

Brief communications

Desensitization treatment for anaphylactoid reactions to desferrioxamine in a pediatric patient with thalassemia

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Desferrioxamine (DF), which is used to reduce iron overload in patients with thalassemia major, has been reported to elicit untoward reactions. A bibliographic search revealed that anaphylactoid reactions have been reported in four adult patients with thalassemia who were receiving DF for a long period and who were successfully treated by rapid desensitization.¹⁻⁴ An anaphylactoid reaction to DF has been reported in only one child, who did not receive rapid desensitization, but was treated with calcium diethylenetriamine-pentaacetic acid.⁵ In three cases¹⁻³ no immunologic studies were performed, but in the fourth case⁴ a careful immunologic analysis was carried out. We report a case of anaphylactic reactions to DF in a very young child with thalassemia who underwent successful desensitization. We also report results of an immunologic study of the case.

CASE REPORT

A 4-year-old girl with β -thalassemia major began receiving blood transfusions at the age of 17 months. One year later, she also began to receive continuous subcutaneous DF (40 mg/kg/day over the course of 12 hours, 4 days a week). Her high serum ferritin levels led us to increase the dose of DF to 60 mg/kg/day. A further increase in ferritin levels, 8 months later, led us to initiate intensive therapy that consisted of intravenous infusion of DF (100 mg/kg/day over 12 hours, 5 days a month) and subcutaneous infusion of DF at 60 mg/kg/day for 5 days a week. During a home subcutaneous infusion of DF, the patient had an asthma attack that was accompanied by urticaria and generalized itching, which were resolved by inhalation of salbutamol and parenteral administration of steroids. A similar episode occurred during the next infusion of DF 1 week later,

Abbreviation used

DF: Desferrioxamine

and it was treated in the same way. We did not link these two episodes to an anaphylactoid reaction to DF.

In fact, after a few days, the patient was again given a venous infusion of DF in the same way as before. A few minutes after the beginning of the infusion, the little girl had generalized itching with cough, wheezing, dyspnea, cyanosis, and vomiting. The infusion was stopped immediately, and the patient was treated with parenteral steroids (200 mg of hydrocortisone, administered intravenously) and antihistamines (50 mg of diphenhydramine). On this occasion the relationship between the anaphylactoid reaction and DF was recognized, and 1 month later, the little girl was admitted to the intensive care unit for desensitization to DF by the method of Miller et al.² as modified for the patient's age.

The desensitization was started with a venous infusion of DF (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 and then 750 mg in 10 ml at 30-minute intervals. Then the patient began receiving a 24-hour continuous subcutaneous infusion of DF (750 mg in 10 ml in the first day), which was followed by three other infusions of the same dose of DF over the course of 18, 16, and 12 hours on the next 3 days. After the patient was discharged, she continued to receive 750 mg of DF (50 mg/kg/day) 5 days a week without any side effects. Two months later, 30 minutes after the start of subcutaneous infusion at the normal dose, the patient had generalized itching and urticaria. The infusion was stopped, and the patient was immediately hospitalized. Because of her inability to tolerate DF, the patient was treated with diethylenetriaminepentaacetic acid (30 mg/kg/day over 4 months).

Her increased ferritin and transaminase levels then led us to attempt a second desensitization by the method of Miller et al.,² as described above, until a final dose of 1500 mg in 10 ml of saline solution was reached. When the last infusion was completed, the little girl had a cutaneous rash, headache, and dyspnea, which were

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immediately resolved by administration of dexamethasone and diphenhydramine. Her mother refused permission to continue the trial at that time. The next day the patient had a fever (39°C) and bronchitis. Ten days later, when she had completely recovered, we attempted the subcutaneous infusion of DF at a dose of 500 mg in 20 ml of saline solution over 24 hours. No adverse reaction occurred, and more DF was administered as follows: second day, 750 mg in 20 ml; third day, 1 gm in 20 ml over 24 hours; and from the fourth to thirteenth days, 750 mg in 10 ml over 12 hours. Now, 12 months after this second desensitization, the patient regularly receives subcutaneous infusion of DF at a dose of 1 gm (50 mg/kg day over 12 hours, 6 days a week).

