Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.57, No.6(2017). p. 329-36; doi: http://dx.doi.org/10.14238/pi57.6.2017.329-36

Evidence-based Case Report

Side effect of deferiprone as iron chelator in children with thalassemia

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Abstract

Background There are currently three available iron chelators: deferoxamine (DFO), deferasirox (DFX), and deferiprone (DFP). In Dr. Cipto Mangunkusumo Hospital and Indonesia, in general, the accessibility of DFP for thalassemia patients has been adequate. Even though its efficacy in removing iron has been proven by countless studies, questions relating to its safety and possible side effects continue to be raised.

Objective To assess common side effects of DFP usage by an intensive literature search and compare them to that in a pediatric thalassemia patient, in order to determine if the child's symptoms were potentially caused by DFP.

Methods A literature search using MeSH terms was done in PubMed. Full copies of articles that fulfil the inclusion criteria, based on their title, abstract, and subject descriptors, were critically appraised using The Joanna Brigs Institute (JBI) critical appraisal tools.

Results A total of 10 original articles from 1998-2013 were deemed applicable to this study including: 2 case reports, 5 prospective cohort studies, 2 retrospective cohort studies, and 1 randomized control trial with a grand total of 1,026 subjects.

Conclusion Side effects of DFP include neutropenia, agranulocytosis, increased ALT, gastrointestinal problems, arthralgia or arthropathy, increased appetite or weight, thrombocytopenia, urine discoloration, as well as auditory and visual disturbances. Our case report patient's symptoms of gum bleeding and haemorrhagic mass are not related to her DFP consumption. **[Paediatr Indones. 2017;57:329-36 ; doi: http://dx.doi.org/10.14238/pi57.6.2017.329-36]**.

Keywords: *thalassemia; deferiprone; side effect*

Thalassemia is a condition involving reduction in globin chain (-a or -b) production thus resulting in abnormal hemoglobin which leads to anemia. Anemia often needs to be controlled via continuous blood transfusion. This transfusion, coupled with hemolysis of abnormal hemoglobin and increased rate of iron absorption, results in the build-up of iron in the body. If left untreated, the excessive iron level may harm vital organs (liver, heart, and endocrine organs) and manifest as complications of thalassemia. Thus, iron chelators were introduced as drugs capable of bonding with iron, creating an iron-chelator complex which can then be excreted from the body, ultimately reducing the patient's iron load.[1]

There are currently three available iron chelators: deferoxamine (DFO), deferasirox (DFX), and deferiprone (DFP), each with their own benefits

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and drawbacks. Deferoxamine was the first and most studied iron chelator worldwide, but due to its subcutaneous or intravenous mode of delivery, it has become unpopular with patients. The DFP and DFX are available in oral form, which eases usage and increases adherence (thus increase the overall survival rate) in thalassemia patients.[2] Differences in molecular size of the chelators result in different iron-chelator interactions. Hence, each chelator has its own effectivity and side effects.

In Dr. Cipto Mangunkusumo Hospital and Indonesia, in general, accessibility to DFP has been adequate. The fact that this particular iron chelator is available in both tablet and syrup form, adds to its popularity among patients. Though its efficacy in removing iron has been established by many studies, 21 questions relating to DFP safety and possible side effects continue to be raised.[3] We aimed to compare a case in a real clinical scenario to the published side effects of DFP from a literature review, and to determine if the patient's symptoms were related to consumption of DFP.

The Case

An 11-year-old girl was diagnosed with beta-thalassemia major at the age of 5. She had routine blood transfusion every 2 weeks and had been prescribed with DFP (100 mg/kg body weight/day) for 4 years. For 3 months, she had gum bleeding, especially when brushing her teeth. Soon after, a hemorrhagic mass developed in her oral cavity and emitted a pungent odor. She was taken to a dental clinic; the dentist administered treatment and drugs, but to no avail. After 2 weeks of treatment, her bleeding episodes had not subsided, so her mother took her to Dr. Cipto Mangunkusumo Hospital, where she was diagnosed with suspected gingival enlargement and oral cavity infection by an oral surgeon. The surgeon recognised that her condition might have been caused by toxicity of DFP. Her blood examinations revealed hemoglobin level of 8.5 g/dL, hematocrite 25.1%, leucocyte 6,490/μL, platelet 184,000/μL, AST 23 U/L, and ALT 10 U/L.

