Opinion

Safety of Iron Chelation Therapies in Kidney Disease

Timothy Nguyen [1],* Zhe Amy Wang [2]

[1] Long Island University, 75 DeKalb Ave, Brooklyn, NY 11201
[2] Touro college of pharmacy
* Correspondence: timothy.nguyen@liu.edu

Abstract: : (1) Background: Iron chelation medications (desferoxamine, desferasirox, desferiprone) are used to manage iron overload. These medications are partially excreted via the kidneys, desferoxamine and desferiprone excretes primarily in the urine, and desferasirox had about 8% excreted in the urine. Their use in severe kidney disease and dialysis patients is caution as "avoided" concerning adverse effects; however, there are reports safe use. This manuscript reviews the literature in this population; (2) Data sources: Pubmed: desferasirox, deferiprone, deferoxamine, kidney disease, ESKD, Dialysis. Case reports and case series that described experiences with using iron chelation medications in ESKD patients are included. Data also gathered from reading-related sources; (3) ResultsThis is a review of desferoxamine, desferasirox, and deferiprone use in kidney disease from 1976 to the present time. Table 1 provides a summary of findings. These are mostly reports and brief descriptions of the experiences used in severe kidney disease and dialysis, but lack of randomized control trials and small number of participants; (4) Conclusions: Iron chelation medications are important for treating iron overload but concerns with adverse effects. Due to limited medications available to treat iron overload in patients with severe kidney disease, their safe use has been reporting in the literature. This is an area that warrants further research.

Keywords: Iron chelation, Iron overload, kidney disease, deferoxamine, deferasirox, deferiprone

1. Introduction

Iron chelation medications are used to manage iron overload. The goal of iron chelation therapy is to preserve organ functions (eg, liver, heart, and endocrine), improve survival, and minimizing the production of reactive oxygen species [1]. There are three Food and Drug Administration (FDA) approved iron chelation medications in the U.S.: Deferoxamine (Desferal®, DFO), Deferasirox (Exjade, Jadenu, DFX), and Deferiprone (Ferriprox) [2]. Deferoxamine was the first medication introduced decades ago and it is usually administered by intravenous (IV) [2]. Deferasirox is an oral iron chelation medication that is administered once a day and available as two formulations (Exjade and Jadenu) [2]. Deferiprone (Ferriprox) is also an oral iron chelation medication which is available as tablet and oral solution [2].

These iron chelation medications are partially excreted via the kidneys, desferoxamine and desferiprone excretes primarily in the urine, and desferasirox had about 8% excreted in the urine [2]. Due to the potential of adverse effects (AEs) associated with these medications, their use in severe kidney disease and/or dialysis patients should be avoided [2]. The data on its use and safety in severe kidney disease and dialysis are lacking. This research manuscript reviews the literature on these iron chelation medications and their use in patients with severe kidney disease and dialysis. .

2. Materials and Methods

Pubmed Search: desferasirox, deferiprone, deferoxamine, kidney disease, ESKD, Dialysis.

Case reports and case series that describe experiences with using iron chelation medications in ESKD patients are included. Data also gathered from reading-related results, and performed by two independent academic pharmacists (researchers) with expertise in kidney disease and cardiology.

 doi:10.20944/preprints202305.1989.v1

3. Results

Table 1 provides a summary of findings on iron chelation medications use in CKD/Dialysis [3-32]. This is the most comprehensive and extensive information presented on DFO and DFX use in severe kidney disease and ESKD ranging from reports from 1976 to the present time. These are mostly reports and brief descriptions of the experiences of using DFO and DFX in severe kidney disease and ESKD/dialysis. There is a lack of randomized control trials and large number of participants involved in these reports.

Table 1. Summary of Findings on Iron Chelation Medications Use in CKD/Dialysis [3-32].

