairment on the pharmacokinetics of iron chelators. This study evaluated the pharmacokinetics and safety of the iron chelator deferiprone (DFP) in subjects with renal impairment in comparison with healthy volunteers (HVs).

METHODS

Thirty-two subjects were categorized into four groups based on degree of renal impairment: none, mild, moderate or severe, as determined by estimated glomerular filtration rate (eGFR). All subjects received a single oral dose of 33 mg kg^{-1} DFP, provided serum and urine samples for pharmacokinetic assessment over 24 h and were monitored for safety.

RESULTS

Renal clearance of DFP decreased as renal impairment increased. However, based on C_{max}, AUC(0,t) and AUC(0,∞), there were no significant group differences in systemic exposure, because less than 4% of the drug was excreted unchanged in the urine. DFP is extensively metabolized to a renally excreted, pharmacologically inactive metabolite, deferiprone 3-O-glucuronide (DFP-G), which exhibited higher C_{max}, AUC(0,t), AUC(0,∞) and longer t_{max} and $t_{1/2}$ in the renally impaired groups compared with HVs. The C_{max} and AUCs of DFP-G increased as eGFR decreased. Overall, 75%–95% of the dose was retrieved in urine, either as DFP or DFP-G, regardless of severity of renal impairment. With respect to safety, DFP was well tolerated.

CONCLUSIONS

These data suggest that no adjustment of the DFP dosage regimen in patients with renal impairment is necessary, as there were no significant changes in the systemic exposure to the drug.

Introduction

Deferiprone (DFP; trade name Ferriprox™; chemical name 3-hydroxy-1,2-dimethylpyridin-4-one) is an orally active bidentate iron chelator that preferentially binds trivalent iron cations (Fe^{3+}) in a 3 : 1 (deferiprone : iron) complex. It is currently approved for the treatment of patients with transfusional iron overload due to thalassemia syndromes. Chronic blood transfusion therapy reduces disease-related morbidity and mortality in these patients, but introduces a progressive iron overload that damages the heart, liver and endocrine organs in particular [1, 2]. Therapy with DFP has been shown to result in reduction in iron burden in regularly transfused iron-overloaded patients [3], as well as reduction of iron-induced cardiac disease and prolongation of survival [4].

Over the last decade, there has been an increased level of attention directed towards renal disease in patients with thalassemia. Case reports and natural history studies have revealed varying degrees of both tubular and glomerular dysfunction, which tends to increase with age and the presence of co-morbidities. Proteinuria is common. Some patients with thalassaemia develop renal tubular dysfunction that is related to the disease itself (including chronic hypoxia from anaemia), the effects of iron overload and the effects of chelator therapy, while other patients have an increased creatinine clearance, leading to hyperfiltration [5–8]. In light of the growing recognition of renal disease in thalassaemia, it is important to understand the impact of renal impairment on the pharmacokinetics of iron chelators.

In patients with kidney disease, administration of the usual doses of many drugs often leads to inappropriate responses and a higher incidence of adverse reactions [9, 10]. The most obvious explanation for these effects is increased drug concentrations due to a reduction in drug clearance, particularly because of a decreased glomerular filtration rate (GFR) [11]. This is of particular relevance to elderly patients where GFR is reduced [12]. However, several mechanisms other than GFR might also contribute, including changes in renal transporters [13], down-regulation of cytochrome P450 (CYP450) enzymes [14, 15], possible suppression of phase II metabolic enzymes [16] and abnormal plasma protein binding [17], which could alter drug disposition, leading to altered drug concentration–time profiles. Techniques for determining the appropriate drug dosage in patients with renal impairment have been well worked out [9, 10, 18, 19], but generally require a good understanding of the fraction of drug excreted unchanged, the fraction bound to plasma proteins and whether or not active transport is a prominent contributor to renal elimination.

DFP glucuronidation seems to depend almost totally on UDP glucuronosyltransferase 1 A6 (UGT1A6), especially in the liver, with the predominant metabolite being an inactive 3-O-glucuronide conjugate (DFP-G) [20, 21]. Glucuronidation of deferiprone results in loss of the iron-binding capacity due to the inactivation of the 3-hydroxy functional group [22]. Both the metabolite and the DFP-iron complex are excreted primarily by the kidneys, and approximately 80% of the dose is recovered from the urine in the form of drug, metabolite and drug bound to iron [2]. Less than 20% is bound to serum proteins (unpublished data).

