# Case Report

# Modified Desensitization Protocols for a Pediatric Patient with Anaphylactic Reaction to Deferoxamine

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*Thalassemia major is an inherited form of chronic hemolytic anemia that results in iron overload due to regular blood transfusions. Deferoxamine is used as chelating agent for treatment of patients with chronic iron overload worldwide. Anaphylactic reaction to deferoxamine is rare, and the mechanism of deferoxamine-induced anaphylaxis is not well understood. Only a few pediatric cases of successful desensitization for deferoxamine hypersensitivity have been described, and a different protocol has been used in each report. We report a case of anaphylaxis to deferoxamine in a thirteen-years-old Thai boy with Hemoglobin E/β-thalassemia disease who underwent successful desensitization. He had been receiving blood transfusions since the age of ten months. At age eleven, the patient began treatment with deferoxamine. Treatment was interrupted after the occurrence of anaphylaxis, with urticaria, wheezing and gastrointestinal symptoms. A skin prick test was positive, indicating a type 1 hypersensitivity reaction. Deferoxamine desensitization was attempted with various different protocols. Finally, the patient could tolerate deferoxamine therapy at the dose previously administered. We proposed this modified subcutaneous desensitization protocol for pediatric cases that develop allergic reactions to deferoxamine.*

***Keywords:*** *Deferoxamine, Anaphylaxis, Desensitization, Subcutaneous*

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Thalassemia is the most common human single gene disorder worldwide. Hemoglobin E/beta-thalassemia (Hb E/β-thalassemia) is a very common form of beta-thalassemia that exhibits a heterogeneous clinical presentation and variable clinical course. The highest frequencies are observed in India and throughout Southeast Asia, particularly in Thailand, Laos and Cambodia[1,2]. Hb E/β-thalassemia results from co-inheritance of a beta-thalassemia allele from one parent and the structural variant Hemoglobin E from the other. Severe forms are characterized by very low Hemoglobin (Hb) levels, and affected patients are treated as thalassemia major patients with regular blood transfusion and iron chelation. Iron overload may lead to organ toxicity and even fatal complications if iron chelating therapy cannot be achieved.

For clinical use, iron chelators are designed to either promote clearance of excess iron by excretion or maintain safe iron levels in situations that pose a risk for developing toxic levels of iron. Three chelators are approved for therapeutic use: deferoxamine, deferasirox, and deferiprone, and these agents are sometimes are used in combination[3,4]. Deferoxamine (DFO), also known as desferrioxamine or desferal, is the most important drug and commonly used in the treatment of thalassemia major and other hematological diseases following multiple blood transfusions. It is administered by intravenous injection or subcutaneously with iron complexes being cleared mainly by biliary and urinary routes. Allergic reactions to DFO are rare and difficult to manage. The mechanism of hypersensitivity is various and need to be explored. The purpose of this article is to report a pediatric case of anaphylaxis to DFO in which the patient underwent successful desensitization.

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## Case Report

A 13-years-old Thai boy with Hb E/β-thalassemia had been receiving frequent blood transfusions from the age of 10 months. He had a splenectomy at the age of 5 because of hypersplenism and began to receive a transfusion every 1-2 months after that. The iron chelation therapy was started at the age of 11. He was receiving intravenous DFO infusion at a standard dose of 30 mg/kg/day (750 mg of DFO in 50 mL of saline solution) for 3 consecutive days per week at the Thammasat University Hospital. Because

of a further increase in serum ferritin level (>2,000 ng/mL), he also received oral daily deferiprone as a combined therapy. Fourteen months after DFO administration, he had an anaphylactic reaction described as generalized urticaria, itching, wheezing, dyspnea, tachycardia and vomiting 10 minutes after beginning DFO infusion. The infusion was stopped immediately, and the patient was treated with intramuscular epinephrine, antihistamines, corticosteroids and salbutamol nebulization.

