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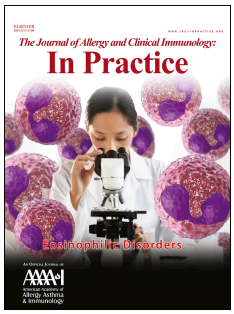

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PII: S2213-2198(19)31052-9

DOI: https://doi.org/10.1016/j.jaip.2019.12.018

Reference: JAIP 2606

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 5 July 2019

Revised Date: 4 December 2019

Accepted Date: 6 December 2019

Please cite this article as: Vethody C, Houser A, Hall L, Volanakis EJ, Norton A, Use of Drug challenge in a Case of Possible Deferoxamine Allergy, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: https://doi.org/10.1016/j.jaip.2019.12.018.

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Use of Drug challenge in a Case of Possible Deferoxamine Allergy

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Conflict of Interest: ALL authors have viewed the conflict of interest statement and have nothing to disclose.

Clinical Implications (word limit 40 words, current: 40)

We report a case of anaphylaxis to Deferoxamine with negative testing and drug challenge. This case illustrates the importance of considering challenge when the reaction is neither IgE-mediated or severe non-immediate, even if no prior description exists in the literature.

To the Editor

Patients with Sickle cell disease often develop iron overload due to multiple blood transfusions which may result in significant morbidity and mortality due to organ hemosiderosis. Subcutaneous deferoxamine(DFO) prevents cardiac disease in patients with thalassemia major and dramatically improves prognosis (1). Local infusion reactions are common, but anaphylaxis has rarely been described. Although desensitization to DFO has been anecdotally reported in the literature, this is the first reported successful drug challenge to DFO(2).

A 20-year-old African American female with a history of Sickle cell disease complicated by stroke, symptomatic anemia, and severe iron overload secondary to chronic blood transfusions was initially referred to our outpatient clinic after a possible adverse drug reaction (ADR) to deferoxamine. Her chelation regimen prior to the reaction included 10-hour subcutaneous infusions of DFO daily, 72 hour intravenous infusions of DFO every 4 to 6 weeks, and oral deferasirox daily. After tolerating this regimen for over three years, she developed an adverse reaction to her subcutaneous DFO infusion. Within 10 minutes of starting her infusion, she developed a raised urticarial rash around the injection site which spread to her bilateral arms, torso and face. Shortly thereafter she developed

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bilateral eye, lip and earlobe angioedema, in addition to vomiting. She required emergency care and was treated with epinephrine for presumed anaphylaxis. H1 and H2 blockers, intravenous steroids, intravenous fluids and albuterol were used as adjunct therapies in the emergency room. Notably, there was no hemodynamic instability. Coincidently, the patient was on an angiotensin-converting enzyme inhibitor(ACEI) and was taking this medication concurrently at the time of her reaction. All DFO infusions were discontinued, and she remained on deferasirox monotherapy. This was considered inadequate to prevent progression of her hepatic and myocardial hemosiderosis, so she was transitioned from chronic blood transfusions to hydroxyurea for secondary stroke prophylaxis. However, she developed additional silent cerebral infarcts, necessitating a switch back to transfusions. To handle the additional iron loading it was imperative to resume DFO. In addition, the patient had another episode of facial angioedema remote to this episode, despite discontinuing DFO. Due to concern that the ACEI was contributing to angioedema and may have been a co-factor in her anaphylactic reaction to DFO, she was transitioned from an ACEI to an angiotensin receptor blocker. No further episodes of facial angioedema were reported after discontinuing this medication.

As DFO was essential for her care, we subsequently admitted the patient to the PICU for skin testing and possible challenge or desensitization, depending on testing results (Figure 1). Written informed consent was obtained as approved by the Ethics Committee. In the PICU, the patient initially underwent skin prick testing with 1:10 dilution of full strength deferoxamine (213 mg/mL) which was negative. Subsequently, intradermal testing was conducted every 15 minutes beginning with a 1:100,000 dilution followed by 1:10,000 dilution, 1:1,000 dilution, and 1:100 dilution. These testing dilutions were chosen, based on previous literature identifying a non-irritating concentration, using five controls(2). Our healthy control showed irritant response to the 1:1,000 and 1:100 dilutions. Given negative skin testing, a graded subcutaneous deferoxamine challenge was initiated, after reaching out to our pharmacists for guidance. The challenge was performed as follows using a deferoxamine 213 mg/mL solution:

- Day 1: 30mg SQ over 10 hours
- Day 2: 300mg SQ over 10 hours
- Day 3: 2500mg SQ over 10 hours
- Day 4: 2840mg SQ over 10 hours

The patient received cetirizine 20 mg and ranitidine 150 mg prior to the graded challenge and twice daily throughout the challenge. Her flow rate of her target dose was not altered. She had no adverse reactions throughout her stay in the PICU. After discharge, she tolerated subcutaneous infusions of her deferoxamine nightly at a dose of 40 mg/kg over 10 hours. This dose was the same dose she was on previous to her reaction. She was slowly weaned off all antihistamines except for 10 mg of cetirizine but has continued to tolerate infusions, even with disruptions in drug schedule.