To our knowledge, the current study is the first systematic investigation of the pharmacokinetics and safety of DFP in subjects with impaired renal function, and provides guidance on whether dose adjustment is required in this population.

Methods

Study design and study subjects

This non-randomized, open label, single dose, parallel group study was conducted to compare the safety and pharmacokinetics of DFP in subjects with and without renal impairment. A total of 32 participants aged 31 to 75 years were enrolled, comprising 24 patients with different stages of renal impairment and eight healthy volunteers (HVs). The degree of impairment was determined using the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease Study [23], which is the equation recommended by the FDA Guidance for Industry for the estimation of creatinine clearance [24]. (Arguably, estimation of GFR based on cystatin C might have provided more accurate results. However, any difference would not have changed the interpretation of the pharmacokinetic analyses.) Subjects were categorized into four groups, eight per group: no renal impairment (eGFR ≥90 ml min^{-1} 1.73 m^{-2}), mild impairment (eGFR 60–89 ml min^{-1} 1.73 m^{-2}), moderate impairment (eGFR 30–59 ml min^{-1} 1.73 m^{-2}) and severe impairment (eGFR 15–29 ml min^{-1} 1.73 m^{-2}). All renally impaired subjects, including those categorized as severe, had to be clinically stable in the opinion of the investigator. Exclusion criteria included history of renal transplant, current dialysis, a clinically significant medical condition other than renal impairment (history or presence, in the investigator's opinion, of clinically significant unstable respiratory, cardiovascular, pulmonary, hepatic, haematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric

disease) and presence of a gastrointestinal disorder that might have interfered with drug absorption or otherwise affected PK parameters. The renally impaired subjects and the HVs were matched as far as reasonably possible for age, weight and tobacco use, and an attempt was made to have a similar number of males and females within each group. Prior to enrolment of the first subject, the study was approved by the ethics committee IRB Services, and was posted on ClinicalTrials.gov (trial registration number NCT01770652). Written informed consent was obtained from each participant prior to enrolment in the study.

Following an overnight fast of at least 10 h, all subjects received a single oral dose of 33 mg kg^{-1} of DFP, provided as 500 mg Ferriprox tablets rounded to the nearest half-tablet (250 mg).

Sample collection and analysis

Blood samples (5 ml) were collected in Vacutainer tubes without anticoagulant or separating gel at the following time points: prior to dosing and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.66, 2.0, 2.5, 3, 4, 6, 9, 12, 16 and 24 h post-dose. Samples were centrifuged and the serum was divided into two aliquots and stored at −20°C until shipped for analysis. Urine samples to determine the urinary excretion of DFP were collected at the following intervals: −2 to 0 h prior to dosing and at 0–2, 2–4, 4–8, 8–12 and 12–24 h post-dose. All urine collected during an interval was pooled and two 10 ml aliquots from each sampling interval were stored at −80°C until shipped for analysis.

Both serum and urine samples were analyzed for concentrations of DFP and its metabolite DFP-G, using validated high-performance liquid chromatography with mass spectrometric detection method (HPLC-MS/MS). (The method was developed and validated by Celerion, 624 Peach Street, Lincoln, Nebraska, 68 502, USA.) Quality control (QC) samples were used to demonstrate adequate precision and accuracy of the assay. Acceptable sample stability and sensitivity were also demonstrated. For the quantification of DFP and DFP-G in serum, the limit of quantitation (LOQ) was 0.1 μg ml^{-1}. Concentrations were determined using a weighted linear regression analysis of peak area ratios of the analyte and internal standard (over a concentration range from 0.1 to 20 μg ml^{-1} for both analytes). Dilution integrity, up to 100 μg ml^{-1} (diluted 10-fold), was also demonstrated for both analytes. Precision and accuracy for both intra- and inter-day variability ranged from 1.9% to 5.1% and from −3.0 to 2.0%, respectively. For the quantification of DFP and DFP-G in urine, the LOQs were 0.5 μg ml^{-1} and 50.0 μg ml^{-1}, respectively. Quantitation was determined using a weighted linear regression analysis of peak area ratios of the analyte and internal standard (over a concentration range from 0.5 to 100 μg ml^{-1} for DFP and 50.0 to 10 000 μg ml^{-1} for DFP-G). Dilution integrity up to 500 μg ml^{-1} and 20 000 μg ml^{-1} (diluted 10-fold) has also been demonstrated for DFP and DFP-G, respectively. Precision and accuracy for both intra- and inter-day variability ranged from 1.1% to 9.4% and from −10.6 to 8.0%, respectively.