Clinical Questions

1. What were the common side effects of DFP?
2. Were the patient's symptoms related to DFP usage?

Methods

Literature included in this review comprised studies with human subjects of any age with thalassemia, intervention included continuous usage of DFP monotherapy at any dose, outcomes measured were any observed or suspected short-term or long-term side effects or adverse reactions to DFP. All randomized control trials (RCTs), prospective, retrospective, as well as cross-sectional studies, with full text available in English or Indonesian ,which were published within the last 20 years, were included.

The initial search terms used were 'deferiprone', 'side effect', 'safety', and 'thalassemia', followed by proper MeSH search terms in PubMed (**Table 1**). Full copies of articles identified by the search that fulfilled the inclusion criteria, based on their title, abstract, and subject descriptors, were critically appraised using The Joanna Brigs Institute (JBI) critical appraisal tools.[22] Pubmed search was done in 10 April 2017.

Table 1. MeSH search terms in PubMed followed by number of hits and articles selected

Database	Search Terms	Hits	Selected articles
PubMed	("thalassaemia"[All Fields] OR "thalassemia"[MeSH Terms] OR "thalassemia"[All Fields]) AND ("deferiprone"[Supplementary Concept] OR "deferiprone"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields])	70	12

Results

The search procedure is shown in **Figure 1**. A total of 10 original articles from 1998-2013 were included in this study. A summary of characteristics (including total number of subjects with/without side effects) of included literatures is shown in **Table 2**, whilst the list of side effects observed in each study was recorded in **Table 3**. Frequency of each side effect are presented in **Table 4**, with the total frequency from all the studies (total subjects showing side effects n=427) is presented in the last column. Note that only one study reported skin rash and one other study reported auditory and visual disturbances.

A case report by Chand *et al.* reported an 8-year-old arthropathy patient with uncontrollable ferritin level due to poor adherence to DFP. After 1 year of consuming DFP, the patient complained of pain in both knees. The administering doctor stopped the DFP for 3 months and the symptoms subsided.[5] A second case study by Tewari *et al.*[11] reported a possible periodontal manifestation of agranulocytosis caused by DFP. This patient complained of grayish-white discoloration of his gingiva, followed by tooth pain. He had consumed DFP for 3 years and suffered from episodes of neutropenia and agranulocytosis. After four weeks of stopping DFP consumption, the neutropenia subsided and signs of clinical improvement were present. All studies were appraised using the appropriate JBI critical appraisal tools (**Table 5**).