Subcutaneous deferoxamine is the standard of care in patients with iron overload and has substantially improved their quality of life (1). Although local infusion reactions are common with subcutaneous administration of DFO, there have only been 9 cases of anaphylaxis described(2-4). Prior attempts of

desensitization to DFO have been lengthy, some lasting for several days to weeks(2-4). This may be due to the often-urgent need for the drug coupled with the lack of clear understanding of the reactions, as well as little data for guidance on alternative management plans, other than previously described desensitization. There is evidence in the literature of four patients with severe allergic reactions to DFO via subcutaneous route that tolerated it intravenously without allergic reactions for one year(3). The most effective method of chelation is via the subcutaneous route, and the intravenous route can be cumbersome, both for convenience of administration and risk of dangerous long term side effects(1) . There have also been reports of patients receiving infusions with lower DFO concentrations, which is thought to prevent allergic reactions by allowing a greater pharmacological bioavailability and preventing subcutaneous drug overload (5). Studies have shown a local activation of dermal mast cells as a possible mechanism causing allergic reactions which suggests an IgE independent process (6).

Although there is no previous literature describing anaphylactic reactions to DFO in a patient who is concurrently on an ACE inhibitor, we hypothesized that the ACEI as a possible exacerbating factor behind our patient's reaction. Additionally, her negative skin testing to the DFO product, confirmed our suspicion that her reaction was not IgE mediated and could be managed differently, departing from the lengthy desensitizations described in the literature. Furthermore, her history of recurrent facial angioedema while on an ACEI, despite discontinuing subcutaneous DFO supported our assumptions that the concomitant use of an ACEI may have decreased her threshold for a systemic reaction. Although this is controversial, a recent Meta-analysis of observational studies suggest that ACEI may increase the severity of anaphylactic events (7).

After careful review of prior literature and evidence of hypersensitivity reactions to DFO being an IgE independent process, we chose to skin test (2). Our testing experience suggests that the intradermal dilutions greater than or equal to 1:1000 may cause an irritant response to healthy controls, though more controls are needed to confirm this. Due to lack of alternative effective treatments and urgency of the medication, we sought the standard of care which is drug provocation testing (DPT) following negative testing. DPT is the controlled administration of a drug to establish or exclude the diagnosis of drug hypersensitivity (8). We chose to use antihistamines to prevent significant non-IgE mediated direct mast cell release of histamine, a known property of this drug (6), but did not alter her goal flow rate. We were concerned that urticaria due to dermal mast cell stimulation would confound our results of the challenge and make it difficult for our patient to receive her much-needed medication in a timely manner.

If we use strict definitions of DPT and desensitization, this patient's procedure was neither. Pretreatment with antihistamines is not indicated in DPT (9). In desensitization, a state of tolerance is induced which is continued if the drug is continuously given. This tolerance is resolved when there is any interruption of delivery of the drug, usually within days(8). Eight months after our patient's drug challenge, our patient successfully restarted DFO despite a 2 month

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interruption in therapy due to formulary changes, which argues against this procedure as a desensitization protocol. We followed her closely after the drug challenge and guided tapering of antihistamines. Since we used antihistamines during the challenge, we called this protocol a "drug challenge" instead of DPT. Patients who tolerate graded challenges are not allergic to the drug(9). It is important to note, that if she had history of a reaction during the drug challenge, she would be considered allergic and we would have considered a shorter desensitization protocol than those previously described (figure 1). Additionally, we chose to perform our drug challenge using established safety requirements for desensitization, given the severity of her index reaction (9).

This case illustrates not only the complexities of confounding factors, such as concurrent medications in drug reactions, but also the importance of properly phenotyping a reaction, as well as using existing guidelines to mold diagnostic and/or therapeutic care that best fits the patient's needs. Co-factors should be considered in drug reactions and may drive a reaction to be more severe. Using additional medications such as antihistamines and/or reducing flow rate for these non-IgE mediated reactions may allow timely and safe receipt of the product. These measures should be used cautiously with knowledge of the known properties of the drug and proper patient guidance. In addition, our protocol will prevent unnecessary lengthy repeat desensitizations if doses are missed. Drug Challenge should be considered in lieu of desensitization for benign non-IgE mediated reactions, even when it has not been described in the literature.