Two weeks after the first anaphylactic reaction, the patient was admitted for investigation and desensitization. The total serum immunoglobulin E (IgE) was within a normal range. The skin prick test (SPT) with diluted DFO solution (15 mg/mL) was positive (size 25x6 mm) in this patient while the tests were negative in all 5 thalassemia patients of the control group. For further testing with the patient, SPT with common food allergens was negative. The FIRST desensitization protocol was modified by the method of Miller et al[5]. The desensitization was started with a solution of 1/100,000 of the anticipated final intravenous infusion concentrations (0.0075 mg in 50 mL of saline solution) and continued with the following schedule: 0.075, 0.75, 7.5, 75, 750 mg in 50 mL at 30-minute intervals (Table 1). At a dose of 0.75 mg (solution of 1/1,000), he had a similar anaphylaxis episode, and the trial was discontinued. The complete blood count during this episode showed eosinophilia (absolute eosinophil count of 3,066/cu.mm.). One week later, the SECOND desensitization was attempted by increasing the concentrations of DFO as in the first but increasing the interval between doses from 30-minute to 24-hour interval and changing the route from intravenous to continuous subcutaneous infusion (Table 2). This trial was successful without any reactions. The patient was discharged and then admitted one week later for 3 days of daily 24-hour subcutaneous infusion of 750 mg of DFO. However, a similar anaphylactic reaction occurred again on the first day of desensitization. The infusion

**Table 1.** The FIRST desensitization protocol via intravenous infusion at 30-minute intervals for each bottle without premedication

| Bottles | Time (hours) | Dose (mg) of DFO in 50 mL of saline solution | Ratio of DFO in solution to the anticipated final infusion dose (750 mg) |
|---|---|---|---|
| 1 | 0 | 0.0075 | 1:100,000 |
| 2 | 0.5 | 0.075 | 1:10,000 |
| 3 | 1.0 | 0.75 | 1:1,000 → Anaphylaxis |
| 4 | 1.5 | 7.5 | 1:100 |
| 5 | 2.0 | 75 | 1:10 |
| 6 | 2.5 | 750 | 1:1 |

DFO = deferoxamine
Modified by the method of Miller et al[5]

**Table 2.** The SECOND desensitization protocol via continuous subcutaneous infusion* at 24-hour intervals for each bottle without premedication

| Bottles | Time (hours) | Dose (mg) of DFO in 50 mL of saline solution | Ratio of DFO in solution to the anticipated final infusion dose (750 mg) |
|---|---|---|---|
| 1 | 0 | 0.0075 | 1:100,000 |
| 2 | 24 | 0.075 | 1:10,000 |
| 3 | 48 | 0.75 | 1:1,000 |
| 4 | 72 | 7.5 | 1:100 |
| 5 | 96 | 75 | 1:10 |
| 6 | 120 | 750 | 1:1 |

DFO = deferoxamine
* The continuous subcutaneous infusion of DFO was administered via slow subcutaneous infusion uniformly over 24 hours using a portable infusion pump.

was suspended, and the patient received treatment for anaphylaxis.

Two months later, he was admitted for the THIRD desensitization (Table 3). Because of the high risk of anaphylaxis, pretreatment was started with intravenous antihistamines and corticosteroids (chlorpheniramine 0.1 mg/kg and hydrocortisone 5 mg/kg), single dose prior to desensitization. The patient was hospitalized for desensitization with eight continuous cycles of DFO. Finally, they were completed with no untoward reactions. However, anaphylaxis recurred one week later when the patient received 750 mg DFO infusion over 24 hours. Three weeks later, 10 weekends of the FOURTH desensitization were attempted continuously by increasing the concentrations of subcutaneous DFO infusion with premedication. The infusion interval periods were tapered weekly from 6-hour to 10-minute interval (6, 5, 4, 3, 2, 1 hours and 45, 30, 20, 10 minutes, respectively) (Table 4). The THIRD and FORTH desensitization are summarized in Fig. 1.