Pharmacokinetic analyses

The following pharmacokinetic parameters were determined for DFP: C_{max} (maximum measured serum concentration), t_{max} (time to maximum serum concentration), AUC(0,t) (area under the concentration–time curve to the last measureable concentration), AUC(0,∞) (area under the concentration–time curve to infinity), $t_{1/2}$ (terminal elimination half-life), CL/F (total body clearance, corrected for bioavailability), CL$_r$ (renal clearance), V_d/F (apparent volume of distribution, corrected for bioavailability), Ae(0,24 h) (amount excreted in urine from time zero to 24 h), and Fe(0,24 h) (fraction of dose excreted unchanged in urine from time zero to 24 h). For DFP-G, the pharmacokinetic parameters of C_{max}, t_{max}, AUC(0,t), AUC(0,∞), $t_{1/2}$, CL$_r$, Ae(0,24 h) and Fe(0,24 h) were determined.

Pharmacokinetic and statistical analyses were performed using validated software (Phoenix® WinNonlin® version 6.3 and SAS® version 9.2, respectively). The pharmacokinetic parameters of DFP and its metabolite were derived from individual serum concentration– and urinary excretion–time profiles, and were summarized using descriptive statistics. A regression analysis in which the estimated renal function was treated as the predictor variable was used to evaluate the relationship between renal function and the estimated pharmacokinetic parameters of DFP and DFP-G. The eGFR and creatinine clearance were used as the estimate of renal function in separate analyses. As the correlation (slope of trend ≠ 0) between a PK parameter and the renal function was found to be significant ($P < 0.05$), an analysis of variance (ANOVA) was performed to assess the differences in the PK parameter among the control group and the three groups of subjects with impaired renal function, and the 90% confidence interval of the difference was calculated for each pairwise comparison. The Tukey–Kramer method was used for multiplicity adjustment. For AUC(0,t), AUC(0,∞) and C_{max}, the log-transformed data were used in the regression analysis and the ANOVA.

Safety assessment

Safety was assessed throughout the study by collecting information on the following: adverse events (AEs), use of concomitant medications, vital signs, coagulation times, physical examination, standard 12-lead electrocardiogram, haematology, biochemistry and urinalysis. The data for continuous variables were summarized using descriptive statistics and the data for discrete variables were tabulated with frequency tables.

Results

Study subjects

Subject ages ranged from 31 to 75 years, with an overall mean of 59 (± 11) years. The group means ranged from 56 (± 9) years for HVs to 64 (± 5) years for subjects with mild impairment. While males outnumbered females overall, 19 (59.4%) to 13 (40.6%), all groups included subjects of both genders, with the male : female ratio ranging from 3 : 5 in the HV group to 6 : 2 in the severe impairment group. The severe renal impairment group included two Black subjects. All other subjects were White. Mean weight was similar across groups, ranging from 69.3 kg to 74.6 kg, as was BMI, ranging from 24.4 to 27.3 kg m^{-2}. The majority of participants had never smoked or had quit, with just four reporting current smoking. Mean eGFR (ml min^{-1} 1.73m^{-2}) was 99.8 (± 9.5) in the HV group, 75.4 (± 9.3) in the mild group, 45.9 (± 9.1) in the moderate group and 22.5 (± 3.0) in the severe group.