Hiraga et al. Int J Hematology. 2011	**A case of severe aplastic anemia on HD, treated with immunosuppressive & iron chelation therapy.** **A 49-year-old male presented in December 2007 with fever & pancytopenia. He required regular HD following history of CKD 25 years earlier**	**The initial dose was DFX 10 mg/kg/day, due to renal failure, but the serum ferritin level remained above 3000 ng/mL. The dose was increased to 20 mg/kg/day. Six months later, the serum ferritin level was below 1000 ng/mL**	**Iron chelation therapy can be safely used for transfusion-dependent patients. No significant adverse events were identified.**
Kan et al. Nephrol Dial Transplant. 2010	High risk for Al overload 42 HD patients	Standard-dose (5 mg/kg/week) & low-dose (2.5 mg/kg/week) groups	Low-dose DFO may offer similar therapeutic effects as standard-dose DFO therapy.
Yusuf et al. AJKD. 2008	Hypercalcemia 43-year-old female, ESKD on PD	DFX 1500 mg/day (20 mg/kg)	Ca decreased to 5.9 mg/dL (ironized Ca 3 mgEq/L)
Barata et al. Nephrol Dial Transplant. 1996	Al toxicity DFO-related neurological/ophthalmological side-effects were observed in 9 of 11 patients with a post-DFO serum Al level >300 mcg/L & in 2 of 30 patients below this level after a single administration of a 5 mg/kg dose of the chelator in the conventional way (i.e., the last hour of a dialysis session). They were no longer observed after introducing an alternative DFO administration schedule (i.e., administration of the chelator 5 h prior to the start of a HD session	DFO 5 mg/kg, once weekly 5 hr prior to high-extraction dialysis	Serum ferritin levels significantly decreased in both groups. No further side effects were observed during the DFO course. DFO provides a safe and adequate therapy for Al overload.
Vogelsang U. Chweiz Rundsch Med Prax. 1994	Elevated Al 10 HD patients	DFO x 2 months Al >50 mcg/L & positive DFO test, DFO treatment should be initiated. Low doses of 10 mg/kg body weight DFO per week are actually in use for those cases.	DFO induces a dose-dependent mobilization of Al accumulated in the tissue. The level of plasma Al increases distinctly, dialysable Al-DFO complexes are produced, & marked amounts of Al can thus be eliminated by the use of DFO.

 doi:10.20944/preprints202305.1989.v1

Bornsdorff et al. Scand J Urol Nephrol Suppl. 1990	Al overload 17 HD patients	DFO 2 g IV infusion weekly during the last hour of HD	The clinical manifestations of Al & iron overload disappeared and the quality of life improved. No major side effects were observed.
McCarthy et al. Q J Med. 1990	Al toxicity 50 dialysis patients undergoing diagnostic bone biopsy.	DFO infusion test, using a dose of 36.9 +/- 11.2 mg/kg (mean +/- SD). There was a decrease in stainable bone Al in all nine patients with paired bone biopsy specimens (pre- and post-DFO).	Significant side effects occurring during long-term DFO administration were hypotension (11 patients), gastrointestinal upset (7 patients), porphyria cutaneous tarda-like lesions (3 patients), and transient visual disturbance (1 patient).
Felsenfeld et al. Kidney Int. 1989	18 HD patients with Al associated, low bone turnover disease	DFO 1-6 grams per week given during last 1-2 hours of HD	Significant decrease in trabecular stainable bone Al (from 44 + 4.1 to 13 + 3.4%, p <0.001) Significant increase in bone formation rate (from 13 + 7 to 669 + 187 μm2/mm2/day, P < 0.008)
Stivelman et al. Kidney Int. 1989	Iron overload 12 patients, HD, PK & efficacy study	Acute: Single dose DFO 24.3 +/- 2.5 mg/kg Four patients between 60 & 120 minutes prior to initiation of dialysis A single dose of DFO was administered post-HD Chronic studies. Patients received IV DFO (mean dose 42.8 4.2 mg/kg) over 30 to 40 minutes following the termination of each dialysis three times weekly	DFO interdialytically results in slow removal of iron, via both dialytic and GI routes. Studies of acute & chronic DFO infusion suggest that the optimal time for DFO infusion is at the end of a dialytic treatment. The presence of a large fraction of unbound DFO in the face of significant iron: DFO & iron overload overload suggests that doses less than 40 mg/kg are appropriate and that despite chronic treatment, the amount of Fe removed by dialytic and extradialytic routes is small.
Boelaert et al. Clin Nephrol. 1988	Al overload 3 HD patients	DFO	The mechanism by which DFO could precipitate mucormycosis is unsettled. The explanation might be that DFO acts as a siderophore to the Mucorales fungi. High serum levels of DFO in renal failure could enhance this mechanism.
Siefert et al. J Med. 1987	39 patients treated with DFO, ESKD, HD 23 received for Al-related bone disease, & 16 because of iron overload		These results suggest that treatment with DFO does not favor the development of septicemia or bacterial infection independently of iron overload and that iron overload itself may