This trial was completed without further allergic reaction, even after discontinuing the premedication. During 2 years after the fourth desensitization, the patient regularly received subcutaneous infusion of 750 mg DFO in 10 mL of

**Table 3.** The THIRD desensitization protocol via continuous subcutaneous infusion* at 24-hour intervals for each bottle with premedication (antihistamines and corticosteroids) for total eight continuous cycles**

| Bottles | Time (hours) | Dose (mg) of DFO in 50 mL of saline solution | Ratio of DFO in solution to the anticipated final infusion dose (750 mg) |
|---|---|---|---|
| 1 | 0 | 0.0075 | 1:100,000 |
| 2 | 24 | 0.075 | 1:10,000 |
| 3 | 48 | 0.75 | 1:1,000 |
| 4 | 72 | 7.5 | 1:100 |
| 5 | 96 | 75 | 1:10 |
| 6 | 120 | 750 | 1:1 |

DFO = deferoxamine

* The continuous subcutaneous infusion of DFO was administered via slow subcutaneous infusion uniformly over 24 hours using a portable infusion pump.

** For the eight continuous cycles, the first three cycles (Cycle 1-3) were started with a 24-hour interval at DFO infusion dose of 1/100,000 (0.0075 mg, Bottle No. 1) and continued with an increasing concentration until the final dose (750 mg). Then the last five cycles (Cycle 4-8) were attempted by beginning at Bottle No. 2, 3, 4, 5, 6 respectively and continued with an increasing concentration over 24 hours each bottle until the final dose. The Cycle 1 to Cycle 8 is continuing administration without cessation.

**Table 4.** The FORTH desensitization protocol via subcutaneous infusion at different intervals tapering for each cycle with premedication (antihistamines and corticosteroids) for total ten weekend cycles

| Bottles | Dilution (mg) of DFO in 10 ml of saline solution | Ratio of DFO in solution to the anticipated final infusion concentrations (750 mg) |
|---|---|---|
| 1 | 0.075 mg subcutaneous infusion in 6 hours* | 1:10,000 |
| 2 | 0.75 mg subcutaneous infusion in 6 hours* | 1:1,000 |
| 3 | 7.5 mg subcutaneous infusion in 6 hours* | 1:100 |
| 4 | 75 mg subcutaneous infusion in 6 hours* | 1:10 |
| 5 | 750 mg subcutaneous infusion in 6 hours* | 1:1 |
| 6 | 750 mg subcutaneous infusion in 8 hours | 1:1 |

DFO = deferoxamine

* For the ten weekend cycles, the desensitization started with decreased the subcutaneous infusion interval periods for each bottle of DFO from 6-hour to 5-, 4-, 3-, 2-, 1-hour and 45-, 30-, 20-, 10-minute interval, respectively. At the end of each desensitization phase, an 8-hour subcutaneous infusion of 750 mg solution was given.

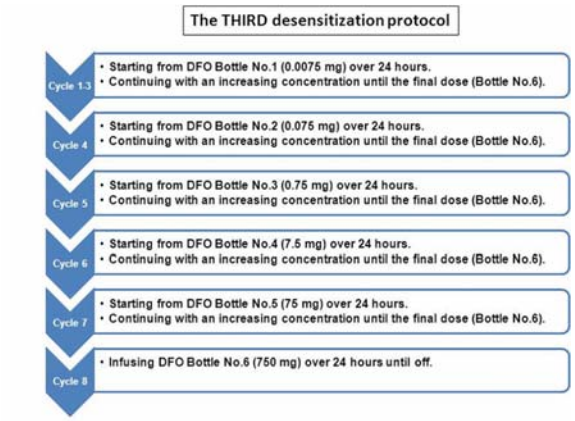


**Fig. 1A** The timeline of THIRD and FORTH Desensitization of deferoxamine. A) The THIRD Desensitization timeline (Please see the Table 3 for additional information of protocol).