All 32 subjects received the assigned dose of study drug and provided serum and urine samples over 24 h post-dose

for the assessment of serum pharmacokinetics and renal clearance of DFP and its glucuronide metabolite. All subjects were included in the safety analysis, but a total of five were excluded from the PK assessments of serum DFP and/or DFP-G: two subjects (one with moderate impairment, one with severe impairment) from the analysis of serum DFP data, one (moderate impairment) from the analysis of serum DFP-G data and two (both with severe impairment) from the analysis of both analytes. The reasons for the exclusions were consecutive missing concentration values adjacent to the observed DFP t_{max} for analytical reasons (haemolysis), several missing samples around the expected t_{max} for clinical reasons (difficulty in blood collection) and a concern over a subject taking a prohibited concomitant medication (furosemide). Accordingly, the population for the analysis of serum DFP data contained 28 subjects (i.e. four excluded) and that for the analysis of DFP-G data contained 29 subjects (i.e. three excluded). The subject who was excluded from the serum analyses due to the use of furosemide was also excluded from the analysis for both urine DFP data and urine DFP-G data. Thus, the population for the analyses of urine data contained 31 subjects. Other than in the cases of consecutive missing concentrations, the decision to exclude a subject was always made prior to conducting the bioanalysis.

Pharmacokinetics

Deferiprone. In all four groups, DFP was detected in serum within 15 min of its administration. Serum concentrations reached a mean maximum value within 0.5 to 1 h and then declined rapidly, with a mean $t_{1/2}$ that ranged from 1.7 to 2.2 h across groups. Importantly, while renal impairment, as expected, had an impact on renal clearance of DFP, with DFP renal clearance declining as the level of impairment increased, it had no impact on total body clearance. The regression analysis indicated no significant differences in C_{max}, AUC(0,t), AUC(0,∞), CL/F and V_d/F between subjects with renal impairment and HVs (see Figure 1 and Table 1). A significant trend for t_{max}, $t_{1/2}$, and CL$_r$ was observed in the
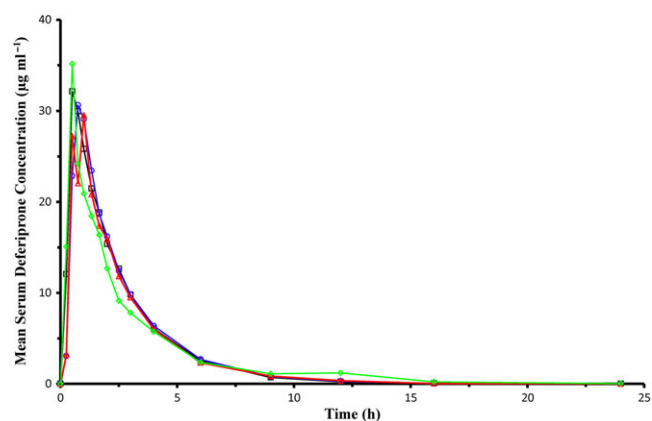

Figure 1

Mean serum deferiprone concentration–time profiles in healthy volunteers and subjects with renal impairment after a single oral dose of 33 mg kg^{-1} deferiprone. ⊸⊸ mild impairment, ▲▲ moderate impairment, ▬▬ normal function, ▬▬ severe impairment

regression analysis using eGFR as the predictor variable. However, when creatinine clearance was used as the predictor variable, only CL$_r$ exhibited a significant trend, with the value decreasing as the severity of renal impairment increased. Pairwise comparisons of group data from the ANOVA revealed significant differences for the following: normal *vs.* moderate, normal *vs.* severe, mild *vs.* moderate and mild *vs.* severe. No significant differences between groups were observed for t_{max} and $t_{1/2}$.

The fraction of DFP excreted in urine relative to the dose administered, as determined by Fe(0,24 h), ranged from 1.0% to 3.5%, which is consistent with biotransformation to DFP-G being the primary determinant of drug clearance. A significant trend ($P < 0.0003$) of decreasing Fe(0,24 h) with increasing renal impairment was observed. Significant differences ($P < 0.05$) were observed between the normal *vs.* moderate, normal *vs.* severe, mild *vs.* moderate and mild *vs.* severe groups.

The mean Fe(0,24 h) values for DFP are shown in Table 2, and the cumulative mean Fe(0,24 h) values are shown in Figure 2.