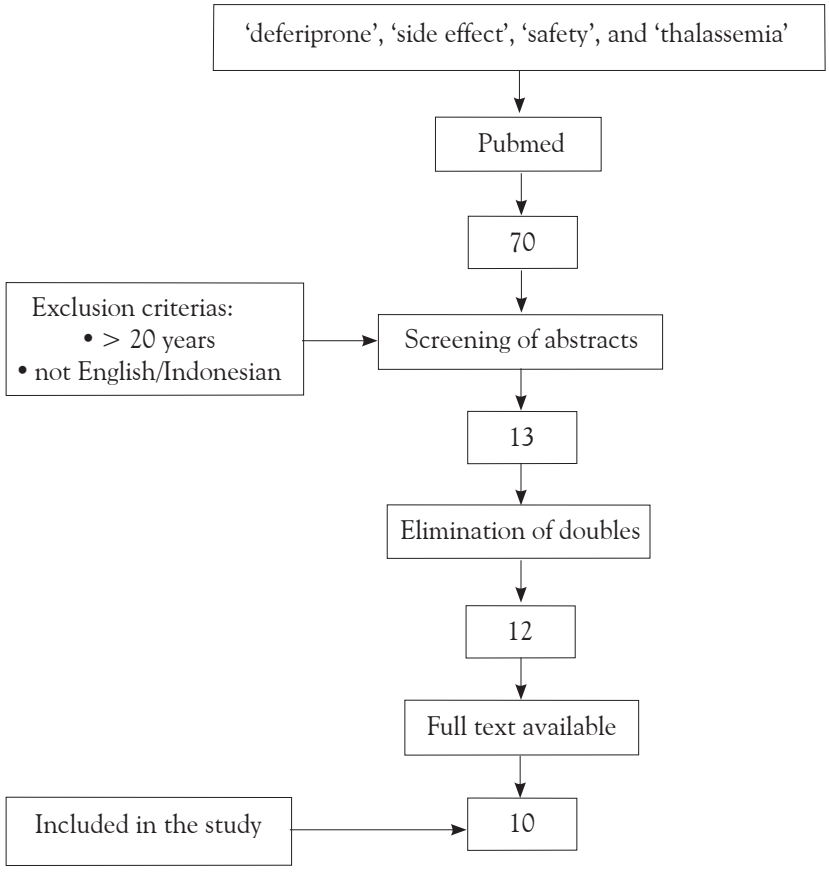

Figure 1. Flow chart of the literature search procedure

Table 2. Summary of study design and characteristics

Design	Year of study	Age range, years	Subjects, n	Length of study, months	Dose range, mg/kg body weight/day	Author
Prospective cohort	2002	6-54	532	36	75	Ceci *et al.*[4]
Case report	2009	8 months[a]	1	-	40-80	Chand *et al.*[5]
Prospective cohort	2004	4-14	75	12	50 and 75	Choudhry *et al.*[6]
Prospective cohort	1998	10-41	187	12	75	Cohen *et al.*[7]
Prospective cohort	2010	1-10	100	6	50-100	El-Alfy *et al.*[18]
Randomized controlled trial	2006	8-40	6	18	75	Ha *et al.*[8]
Prospective cohort	1998	22-38	51	24-48	50-79	Hoffbrand *et al.*[9]
Retrospective cohort	2005	2-6	44	-	75	Naithani *et al.*[10]
Case report	2009	14[a]	1	-	75	Tewari *et al.*[11]
Retrospective cohort	2013	5-52	29	-	26-85	Uygun *et al.*[12]

[a]Case report with one patient used the exact age

Table 3. Summary of reported side effects

Author	Reported side effects
Ceci *et al.*[4]	Neutropenia, agranulocytosis, increased ALT, gastrointestinal problem, arthralgia/arthropathy, increased weight
Chand *et al.*[5]	Arthralgia/arthropathy
Cohen *et al.*[7]	Neutropenia, agranulocytosis, increased ALT, gastrointestinal problem, arthralgia/arthropathy, increased in appetite/weight, thrombocytopenia
El-Alfy *et al.*[18]	Neutropenia, arthralgia/arthropathy, increased ALT, gastrointestinal problem
Ha *et al.*[8]	Arthralgia/arthropathy, increased ALT, gastrointestinal problem
Hoffbrand *et al.*[9]	Neutropenia, agranulocytosis, arthralgia/arthropathy, gastrointestinal problem (nausea)
Naithani *et al.*[10]	Gastrointestinal symptoms, urine discoloration, arthralgia/arthropathy, neutropenia, thrombocytopenia
Tewari *et al.*[11]	Agranulocytosis (manifest as necrotizing stomatitis)
Uygun *et al.*[12]	Gastrointestinal symptoms, neutropenia, increased ALT, auditory disturbance, visual disturbance

ALT: alanine aminotransferase

Discussion

The aim of this study was to compare common side effects of DFP usage found in the literature to symptoms in a pediatric thalassemia patient who consumed DFP. None of the articles mentioned side effects similar to the symptoms presented in the clinical scenario (bleeding gums, followed by a mass growing in the oral cavity). The patient's however did not suffer from any other side effects mentioned in all the literatures. Other examinations need to be done in order to determine the exact cause of symptoms in our thalassemia patient.

Neutropenia and agranulocytosis

Severe neutropenia is defined as absolute neutrophil count (ANC) <500/uL, while agranulocytosis is defined as ANC <100/uL.[13] In the literature review, a total incidence (from literature reporting on neutropenia) of 5.5% was established, which was slightly lower than that on the DFP package insert (6.2%) submitted to the FDA (**Table 6**). Neutropenia after DFP consumption is hard to determine, as there is no known underlying mechanism to explain the event.[4] Maggio *et al*. compared sequential DFO and DFP therapy *vs.* DFP monotherapy and found that no agranulocytosis occurred in those who underwent sequential therapy, while 3.7% of

those who underwent DFP monotherapy developed agranulocytosis. They proposed that the reduced bone marrow exposure to DFP in sequential therapy might reduce the chance of agranulocytosis.[14] Masera et al. reported on a patient with agranulocytosis; when treatment with DFP was stopped and corticosteroids were administered, the neutrophil count increased after one day. They reckoned that an immune mechanism blocked myeloid differentiation during promyelocyte phase.[15] Most of the literature included in this study recommended an immediate switch to another available iron chelator, whenever neutropenia or agranulocytosis occurred due to DFP consumption. Tewari *et al.* reported that agranulocytosis resulted in necrotizing stomatitis, which was manifested by white-grayish discoloration on the palatum with no signs of bleeding or inflammation. No other study reported or explained any mechanism resulting in a periodontal manifestation, such as our patient had.