			predispose patients on regular HD to bacterial infection.
Praga et al. Nephrol Dial Transplant. 1987	Al intoxication 7 HD patients	DFO 2 g IV after every HD session for 6 months	The tolerance to DFO was excellent. We conclude that DFO therapy should be considered in HD patients with severe anaemia & increased blood transfusion requirements.
Molitoris et al. Kidney Int. 1987	CAPD DFO IV & intraperitoneally	DFO 2 g IV & intraperitoneal	CAPD, DFO 2 g IV DFO resulted in the removal of 560 +/- 267 mcg of Al over 24 hours; while DFO 2 g intraperitoneally gave 91 +/- 13% of the IV response. Al clearance over 48 hours was twice that for 24 hours for both IV & IP DFO.
Hercz et al. Kidney Int. 1986	7 patients CAPD, CCPD	DFO 40 mg/kg IV & IP	The efficacy & safety of long-term treatment with intraperitoneal DFO requires further study.
Kovarik et al. Contrib Nephrol. 1985	7 HD patients	30 mg/kg body weight DFO were given after the end of HD.	DFO was able to remove more than 500 mg iron/month. This treatment schedule might be superior compared to the previously used methods of administration where DFO was given at the beginning or throughout HD.
Payton et al. Lancet. 1984	A 56-year-old female, ESKD, on HD since 1975. Al concentration in her water supply was measured regularly & varied between 20 & 67 g/L. Due to vascular access problems she changed to CAPD in June, 1983. The following month, when her serum Al level was 7′ 0 mol/L, she started to display features of encephalopathy.	Treatment with intraperitoneal DFO therapy and the patient achieved substantial improvement.	Al encephalopathy may be achieved in the CAPD patient with the use of intraperitoneal DFO. Intraperitoneal administration of DFO is easy & apparently safe. It is an effective alternative to IV treatment when vascular access is difficult.
Falk et al. Kidney Int. 1983	A 37-year-old Black Female with sickle cell disease & a history of multiple blood transfusions Maintenance HD (1978-1980), CAPD (1980 & after)	Between 1978 & 1980, DFO IV 1.5 g per dialysis treatment. CAPD, iron removal was evaluated under two circumstances: (1) during DFO IV (1.5 g TIW), and (2) during intraperitoneal DFO (250 mg/liter): (a) to each exchange every day for 7 days (1250 mg of DFO per day); (b) to each exchange every other day for 7	In the course of these studies IV DFO (1500 mg 3 times a week) was given during MHD without interruption for 2 years, 1978 to 1979. The longest period of continuous intraperitoneal administration of DFO (1250 mg/day) was for 3 months in 1980. No toxicity was apparent.

		days (1250 mg of DFO every other day); and (c) to the first, third and fifth exchanges every day for 7 days (750 mg of DFO per day). The small peritoneal capacity of this patient necessitated five 1-liter exchanges of Dianeal® (Travenol Laboratories, Inc., Deerfield, Illinois), 1.5% dextrose alternating with 4.5% dextrose solutions. DFO was given intraperitoneally by direct addition to the dialysis bags (250 mg/liter of dialysate).	
Kingswood C, et al. Lancet. 1983	A 46-year-old female, ESKD, on CAPD Serum aluminum, measured by atomic absorption spectrophotometry at the time of fracture, was raised: on three occasions serum concentrations of 117, 12-8, and 11-6 mmol/L	A 14 day course of DFO IM (cumulative dose 1 g) as a chelating agent.	1 month after DFO there is radiological healing & clinical union, & the cast has been removed. CAPD patient has been effectively treated with IM DFO. Not much discussion of anything else related to safety.
Brown et al. Lancet. 1982	2 HD patients (29-yo M, 38-yo M), long-standing osteomalacia, treated with DFO.	6 g DFO in 100 mL normal saline given once a week during HD. Ca levels began to fall soon after DFO treatment was started & calcitriol was necessary to maintain normal levels.	Dramatic improvement in the clinical condition, skeletal radiology, and bone histology after treatment with DFO. This represents a major advance in the treatment of dialysis osteomalacia.
Simon et al. Nephrologie. 1981	33 CKD patients, divided into 2 groups. Group I, 8 non-dialysed patients without any clinical or biochemical sign of liver disturbance nor any iron supplementation. Group II, 25 maintenance HD patients treated from 2 to 13 years. Total exogenous iron load parenteral iron and/or blood transfusions) was calculated. Body iron overload (hemosiderosis) was assessed by liver iron concentration (LIC) in needle biopsy specimens according to Barry's method (less than 200 microgram/100 mg dry weight) and serum ferritin levels (less than 360	Infusions of DFO in doses of 2 g at each dialysis.	Body iron stores fell and organ dysfunction (heart failure, hepatic cytolysis, anaemia, diabetes mellitus improved.) Long-term chelation therapy by DFO was effective & the chelated iron was readily removed by dialysis. These data show the importance of precise evaluation of iron stores in MHD patients.