Deferiprone 3-O-glucuronide. For DFP-G, serum concentrations reached their mean maximum value within 2.5 to 4 h and then declined, with a mean $t_{1/2}$ of 2.1 to 3.4 h in all groups. A significant trend was observed for all parameters in relation to eGFR or creatinine clearance. As the severity of renal impairment increased, the values of C_{max}, AUC(0,t), AUC(0,∞), t_{max} and $t_{1/2}$ increased and that of CL$_r$ decreased (see Figure 3 and Table 3). The rate of decrease in CL$_r$ was greater in subjects with more severe renal impairment. This resulted in a greater rate of increase in C_{max}, AUC(0,t) and AUC(0,∞) in subjects with moderate or severe renal impairment than in subjects with mild renal impairment or HVs. This is supported by the metabolite : parent drug ratio of AUC(0,∞), after accounting for their difference in molecular weight, which clearly showed that exposure to DFP-G relative to that of DFP increased disproportionately as the severity of renal impairment increased. For AUC(0,t) and AUC(0,∞), significant differences were observed for all pairwise comparisons, and for C_{max}, significant differences were observed for all but moderate *vs.* severe.

In contrast to the low fraction of DFP excreted in urine, mean urinary excretion of DFP-G ranged from 73.2% to 92.1%. As with DFP, a significant trend was observed, with the values of Fe(0,24 h) decreasing as the severity of renal impairment increased. The only group difference that reached significance was between the mild and moderate groups. Regardless of the level of renal impairment, the majority of the dose of DFP was excreted as DFP-G. Overall, between 75% and 95% of the dose was retrieved in urine, either as DFP or DFP-G.

The mean Fe(0,24 h) values for DFP-G are shown in Table 3, and the cumulative mean Fe(0,24 h) values are shown in Figure 4.

Safety results

The dose of DFP was well tolerated by all subjects. There were no serious AEs, no AEs rated as severe, no withdrawals from the study for safety reasons and no clinically significant

Table 1

Summary of serum deferiprone pharmacokinetic parameter values following a single oral dose of 33 mg kg^{-1} deferiprone

| Renal function/ impairment	Normal (n=8)	Mild (n=8)	Moderate (n=7)	Severe (n=6)
C_{max} (µg ml^{-1})	37.1 (32.4), **35.1**	33.4 (28.3), **32.0**	43.3 (52.9), **39.3**	30.6 (53.0), **26.1**
t_{max} (h)	0.50 (0.25-1.00)	0.75 (0.50-1.00)	1.00 (0.50-2.00)	0.75 (0.25-4.00)
AUC$(0,t)$ (µg ml^{-1} h)	77.8 (35.7), **73.3**	76.5 (20.5), **74.9**	74.0 (20.1), **72.5**	70.1 (12.7), **69.6**
AUC$(0,\infty)$ (µg ml^{-1} h)	78.1 (35.5), **73.7**	76.9 (20.4), **75.3**	74.9 (20.1), **73.4**	70.9 (12.0), **70.5**
$t_{1/2}$ (h)	1.7 (16.0)	1.8 (9.6)	2.0 (15.9)	2.2 (41.2)
CL/F (l h^{-1})	33.4 (47.0)	31.5 (23.8)	34.8 (20.9)	34.0 (20.9)
CL$_r$ (l h^{-1})	1.0 (20.3)	0.9 (22.2)	0.5 (27.7)	0.3 (44.0)
V_d/F (l)	77.7 (38.2)	79.8 (22.8)	102.8 (26.1)	114.1 (57.1)

*Results are presented as arithmetic mean (CV%) and for C_{max}, AUC$(0,t)$ and AUC$(0,\infty)$, the geometric mean is also presented. For t_{max}, results are presented as median (range).

Table 2

Deferiprone and deferiprone-3-O-glucuronide excreted in urine as fractions of a single oral dose of 33 mg kg^{-1} deferiprone

Renal function status	Fe(0,24 h) (%)	
	DFP	DFP-G
Normal	3.5 (47.0)	86.0 (14.1)
Mild impairment	2.9 (20.5)	92.1 (10.3)
Moderate impairment	1.5 (32.3)	78.2 (11.0)
Severe impairment	1.0 (36.9)	73.2 (29.1)