Table 4. Summary of side effect frequencies for each study

Side effect observed	Frequencies (%)[a]								
	Ceci *et al.*[4]	Choudry *et al.*[6]	Cohen *et al.*[7]	El-alfy *et al.*[18]	Ha *et al.*[8]	Hoffbrand *et al.*[9]	Naithani *et al.*[10]	Uygun *et al.*[12]	Total[b]
Neutropenia	21 (3.9)	12 (16)	10 (5)	6 (6)		2 (3.9)	2 (4.5)	3 910.3)	56 (5.5)
Agranulocytopenia	5 (0.9)					1 (1.9)			6 (1)
Thrombocytopenia			2 (1)				20 (45.4)		22 (9.5)
Increased ALT	15 (2.8)			12 (12)	6 (23)			2 (6.9)	35 (5.2)
Gastrointestinal problem	17 (3.2)		70 (37)	11 (11)	8 (31)	5 (9.8)	12 (27.2)	6 (20.6)	129 (13.6)
Athralgia/ arthropathy	21 (3.9)	15 (20)	12 (6)	4 (4)	4 (15)	5 99.8)	4 (9.1)		65 (6.5)
Increaste in appetite/weight	1 (0.2)		10 (5)						11 (1.5)
Urine discoloration			74 (40)				23 (52.2)		97 (42)
Skin rash					1 (4)				1 (4)
Auditory disturbance								3 (10.3)	3 (10.3)
Visual disturbance								2 (6.8)	2 (6.8)

[a]Frequencies are number of side effect observed, percentage was done based on frequency/total subject in the same study article
[b]For total accumulation of frequencies, percentage was done by dividing the total frequency by the total number of subjects from literatures reporting that side effect.

Table 5. Results of critical appraisal using appropriate JBI appraisal tools

Author	Design	Score based on appropriate JBI appraisal*													Overall appraisal
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Ceci *et al.*[4]	Prospective	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
Chand *et al.*[5]	Case report	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	Included
Choudhry *et al.*[6]	Prospective	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	NA	NA	Included
Cohen *et al.*[7]	Prospective	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
El-alfy *et al.*[18]	Prospective	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
Ha *et al.*[8]	RCT	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Included
Hoffbrand*et al.*[9]	Prospective	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
Naithani *et al.*[10]	Retrospective	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included
Tewari *et al.*[11]	Case report	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	Included
Uygun *et al.*[12]	Retrospective	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	NA	Included

*Appropriate appraisal for either RCT, cohort (prospective or retrospective), case report study was used.
RCT:13 criteria; cohort:11 criteria.
Y=yes, N=no, U=unclear, NA=not applicable.

Table 6. Side effects of DFP observed in 642 patients (from the DFP package insert)[19]

Body sistem Preferred term	Subjects, %
Blood and lymphatic system disorders	
Neutropenia	6.2
Agranulocytosis	1.7
Gastrointestinal disorders	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3
Dyspepsia	2
Investigations	
ALT increase	7.5
Neutropenia	7.3
Increased body weight	1.9
Metabolic and nutritional disorders	
Increased appetite	4
Decreased appetite	1.1
Musculoskeletal and connective tissue disorders	
Athralgia	9.8
Back pain	2
Pain in extremities	1.9
Arthropathy	1.4
Nervous system disorders	
Headache	2.5
Urinary disorder	
Chromaturia	14.6

Thrombocytopenia

Naithani *et al.* observed thrombocytopenia in nearly half of their subjects, which subsided after discontinuation of DFP. However, they recommended that extra scrutiny to be taken due to the small sample size.[10] Cohen *et al.* had a larger sample, but found that only 1% of thrombocytopenia incidence was associated with DFP.[7] Other literature had reported various incidence rates, yet many agreed that there was an association between DFP consumption and thrombocytopenia. The mechanism of thrombocytopenia is still unknown.