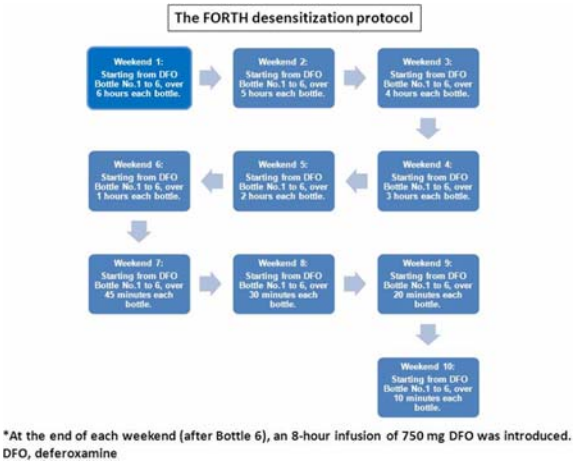


**Fig. 1B** The FORTH desensitization timeline (Please see the Table 4 for additional information of protocol).

saline solution (30 mg/kg/day, over 8 hours/day for three consecutive days per week) at the hospital without any allergic reaction. Thereafter, the subcutaneous infusion was given to the patient for self-therapy at home. He has continued home DFO subcutaneous infusions for the last 1.5 years. Finally, his chelation therapy was switched to oral deferiprone as monotherapy, when the serum ferritin was less than 1,000 ng/mL. A repeat SPT with DFO (using a 1/10 dilution of DFO 15 mg/mL solution) 6 months after cessation of DFO was still positive (size 15x15 mm).

## Discussion

There have been rare case reports of desensitization for DFO anaphylactic reactions from the United States of America, France, Italy, Turkey[5,7-10]. This is the first case report of a successful subcutaneous desensitization in a pediatric patient who had experienced an anaphylactic reaction to DFO. For immediate-type drug reactions, allergy skin testing may be useful, although there is a lack of standardized testing reagents. Skin testing by prick or intradermal methods is practicable, but it is important to establish a non-irritating drug dose for skin testing. In our case, the SPT with diluted DFO was positive, whereas the same test dose was negative in 5 other thalassemia patients. This suggests that the patient had an IgE-dependent hypersensitivity reaction to DFO. However, due to the lack of standardized reagents, the positive and negative predictive values of skin testing for DFO remain unknown. Furthermore, our results do not rule out the possibility that DFO allergy is related to direct mast cell activation as previously described[6]. Such a non-IgE mediated allergic reaction has been proposed to explain DFO-induced anaphylaxis in adult and pediatric patients who have negative skin prick tests and absent specific serum IgE to DFO[8-10]. Finally, it is possible that both IgE-mediated and non-IgE mediated direct mast cell activation coexist in some patients. A limitation of the present study is that the authors did not test the patient with validated in vitro immunological testing for serum IgE to DFO; however, this test is not widely available.

Desensitization using gradual titration of drug administered parenterally is the gold standard for management of many types of drug allergies. However, this procedure should only be performed by experienced and trained physicians in an appropriate setting. The time required for successful desensitization varies with the type of medication and is patient-specific. Intravenous DFO as previously described[5,8,9] can provide an avenue for early challenging during desensitization. Why intravenous therapy as opposed to subcutaneous therapy is generally well tolerated is not fully understood. Suggested mechanisms range from the simple mechanics of putting small volumes of DFO intravenously with subsequent rapid distribution (particularly relevant for localized reactions) to differences in the immune system response depending on the route of DFO administration, e.g. dermal mast cell activation[11]. Eventually, complications can still occur, with anaphylaxis documented in our patient during intravenous desensitization. The successful use

of a subcutaneous desensitization protocol in this patient with DFO hypersensitivity represents a novel finding. For premedication, systemic treatment with antihistamines and/or corticosteroids were used as described in previous reports[5,8,9]. Antihistamines and corticosteroids may have provided some benefit during our desensitization therapy, but they were insufficient alone to account for the success of the protocol.

## Conclusion

This report illustrates the utility of using a subcutaneous desensitization approach with premedication for treatment of immediate-type hypersensitivity to DFO. The modified desensitization protocol proposed in the present study was effective in preventing allergic reactions and in reducing iron overload. The authoes propose this as an alternative desensitization protocol for pediatric cases that are anaphylaxis to DFO and require long-term iron chelation therapy.