 doi:10.20944/preprints202305.1989.v1

	ng/mL). 4 patients whose serum ferritin was increased with or without hepatic fibrosis & with or without any organ dysfunction due to hemochromatosis received IV. Serum ferritin levels were correlated with LIC (p less than 0.001) & iron load (p less than 0.001). Hemosiderosis was noted in 16 MHD patients (group II) & correlated with iron load. Hemochromatosis was noted in 4 patients (group II). 4 HD patients with iron overload were treated by DFO from 6 to 18 months.		
Ackrill et al. Lancet. 1980	A 36-year-old man, had been on home self-supervised HD since 1970. Up to 1978, the dialysis water supply contained 100-500 g/L Al.	DFO 6 g in 500 mL saline was infused into the arterial line during the first 2 h of a dialysis, once weekly. Dialysis was done on a 'Meltec Multipoint' single pass dialyser (11 m^2) for 4-hr thrice weekly.	DFO, a chelating agent effective in the treatment of iron overload, has been used successfully in the management of Al-induced encephalopathy & osteomalacia in patients with CKD. Although our study refers to one patient only, the improvement has been so striking and the quantitative removal of Al so conclusive, that we think this technique is worth considering for application in similar cases.
Baker et al. Clin Nephrol 1976.	HD	Infusions of DFO in doses of 2, 3 and 4 g each resulted in the removal of approximately 45 mg of iron during dialysis. DFO 2 g was infused thrice weekly during dialysis for twelve months.	Body iron stores, as judged by liver iron & serum ferritin concentrations, fell by about half. This agrees well with the result calculated from the amount of iron administered & the amount removed during dialysis.

Abbreviations: AE (adverse effect), Al (aluminum), AKI (acute kidney injury); DFO (desferoxamine), DFX (desferasirox, ESKD (end stage kidney disease); HD (hemodialysis); IM (intramuscular); IP (intraperitoneal); IV (intravenous); PD (peritoneal dialysis).

4. Discussion

Kidney disease patients often experience anemia as a common complication especially in severe stages of chronic kidney disease (CKD) and end stage kidney disease (ESKD) [33]. Blood transfusion is often used to manage anemia; however, iron accumulation can also occur [33-36]. In patients who receive multiple transfusions. Iron chelation medication is usually started in patients who have received 10 units of packed red blood cell (RBC) transfusions and serum ferritin level >1000 ng/dL or liver iron concentration >3 mg/g/dry weight or cardiac T2* <20 milliseconds [1]. In hematology and oncology practice settings, iron chelation medications are used in transfusion-dependent patients, including myelodysplastic syndromes (MDS), sickle cell anemia, aplastic anemia, post-hematopoietic cell transplantation (HCT) and beta thalassemia [37-45].

Deferoxamine (DFO) is a chelation medication used principally in the treatment of iron overload and iron poisoning [2]. It has a high affinity for loosely bound ferric ion, which is then excreted in the

 doi:10.20944/preprints202305.1989.v1

urine with DFO and its metabolites [2]. It has a lower affinity for aluminum and a low affinity for ferrous ion and other divalent ions [2]. The successful removal, by deferoxamine infusion, of iron from the liver of a long-term dialysis patient; suggested the use of a similar procedure for removal of aluminum in dialysis encephalopathy [13-17]. It has been reported to help dialysis dementia in association with loss of aluminum into the dialysate [2,11,13,14,15,17].

DFO was the first medication introduced decades ago and it is usually administered by intravenous (IV) [2]. It is usually administered by continuous subcutaneous (under the skin) infusion over 8 to12 hours per day for 5 days per week using a small portable pump about the size of a CD player owing to its short half-life of 30 minutes [2]. DFO has side effects such as hypotension, infections, allergic reactions, pulmonary, kidney, and neurological effects [2]. It has a kidney disease warning such as acute kidney injury (AKI), and to avoid in patients with low creatinine clearance <40 mL/min, or serum creatinine >2-fold upper limit of normal [2]. Due to its inconvenient administration requirement and cumbersome, patient compliance has shown to be low with this therapy.

