

Refractory Anaphylaxis Needing Emergency Intubation Supported by Expert Opinion and Published Guidelines: Could We Use Off-Label Drugs to Avoid It?

To the Editor:

In a recently issue of *Critical Care Medicine*, Krishaswamy (1) discussed about refractory cases of anaphylaxis and states that if angioedema does not respond to epinephrine, prompt endotracheal intubation is indicated and is supported by published guidelines (2). The situation of “epinephrine resistant” might be the first clue to the suspicion of bradykinin angioedema or anaphylactoid reaction. The resemblance of this condition to the much more common picture of histamine-induced angioedema means that many patients have been treated as such with epinephrine, corticosteroids, and antihistaminic (1). In a few cases, treatment failure will occur and bradykinin-mediated angioedema may become a valid alternative diagnosis (2). In recent years, new medical treatments have been introduced in the treatment of hereditary angioedema (HAE), a genetic disease characterized by bradykinin-mediated recurrent angioedema. Selective bradykinin B2 receptor antagonists and complement C1-esterase inhibitors are the most promising medical alternatives (2). Angiotensin-converting enzyme inhibitors (ACEIs) are common drugs widely used for renal and cardiovascular disorders (2). Acquired angioedema related to the use of an ACEI is an uncommon adverse reaction that can lead to life-threatening airway obstruction. The onset of angioedema is not due to a classical allergic reaction mediated by histamine but, rather, a symptom of an increased level of bradykinin (2). In a large patient series from Tai et al (3), 367 patients presented to a hospital because of angioedema during a 11-year period. Of those, nearly 50% were prescribed an ACEI. Twelve patients needed intubation but only one required tracheostomy (3). While histamine-induced angioedema treated with epinephrine, corticosteroids, and antihistaminic drugs will improve (1), bradykinin-mediated angioedema will not. A case report described a patient with angioedema who was treated IV with antihistamine and glucocorticoid in combination with epinephrine inhalations (4). After 6 hours, the swelling progressed, and the patient was admitted to the ICU and treated with icatibant, and the swelling resolved within 2 hours avoiding intubation (4). Icatibant is a bradykinin receptor antagonist, treatment of choice instead of anti-allergic medications, which have no proven efficacy in this condition (4). In HAE, the abnormal elevated production of bradykinin is caused by dysregulation of kallikrein activity due to an inherited C1-inhibitor deficiency or mutation in patients with HAE (5). In case of life-threatening airway obstruction due to HAE, plasma-derived C1-inhibitor (or recombinant C1-inhibitor—ruconest) and icatibant (plus ecallantide—recombinant plasma kallikrein inhibitor; CSL Behring, King of Prussia, PA) could be used to avoid

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rescue intubation (5); if none of those are available, solvent detergent-treated plasma or fresh frozen plasma can be used also. Early consideration of alternate etiologies might lead to a different choice of therapies. Given the extraordinary cost of ruconest and icatibant, the key point is to whom ruconest and icatibant ought to be prescribed absent an established diagnosis of HAE. When high suspicion of HAE, ruconest should be the drug to be used and when high suspicion of just bradykinin angioedema (ACEI, other drugs, other etiologies...) icatibant should be used. Obviously, they should be used off-label as there is no formal indication and labeling.

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The author replies:

Honore et al (1) suggest that inhibitors of the kinin-kallikrein-bradykinin axis should be considered in the management of severe anaphylaxis-related angioedema of the airway, especially when the disease is resistant to epinephrine and intubation becomes imminent. The authors refer to this as an “anaphylactoid reaction.” The premise of the authors and the suggestion is a very good one, and this has also been recommended in a recent editorial by Kaplan (2). Bradykinin is a potent mediator, and we recently reviewed the relative molecular roles of the histamine-nitric oxide and the kinin-kinin receptor systems in endothelial gap junction biology and in the genesis of angioedema and distributive shock (3). However, there are two problems with the recommendation of the authors, summarized below.

First, the nosology of anaphylaxis has changed, and almost 17 years ago, the World Allergy Organization recommended dropping the term anaphylactoid reaction due to confusion of its implications and instead, classifying anaphylaxis into two major groups, allergic and nonallergic, with kinin and complement-mediated reactions falling into the nonallergic category, as pointed out in my review (4).

Second, the authors are confusing isolated angioedema with anaphylaxis, and this is an important distinction that needs to be made. We have reviewed the management of angioedema recently and discuss its broad division into two categories, histamine-dependent and bradykinin-dependent (5). In isolated angioedema, several studies have been done that have allowed U.S.

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