Results are presented as arithmetic mean (CV%)
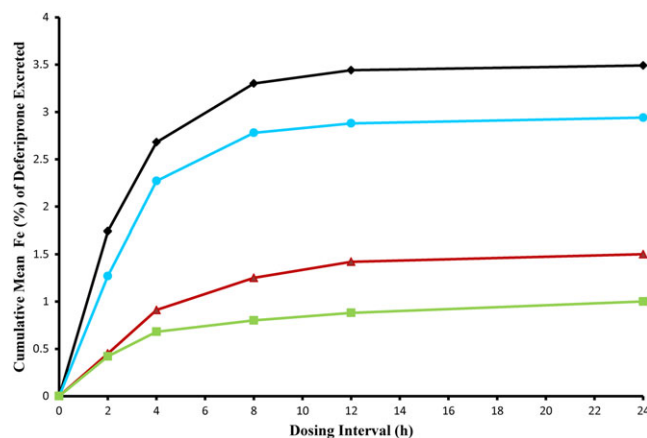
Figure 2

Fraction of deferiprone excreted in the urine over time, after a single oral dose of 33 mg kg^{-1} deferiprone. ◆ normal, ■ mild impairment, ▲ moderate impairment, ■ severe impairment

abnormalities in laboratory tests, vital signs, ECG parameters or physical examination findings either within 24 h of deferiprone administration or at the follow-up 24 to 72 h after discharge. Overall, nine subjects reported a total of 16 AEs, with the majority of AEs occurring in HVs and in subjects with mild renal impairment: seven events in two HVs, seven events in five subjects with mild renal impairment, and one event in one subject each in the groups with moderate and severe renal impairment.

The most commonly reported AEs were somnolence and headache, which were experienced by four subjects each. Somnolence was reported by one subject in the HV group and by three in the mild renal impairment group and headache was reported by one subject in each of the four groups. All eight of these events were considered related to study product.

All AEs in the study were of mild intensity except for one occurrence of moderate headache in a HV. The AEs were resolved prior to discharge, and only one required treatment (the use of ibuprofen to relieve a headache in a subject in the severe impairment group).

Discussion

The first clinical use of DFP was published in 1987 [25, 26]. Early on, it was recognized that almost all of a given dose of DFP could be recovered in the urine as the parent compound, its glucuronide metabolite and the DFP-iron complex [27]. This information has led to an assumption that dose adjustment is necessary in renal impairment to minimize risks emanating from an anticipated elevated concentration of DFP in such patients [28]. However, there has never been a study that compared the disposition of DFP in subjects with renal impairment and in healthy volunteers.

The current investigation studied the impact of renal impairment on the pharmacokinetics of DFP by comparing the
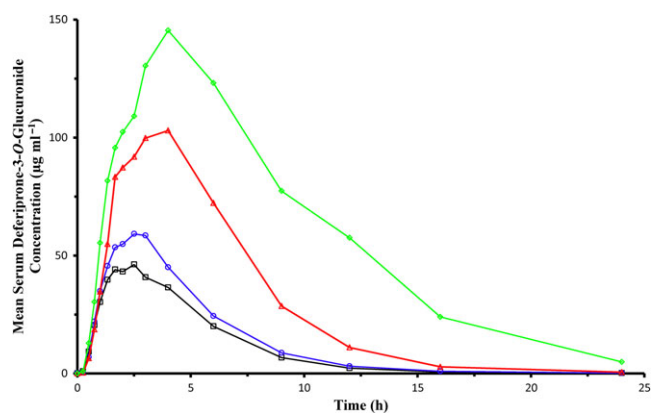
Figure 3

Mean serum deferiprone-3-*O*-glucuronide concentration–time profiles in healthy volunteers and subjects with renal impairment after a single oral dose of 33 mg kg^{-1} deferiprone. —●— mild impairment, —●— moderate impairment, —□— normal function, —●— severe impairment

Figure 4

Fraction of deferiprone-3-*O*-glucuronide excreted in the urine over time, after a single oral dose of 33 mg kg^{-1} deferiprone. —◆— normal, —■— mild impairment, —▲— moderate impairment, —■— severe impairment

disposition of DFP and its principal metabolite, DFP-G, in HVs with that in subjects with varying degrees of renal impairment. Safety parameters were also monitored in all groups. Subjects with renal impairment had serum concentrations of DFP that were similar to those of HVs. While renal clearance of DFP decreased more than three-fold as renal function declined from no impairment to severe impairment, there was no significant change in total body clearance. This can be explained by the fact that renal clearance ($CL_r = 1.0$ l h^{-1}) constituted only 3% of total body clearance ($CL/F = 33.4$ l h^{-1}) in subjects with normal renal function, as reflected by Fe(0,24 h) < 3.5% in this study and also reported in a previous study [21]. The majority of a dose of DFP is metabolized and excreted as DFP-G in the urine. As a result, no significant impact on DFP systemic exposure occurred, and the C_{max} and AUC of DFP were not significantly different among subjects with renal impairment and those with normal renal function.