No specific serum IgE or IgG to DF was detected in the patient's serum before, immediately after, and 15 days after the two rush immunotherapy procedures. The specific IgE to DF was detected by Magic Lite SQ system (Ciba Corning Diagnostic Corp., Medfield, Mass.), which combines the magnetic immunochemistry and chemiluminescent technologies. In this system the DF material is immobilized by a coupling to paramagnetic particles, which are used as the solid phase in the assay. The drug is first coupled to human serum albumin, and after this, covalently to the paramagnetic particles. Serum is incubated with solid phase and, after a washing step, with labeled anti-IgE. The labeling agent is acridinium ester, and we measure the emittance of light in a luminometer. The specific IgG to DF was detected with counter-current immunoelectrophoresis. The serum sample and the antigen are placed in holes in an agarose gel opposite each other. With the electric current the antigen will move toward the antibodies of the serum sample, and a precipitation will occur if specific antibodies are present.

This method is dependent on the transportation of the antigen in the gel. The serum sample is applied in different dilutions, and the results are given as the last dilution in which a precipitation is visible. As a control, we use a pool of serum from 1000 normal human beings. The techniques used for measurement of specific serum IgE and IgG are commonly used in ALK Laboratories (Hørsholm, Denmark) for "rare antigens."

In this case the total IgE level was within the normal range (mean, 40 U/L) for the patient's age. Total eosinophil counts and the C3 and C4 fractions of complement were also within normal ranges. As described elsewhere,⁴ a prick test to DF was not appropriate.

DISCUSSION

The reactions experienced by our patient receiving DF can be referred to as anaphylactic-like in

view of the immediacy of onset, multisystem involvement, and life-threatening aspects such as dyspnea, cyanosis, and vomiting.

The precise mechanism responsible for DF anaphylactic-like reactions has not been established. In this case no increase of specific antibodies to DF for IgE and IgG was found, so the anaphylactic-like reactions could be attributed to mediator depletion or hyporesponsiveness of mast cells resulting from subclinical mediator release caused by the lower doses of DF. The long-term tolerance of the drug could be explained by the continuous (day-by-day) administration of DF for iron chelation. The desensitized state depends on the continuous presence of the antigen. Anaphylactic sensitivity can return within 48 hours of discontinuation of the drugs and long-term administration of a twice-daily dose can sustain the desensitized state, as happens with patients allergic to penicillin who are receiving penicillin orally.

This report describes the fourth successful desensitization of a patient who became intolerant to DF, the first such report in the pediatric literature. Our patient resembles the adult patient of Bousquet⁴ in that she had low total IgE, absent specific IgE and IgG to DF, and long-term successful desensitization. Our case highlights the utility of rapid intravenous desensitization approach in the treatment of hypersensitivity to a life-sustaining drug, when no other therapy is available.

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REFERENCES

1. Athanasiou A, Shepp MA, Necheles T. Anaphylactic reactions to desferrioxamine. *Lancet* 1977;2:616.
2. Miller KB, Rosenwasser LJ, Besette JA, Beer DJ, Rocklin RE. Rapid desensitisation for desferrioxamine anaphylactic reactions. *Lancet* 1981;1:1059.
3. Davies SC, Marcus RE, Hungerford JL, Miller MH, Arden GB, Huehns ER. Ocular toxicity of high-dose intravenous desferrioxamine. *Lancet* 1983;1:181-4.
4. Bousquet J, Navarro M, Robert G, Aye P, Michel FB. Rapid desensitisation for desferrioxamine anaphylactoid reactions. *Lancet* 1983;2:859-60.
5. Romeo MA, Di Gregorio F, Schiliro' G. Allergy to desferrioxamine. *J Inher Metab Dis* 1984;7:121.