



Letter

Effect of use of inhaled epinephrine on intramuscular epinephrine use in patients with idiopathic anaphylaxis and angioedema

Idiopathic anaphylaxis is a difficult to manage symptom complex with a variety of causes¹ whose treatment ultimately centers on finding an appropriate combination of therapies that is often unique to each patient. We report 2 cases of patients with frequent attacks of throat angioedema who have benefitted from the use of inhaled epinephrine in reducing the frequency with which they have required intramuscular epinephrine.

The first patient is a 36-year-old African American woman who presented with stereotypical episodes of anaphylaxis and upper airway angioedema in 2011. Skin test results were negative for any food allergies, and environmental test results were positive for mold only. Test results for hereditary and acquired angioedema and for α -gal allergy were negative. Having never had these episodes before 2011, she subsequently became well known to our service as a patient whose episodes would lead to 3-times-weekly use of intramuscular epinephrine and visits to the emergency department. Between 2012 and 2014, she required 3 overnight intensive care unit stays for an epinephrine drip because of urticaria, facial and throat angioedema, hypotension, vomiting, diarrhea, and severe wheezing, but she never required intubation. She had these episodes with normal tryptase levels and no evidence of clonal mast cell populations on bone marrow biopsy. We were unable to gain control over her episodes with the addition of histamine₁ and histamine₂ receptor blocking agents, montelukast, doxepin, and hydroxychloroquine. She gained some improved control over gastrointestinal symptoms by using cromolyn and compounded ketotifen but continued to have upper airway angioedema at a rate of multiple episodes per week. An hour after her first administration of a trial of omalizumab, the patient had a severe episode of anaphylaxis, leading to a hospital stay. Because we were unsure whether the omalizumab had contributed to this episode, we attempted an inpatient desensitization to omalizumab with seeming success for the second and third doses, but the patient had another episode of anaphylaxis within 10 minutes of her fourth dose of omalizumab, leading to an intensive care unit admission with an epinephrine drip. In late 2014, noticing that the patient had developed a new positive anti-nuclear antibody titer result at 1:160 with signs of Raynaud disorder, hand arthralgias, and capillary telangiectasias, we attempted to treat her with cyclosporine at 50 mg twice a day, which finally reduced the frequency of her episodes from 3 times weekly to 3 times a month. She also required the use of intramuscular epinephrine to abort throat angioedema. With the addition of inhaled racemic epinephrine in the form of a 2.25% solution formulated as a dry powder inhaler from a

compounding pharmacy, the patient reports that she is able to abort all her throat attacks without the use of injected epinephrine. She has successfully been able to manage these events at home without needing an emergency department visit or use of injectable epinephrine for 6 months, although she continues to carry injectable epinephrine as a back-up treatment.

The second patient is a 19-year-old white woman who initially presented to our care in 2005 at 9 years of age for possible mastocytosis, having frequent episodes of anaphylaxis, urticaria, and throat angioedema and negative skin test results for food or environmental allergies. Test results for hereditary and acquired angioedema and α -gal allergy were also negative. She exhibits baseline elevations in tryptase level to 15 μ g/L, with some measurements as high as 20 μ g/L. On 2 separate occasions, in 2009 and 2014, the patient underwent bone marrow biopsy to evaluate for clonal populations of mast cells with none detected. From September 2014, her symptoms worsened markedly, with nearly constant urticaria and 2- to 3-times-weekly episodes of throat angioedema, nausea, vomiting, diarrhea, and presyncope, requiring use of an epinephrine injection. She had a week-long hospitalization at that time for angioedema and disseminated urticaria with a prolonged corticosteroid taper. Subsequent trials of hydroxychloroquine, sulfasalazine, ketotifen, and cyclosporine failed to improve the baseline control over her symptoms, and their use was discontinued because of adverse effects and inefficacy. She had acute-onset worsening of her symptoms, with a first dose of doxepin requiring an emergency department treatment with epinephrine. A regimen of cromolyn, cetirizine, ranitidine, montelukast, and as needed diphenhydramine was helpful in controlling most of her urticaria and gastrointestinal symptoms, but she had ongoing upper airway angioedema. A trial of omalizumab was successful in inducing remission of her symptoms for almost 3 months, but she was subsequently unable to afford the medication because of insurance and financial constraints. Three months after cessation of omalizumab therapy, she began to experience increased frequency of upper airway angioedema, requiring intramuscular epinephrine 2 to 3 times weekly. We added inhaled racemic epinephrine in the form of a 2.25% solution that she uses with a portable nebulizer, diluted in saline, and she reports that this is satisfactory for aborting most of her throat angioedema episodes. Low-dose tacrolimus at 0.5 mg twice a day has reduced her episode frequency to once per month, and she has not required the use of epinephrine since its introduction; inhaled epinephrine has been sufficient for aborting her upper airway angioedema.

To our knowledge, this is the first report of using racemic epinephrine as an adjunctive therapy to spare use of intramuscular

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epinephrine in patients with a high attack rate of throat angioedema. Inhaled racemic epinephrine has been attempted for hereditary angioedema with limited success, but this is likely reflective of the mixed success of epinephrine for hereditary angioedema.² We have also encountered 2 additional patients in our clinic who reported benefit for throat angioedema by using previously available over-the-counter racemic epinephrine treatments, although this product is now discontinued.³ There has also been a report of successful local injection of epinephrine to treat uvular angioedema.⁴ Normal treatment algorithms for acute throat angioedema predominantly rely on intramuscular or intravenous epinephrine,⁵ but it is worth noting that systemic symptoms from epinephrine are very uncomfortable, and many patients with frequent throat angioedema will likely welcome an alternative means of abortive therapy even if they need to continue to carry an intramuscular epinephrine injector for severe episodes.

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