This lack of difference in systemic exposure is contrasted with that seen with the 3-*O*-glucuronide metabolite. As this metabolite is extensively eliminated by excretion in the urine (Fe(0,24 h) = 86%), the significant reduction in its urinary excretion resulted in higher C_{max}, AUC(0,t) and AUC(0,∞) and longer t_{max} and $t_{1/2}$ in the renally impaired groups compared with the healthy volunteers. While DFP-G exhibited some plasma accumulation in renal impairment, it is less than what might be anticipated, as there is no biotransformation pathway to offset the reduction in renal excretion, as is the case for DFP. While the study did not measure faecal excretion, it is suspected that increased biliary excretion of DFP-G will have compensated for the decline in renal excretion in those with impaired renal function, limiting the level of accumulation. Since the terminal half-life of the DFP-G increased to only about 3 h in patients with severe renal impairment, little accumulation, beyond that observed in the single dose study, would be anticipated upon chronic dosing in patients with impaired renal function.

Table 3

Summary of serum deferiprone-3-*O*-glucuronide pharmacokinetic parameter values following a single oral dose of 33 mg kg^{-1} of deferiprone

Renal function/ impairment	Pharmacokinetic parameters*						
	C_{max} (µg ml^{-1})	t_{max} (h)	AUC(0,t) (µg ml^{-1} h)	AUC(0,∞) (µg ml^{-1} h)	$t_{1/2}$ (h)	CL_r (l h^{-1})	M : P ratio† AUC(0,∞)
Normal (*n* = 8)	47.8 (13.0)	2.5 (1.3–3.0)	251.8 (14.1)	252.6 (14.0)	2.1 (14.9)	17.8 (17.1)	1.4
Mild (*n* = 8)	60.8 (16.9)	2.5 (2.0–3.0)	318.4 (17.0)	319.1 (16.9)	2.6 (17.6)	15.6 (20.4)	1.8
Moderate (*n* = 7)	118.8 (40.6)	3.0 (2.0–6.0)	698.3 (32.5)	703.2 (32.6)	2.6 (14.9)	6.9 (33.6)	4.1
Severe (*n* = 6)	150.8 (21.5)	4.0 (2.0–6.0)	1413.1 (23.2)	1438.5 (23.3)	3.4 (14.3)	2.9 (47.4)	9.0

*Results are presented as arithmetic mean (CV%). For t_{max}, results are presented as median (range). †Metabolite : parent ratio after molar conversion, calculated as (AUC(0,∞) DFP-G/MWm)/(AUC(0,∞) DFP/MWp). MWp is the molecular weight of DFP (139.17 g mol^{-1}) and MWm is the molecular weight of DFP-G (315.28 g mol^{-1}).
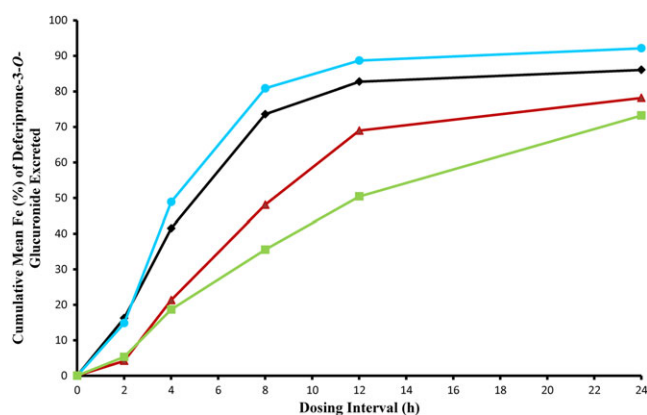
Previous studies in which DFP was administered to iron-overloaded subjects have shown that 60% to 75% of the total dose is excreted renally as either DFP or its metabolite, DFP-G [27, 29, 30]. In the current study, 75% to 95% of the administered dose of DFP was retrieved in the urine, as either DFP or DFP-G. Based on currently available data, the remainder of the dose is likely eliminated in the faeces, via biliary excretion. It is possible that the factor of iron load, i.e. its presence *vs.* its absence, is the reason for the apparent difference in total DFP excretion via the renal *vs.* the faecal route between iron-overloaded and non-iron-overloaded subjects. A recent publication noted a weak negative correlation between serum ferritin and GFR in patients with thalassaemia [8]. Should those findings be confirmed, additional studies should evaluate if the severity of iron overload also modifies the renal : biliary iron excretion ratio with different iron chelators.