Deferasirox (DFX) has high affinity for iron chelation and selectively for Fe3+ [2]. It is primarily metabolized by glucuronidation with subsequent hepatobiliary excretion, predominantly via the fecal route [2]. DFX is an oral iron chelation medication that is administered once a day and available as two formulations (Exjade and Jadenu) [2]. Deferasirox (Exjade®) is a dispersible tablet form that must be dissolved in juice or water and taken by mouth once a day and deferasirox (Jadenu®) is a newer film-coated tablet formulation of deferasirox [2]. It is taken on an empty stomach or with a light meal once a day with water or other liquids. This formulation has an improved bioavailability and is associated with less gastrointestinal (GI) toxicities (eg, nausea, vomiting, diarrhea, and abdominal pain), hence an improved adherence [2]. Deferasirox is the most widely used iron chelation medication due to its availability in oral formulation, convenient dosing schedule (once a day), and favorable safety profile. Its most common adverse event is GI toxicities, and it has also been associated with kidney and liver toxicities [2]. Deferiprone (Ferriprox) is also an oral iron chelation medication which is available as tablet and oral solution. It is usually administered 2 to 3 times daily. It carries a black box warning for agranulocytosis [2].

This research review provides the most extensive and inclusive of the iron chelation medication information in the literature since 1976 to the present time (Table 1). Table 1 provides a summary of these iron chelation medications used in severe kidney disease and ESKD/dialysis. Overall, there is a lack of sufficient evidence regarding pharmacokinetics properties of iron chelation medications in patients with CKD and/or ESKD on dialysis. The majority of these reports are cases and experiences on small number of subjects on the use of these iron chelation therapies in CKD and ESKD with little adverse effects reported. These reports include the use of iron chelation medications for elevated iron, aluminum, and calcium levels in severe kidney disease and ESKD in HD [3,5-12,14-24,26-32], PD [13], CAPD [4,23,24,27,28], and CCPD [24]. Please refer to Table 1 for brief information provided on these reports and the following are some examples of these reports from the study.

A pharmacokinetic study conducted by Maker and colleagues assigned 8 patients who were dependent on HD to receive DFX [9]. No patients in either group experienced any significant adverse events [9]. However, the study was conducted on a small group of patients who were not at high risk for iron overload. Safety of iron chelation medication may vary based on different products. In a study by Huang et al when compared with DFO, patients who received DFX were at higher risks of experiencing AKI (HR 2.18, 95% CI 1.18–4.02, p = 0.01) [46]. Clinical efficacy and safety of iron chelation medication in CKD and/or ESKD is uncertain.

In the Falk et al paper, patients received maintenance HD and CAPD treated with deferoxamine in different doses [27]. Smaller doses removed less iron, while larger doses did not improve iron removal [27]. A study by Chen et al on Taiwanese ESKD patients on HD with iron overload [6]. Retrospective analysis of 8 patients. The author concluded DFX is considered safe in patients with ESKD receiving HD without concern about AKI complications [6]. Additionally, DFX therapy reduced doses of EPO therapy necessary to maintain hematocrit within normal limits [6]. This is potentially due to improved balance of serum iron levels.

Overall, from the data gathering reported in Table 1 on the experiences of these iron chelation medications use in severe kidney disease and ESKD/dialysis. Based on case reports and series, risks of adverse events and further worsening of kidney function are low. The population size was small, and there is insufficient evidence available regarding pharmacokinetics and pharmacodynamic properties to definitely confirm its safety. However, these data provide clinicians with a summary of the clinical experiences of using these medications in CKD and ESKD/dialysis. Limitations of this research report include other information in the literatures might not be captured or oversight during this process. .

5. Conclusions

Iron chelation medications are important for treating iron overload; however, they also have adverse effects on the kidneys. Due to limited iron chelation medications available to treat iron overload in patients with severe kidney disease and ESKD on dialysis, their use have been reported in the literature which is summarized in this research study. This is an area that warrants further research.

Author Contributions: Conceptualization, T.N.; Methodology: T.N.; Writing, T.N., Z.W.; Review and editing, T.N., Z.W. All authors have read and agreed to the published version of the manuscript.

Funding: Please add:

Institutional Review Board Statement:

Informed Consent Statement: Data Availability Statement:
Acknowledgments:

Conflicts of Interest: The authors declare no conflicts of interests

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