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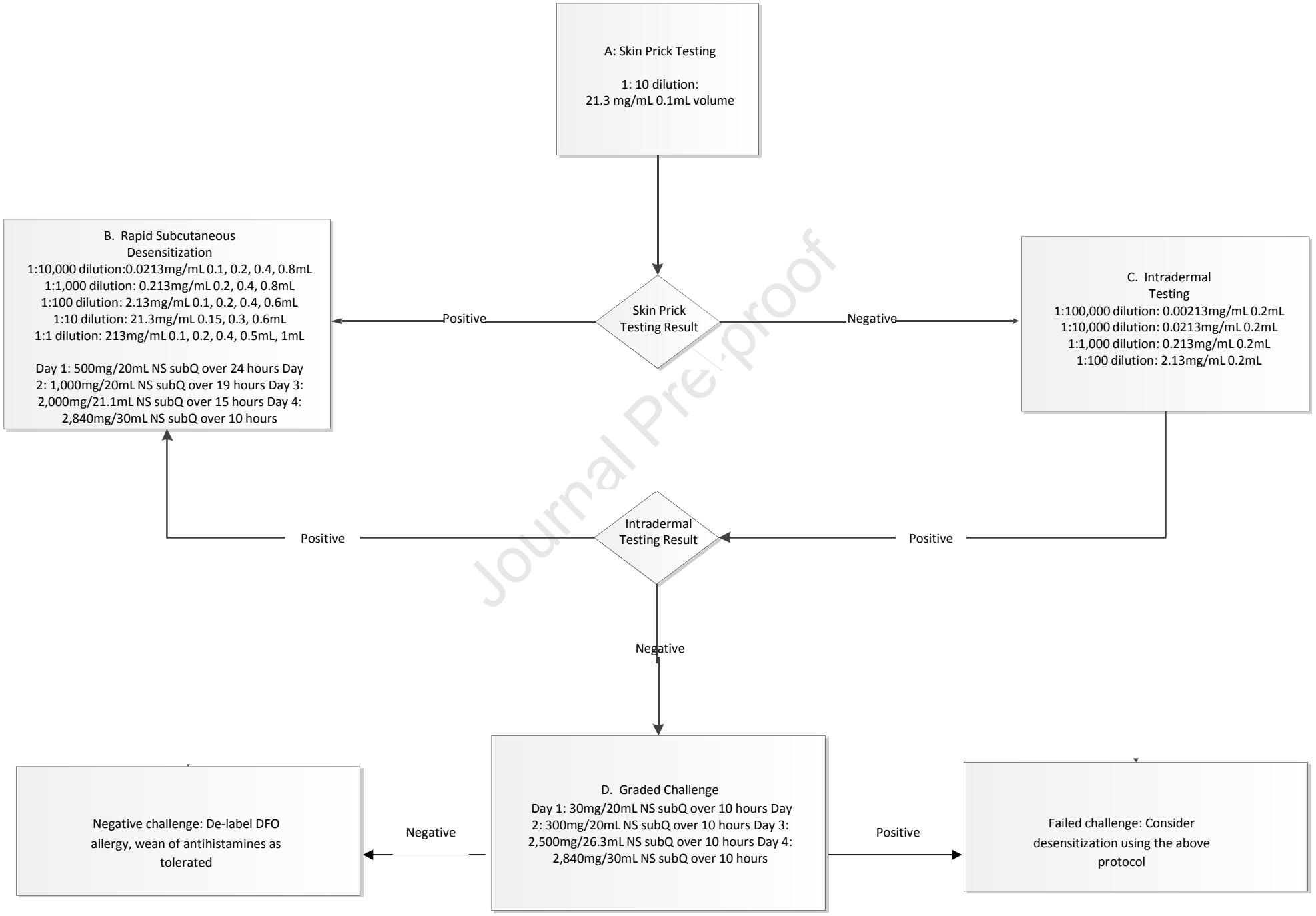
Figure Legend:

(A) Skin prick testing (SPT) is recommended using the concentration described previously in the literature. If SPT is negative, proceed to intradermal testing (C). If intradermal testing is negative, then proceed with the graded challenge as described in (D). If intradermal or skin prick testing is positive, this is suggestive of IgE sensitization, therefore proceed with Rapid Subcutaneous Desensitization protocol (B). If there is a reaction consistent with a severe allergic reaction during the graded challenge (D), consider desensitization(B).

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