Irrespective of the severity of renal impairment, the majority of the dose was retrieved in the form of the metabolite. However, the extent of the dose excreted as DFP-G decreased from 86% (healthy volunteers) to 73.2% (severe renal impairment), possibly due to biliary excretion becoming more prominent in renally impaired subjects. There was no evidence of regeneration of DFP from its glucuronide, as the AUC for DFP did not increase even in patients with severe renal impairment and no signs of secondary peaks in the PK profile were noted.

About 80% of iron that is removed by DFP is via the renal route, although this varies among subjects. The elimination is presumed to be via filtration, not through an active or facilitated renal secretion pathway, but definitive data are lacking. A limitation of the study is that it did not measure elimination of the DFP-iron complex. However, as this was a study in non-iron-overloaded subjects, it was not designed to enable the proper study of the effect of renal impairment on the pharmacokinetics of the DFP-iron complex. It is possible that there would be less iron removal as GFR declines, but that can be established only by studies in an iron-overloaded population.

Al-Refaie and colleagues [27] conducted a study to evaluate the pharmacokinetics of DFP in 24 patients with chronic iron overload given a single oral dose of ~50 mg kg^{-1}. The two patients in this sample who had renal impairment both showed impaired elimination of DFP-G, resulting in high serum concentrations of DFP-G. The results of that study indicated that elimination of DFP-G is influenced by renal function, as there was a significant correlation between the rate of elimination of DFP-G and creatinine clearance. While the authors, at that time, suggested that the lack of such correlation between elimination of DFP and creatinine clearance could be attributed to the differences in the sizes of the DFP and DFP-G molecules, a more reasonable explanation is that the clearance of DFP is primarily via hepatic biotransformation, and DFP is only minimally excreted by the kidneys. Thus, systemic accumulation would not occur in the presence of decreased renal function.

Using population pharmacokinetic methods, Bellanti *et al.* [31] developed a pharmacokinetic model that included creatinine clearance as a covariate, allowing them to assess the influence of creatinine clearance on the disposition of DFP. This model was developed using data from 55 healthy volunteers. They concluded that dosage adjustments are necessary for patients with renal impairment in order to maintain similar exposure (AUC) to DFP in patients with normal renal function. These conclusions were based on the assumption that a reduction in creatinine clearance leads to a similar degree of reduction in total clearance of DFP which, as shown in the data presented here, is not the case. Since renal clearance of DFP accounts for only a minor portion of its total clearance (Table 1), it is predictable that impaired renal function would not result in increased serum concentrations of DFP. Similar elimination half-lives in impaired renal function and healthy volunteers support this prediction.

The short (2 h) half-life of DFP after a single dose of 33 mg kg^{-1} DFP, even in subjects with severe renal impairment, also predicts lack of drug accumulation following multiple doses.

DFP was well tolerated by all subjects. Most AEs occurred in HVs and subjects with mild renal impairment, with only two events reported by subjects with moderate or severe renal impairment. The differences in incidence may possibly be attributable to the effect of different clinical environments (the healthy and mildly impaired subjects were housed at a research site that specializes in phase 1 studies, while the other two groups were housed at a hospital). Also, the HVs may have felt more obligated to report all perceived reactions. Considering that this was a single dose open label study, the AEs that were observed may not be predictive of the AEs that might occur following long term treatment in patients with chronic renal impairment. It is also possible that the open label nature of the study biased the prevalence of safety events. Therefore, enhanced vigilance is warranted, even though no accumulation of DFP is likely to occur.

In summary, the results of the present study indicate that adjustment of the DFP dosage regimen in patients with impaired renal function is unnecessary as the serum drug concentrations did not differ significantly from what is seen in patients without such impairment.

Competing Interests

Contributors

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