## What is already known on this topic?

1. Anaphylactic reaction to deferoxamine is a relatively rare condition in childhood.

2. The standard desensitization protocol for deferoxamine hypersensitivity is not well established.

## What this study adds?

1. Desensitization to deferoxamine in pediatric patients is safe using our protocol. We have had a successful delivery of subcutaneous deferoxamine in our patients with thalassemia major.

2. Skin testing data is not routinely available due to the lack of commercially available testing reagents. Without standardized reagents, the positive and negative predictive values of skin testing for deferoxamine remain unknown.

3. Further establishment of the treatment protocols by a multicenter study for desensitization of life-sustaining drugs and effectiveness of this treatment are required.

## Acknowledgement

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## Potential conflicts of interest

None.

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## การทำ desensitization ในผู้ป่วยเด็กที่มีปฏิกิริยาภูมิแพ้แบบ anaphylaxis ต่อยา deferoxamine

พชรพรรณ สุรพลชัย, อรพรรณ โพชนุกูล, วัลลี สัตยาศัย, ผกาทิพย์ ศิลปมงคลกุล

*โรคธาลัสซีเมียชนิดรุนแรงเป็นโรคโลหิตจางเรื้อรังชนิดหนึ่งที่ถ่ายทอดทางพันธุกรรม ผู้ป่วยโรคนี้จำเป็นต้องได้รับเลือดเป็นประจำส่งผลให้มีภาวะเหล็กเกินในร่างกาย ยา deferoxamine เป็นยาขับธาตุเหล็กที่นำมาใช้ในผู้ป่วยโรคธาลัสซีเมียชนิดรุนแรงและผู้ป่วยโรคอื่นที่มีภาวะเหล็กเกินอย่างแพร่หลาย ปฏิกิริยาภูมิแพ้อย่างรุนแรง (anaphylaxis) ต่อยา deferoxamine พบได้ไม่บ่อยและไม่ทราบกลไกการเกิดที่แน่ชัด นอกจากนั้นยังมีรายงานจำนวนน้อยมากในผู้ป่วยเด็กที่ประสบความสำเร็จจากวิธีการ desensitization หลังเกิดปฏิกิริยาดังกล่าวต่อยา deferoxamine และมีวิธีการที่แตกต่างกันมากในแต่ละรายงาน การศึกษานี้กล่าวถึงผู้ป่วยเด็กชายไทยอายุ 13 ปี ที่เป็นโรคฮีโมโกลบิน อี/บีตาธาลัสซีเมีย ที่ประสบความสำเร็จต่อวิธีการ desensitization หลังเกิดปฏิกิริยา anaphylaxis ต่อยา deferoxamine ผู้ป่วยเกิดปฏิกิริยานี้หลังเริ่มได้รับการรักษาด้วยยา deferoxamine นาน 2 ปี โดยมีอาการแพ้แบบเฉียบพลันทางผิวหนัง (ผื่นลมพิษ) ระบบทางเดินหายใจ (หายใจเสียงหวีด) และระบบทางเดินอาหาร การทดสอบผิวหนัง (skin prick test) ให้ผลเป็นบวก ยืนยันว่าเป็นปฏิกิริยาภูมิแพ้แบบเฉียบพลัน (type 1 hypersensitivity reaction) จึงได้ทำการ desensitization ในผู้ป่วยรายนี้ด้วยวิธีการที่แตกต่างกันจนในที่สุดผู้ป่วยสามารถทนต่อการรักษาด้วยยา deferoxamine ได้ในขนาดและวิธีการบริหารยาแบบเดียวกับที่เคยใช้มาก่อน ทางคณะผู้นิพนธ์ขอนำเสนอวิธีการ desensitization โดยการบริหารยาทางชั้นใต้ผิวหนังนี้เป็นวิธีการหนึ่งในการรักษาผู้ป่วยเด็กที่เกิดปฏิกิริยาภูมิแพ้แบบ anaphylaxis ต่อยา deferoxamine*