Increased alanine transaminase (ALT)

Three of the studies mentioned an increase of ALT due to DFP consumption, though incidence varied between 2.8 to 23%.[4,8,12] Cessation of DFP reduced the ALT level when ALT had increased to a very high level, yet often the ALT increase is only temporary and resolves spontaneously. There were concerns that this condition might progress to hepatic cirrhosis, but an ensuing review by Wanless *et al.* found no strong evidence of a correlation.[16]

Gastrointestinal problems

One of the most common complaints in DFP consumers is nausea, vomiting, abdominal pain, and other gastrointestinal problems. The package insert breaks down the list of gastrointestinal problems as nausea (12.6%), abdominal pain (10.4%), vomiting (9.8%), diarrhea (3%), and dyspepsia (2%).[19] The incidence can reach 37% and usually occur during initial consumption of DFP (±1 year).[7] The symptoms are usually mild and spontaneously resolve in the majority of patients. Cessation of DFP might be needed when symptoms persist. Interestingly, El-Alfy *et al.*[18] compared the use of syrup DFP to the usual tablet form. In the end, the difference in incidence of gastrointestinal symptoms between the two forms of DFP was inconclusive, but availability of the syrup form would surely help patients who cannot swallow DFP tablets.

Arthralgia/arthropathy

Another common side effect of DFP is joint pain without swelling, usually affecting the knee. The time when this side effect occurs after consumption

of DFP varies between individuals. Most of the time, termination of DFP is needed until all symptoms subside. While the underlying mechanism is not known, Berkovitch *et al.*[17] postulated that due to low concentration of DFP in synovial fluid, less inert 1:3 iron-chelator complexes are formed, and a subsequent increase in 1:1 and 1:2 iron-chelator complex (which are very damaging in nature) accumulate, eventually resulting in symptoms. A case study elaborated that there was no prominent sign of inflammation (swelling or erythema), except for the pain. MRI results present in DFP-related arthropathy are synovial thickening, articular cartilage thickening, and subchondral bone erosions.[5]

Increased in appetite/weight

Weight gain has been identified as an effect of DFP consumption. Even though two studies included observations on weight increase, there were no details regarding how much weight was gained or whether it was statistically significant. The DFP package insert also affected increased appetite (4%) and weight gain (1.9%). There has not yet been known mechanism that explains these effects.[4,7]

Urine discoloration

Two studies reported that nearly half of their sample had red-brown urine discoloration without accompanying symptoms of dysuria, increase in urinary frequency, or other urinary complaints.[7,10] Urine discoloration itself is the result of the chromophore iron-chelator complex being excreted in the urine. There is no report on harm that might be caused by urine discoloration.

Skin rash

Only Ha *et al.* reported an observation of skin rash and cited DFP as the main culprit.[8] The explanation for the skin rash in the study itself was limited and no other sources reported a similar observation. Though possible, other studies need to be done to determine a cause-effect relationship.

Auditory and visual disturbance

Uygun *et al.*,[12] however, were the only authors reporting both auditory and visual disturbances after DFP consumption. They recommended using a larger sample size to determine the exact effect and relationship of these side effects, whilst recommending a reduction in dosage until the symptoms subside. Another available study mentioned neurotoxicity as causing visual and auditory disturbances in patients using deferoxamine (DFO).[20] Further studies need to be conducted to determine whether similar neurotoxicity is observed in those consuming DFP.

Studies regarding the efficacy, safety, and side effects of using DFP were numerous, yet disparities in incidence rate still occurred, as well as observations of side effects that were previously not reported by other studies. Surely, for the sake of patient safety, more observations with larger sample sizes in longer trial period would be beneficial in determining incidence and previously unknown side effects of DFP usage.

In conclusion, continuous close monitoring of patients who undergo iron chelation therapy is needed to ensure that side effects are treated promptly. Side effects of DFP include neutropenia, agranulocytosis, increased ALT, gastrointestinal problems, arthralgia or arthropathy, increased appetite or weight, thrombocytopenia, urine discoloration, as well as auditory and visual disturbances. There is no evidence relating symptoms in the clinical scenario of our pediatric thalassemia patient to DFP consumption.

Acknowledgments

The authors would like to thank fellow colleagues at the University of Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital for their support.

Conflict of Interest

None declared.

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