Clinical Commentary Review

Do Corticosteroids Prevent Biphasic Anaphylaxis?

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List of Design Committee Members: Waleed Alqurashi, MD, MSc, FAAP, FRCPC, and Anne K. Ellis, MD, MSc, FRCPC, FAAAAI (authors); Scott H. Sicherer, MD (editor)

Learning objectives:

1. To discuss incidence, nature, and predictors of biphasic anaphylaxis.
2. To describe potential pathophysiologic mechanisms of biphasic anaphylactic reactions.
3. To discuss rationale for the use of corticosteroids in anaphylaxis.
4. To discuss data for and against the use of corticosteroids in the setting of anaphylaxis.

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Anaphylaxis is a severe hypersensitivity reaction that is rapid in onset and can result in death. The pattern of an anaphylactic reaction can be uniphasic (or monophasic), biphasic (also called delayed or late phase), or refractory in nature. The most widely cited definition of biphasic anaphylaxis is a recurrence of anaphylactic symptoms after initial resolution despite no further exposure to the trigger. Corticosteroids are thought by some to prevent the development of biphasic symptoms and, therefore, commonly used in the emergency treatment of anaphylaxis but this has not been systemtically analyzed. In this review, Ovid MEDLINE, Ovid EMBASE, Web of Science, and Scopus were searched for articles using "anaphylaxis" combined with the key terms "biphasic" and/or "corticosteroids" and/or "epinephrine." A total of 31 appropriate studies were identified. Biphasic anaphylactic reactions are more likely to occur in moderate to severe anaphylaxis or when anaphylaxis is not treated with timely epinephrine. Because of the potential detrimental adverse effects of corticosteroids and lack of compelling evidence demonstrating an effective role in reducing anaphylaxis severity or preventing biphasic anaphylaxis, we do not advocate for their routine use in anaphylaxis. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1194-205)

Key words: *Anaphylaxis; Biphasic anaphylaxis; Epinephrine; Corticosteroids*

Anaphylaxis is a severe hypersensitivity reaction that is rapid in onset and can result in death.[1] The population-based prevalence of anaphylaxis from all triggers is unknown.[1,2] However, the

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Abbreviation used
ED- emergency department
PAF- platelet-activating factor

lifetime prevalence estimates range from 0.3% to 5.1%, and it appears to be increasing globally, particularly among children.[3-6] The pattern of an anaphylactic reaction can be uniphasic (or monophasic), biphasic (also called delayed or late phase), or refractory in nature.[7]

The most widely cited definition of biphasic anaphylaxis is a recurrence of anaphylactic symptoms after initial resolution despite no further exposure to the trigger.[8,9] However, the reported definition from published clinical studies to date have been inconsistent. Furthermore, the reported incidence of biphasic anaphylaxis also varies widely, ranging from 3% to 23%.[7,10-34] Nevertheless, biphasic anaphylaxis can be associated with severe outcomes. Previous case series of fatal and near-fatal anaphylaxis among food-allergic children reported 3 cases of fatal biphasic reactions.[35] Although reports of fatal biphasic reactions are rare in recent literature, severe late reactions that require advanced airway intervention, extracorporeal membrane oxygenation resuscitation, and intensive care monitoring continue to be reported.[25,36-38]

Corticosteroids are thought by some to prevent the development of biphasic symptoms and, therefore, commonly used in the emergency treatment of anaphylaxis. Despite their wide clinical use, there is no compelling evidence to support their use.[9,35] This lack of evidence is thought to contribute to the variation in practice among clinicians. As a result, many patients receive therapies of unknown efficacy, and are hospitalized or monitored in the emergency department (ED) for long hours following an anaphylactic reaction due to concerns of biphasic responses.[21,39-41] In this clinical commentary, we review the risk factors and pathophysiology of biphasic anaphylaxis, summarize the literature supporting and opposing the use of corticosteroids in anaphylaxis, and provide recommendations for research studies to overcome current knowledge gaps.

METHODS

We defined a biphasic anaphylactic reaction as the recurrence or new symptoms of anaphylaxis after an anaphylactic event without reexposure to the trigger, following an asymptomatic interval of at least 1 hour. Studies that clearly documented reactions meeting this definition were included. We included relevant case series, prospective and retrospective cohort studies, and clinical trials. Studies that did not describe biphasic reactions and isolated case reports were excluded. We followed the search strategy previously described by Lee et al,[42] and included the following databases: Ovid MEDLINE (1946 to February 2017), Ovid EMBASE (1988 to February 2017), Web of Science (inception to February 2017), and Scopus (inception to February 2017). We also reviewed the bibliographies of included articles and previously published narrative and systematic reviews to identify potentially relevant articles.

Critical appraisal results

Table I provide a list of the studies that attempt to explore prognostic factors associated with biphasic anaphylaxis and, if reported, the treatment effect of corticosteroids. Because of lack of randomized clinical trials addressing therapy and harm of corticosteroids in biphasic anaphylaxis, we based our discussion on the available evidence from observational studies. These studies vary considerably in their design (prospective vs retrospective), enrolled population (adults vs children or mixed), and definition and severity of anaphylaxis and biphasic reaction.[21,42] These epidemiological factors should be carefully considered when making data comparisons. In addition to the significant heterogeneity between these studies, some were not primarily designed to answer a causal question, nor they were appropriately analyzed to minimize confounding factors.[46,47] We also found few studies that were large enough to derive a predictive model for biphasic anaphylaxis.[19,21,45] However, there are several limitations of these models including lack of validation.[48,49]

Pathophysiology of biphasic anaphylaxis

Three important characteristics emerge from our critical review of all observational studies to date: patient or host characteristics, disease characteristics, and treatment characteristics. The wide range of time intervals leads to the supposition that biphasic reactions are likely due to a number of different mechanisms (ie, earlier onset suggesting medication "wear-off," insufficient treatment, or secondary absorption of antigen, whereas those occurring 12-24 hours later could well be a late-phase response from the initial IgE-mediated reaction). Table II provides a summary of the potential predictive factors in the studies we reviewed; a detailed discussion of these factors is beyond the scope of this review. However, below we discuss prognostic factors that have been consistently reproduced by multiple studies, and inform our understanding of the disease process and their relation to pharmacologic therapies.

Association with disease severity. Although early reports were too small to detect a statistically powered association, the association between biphasic anaphylaxis and the severity of the initial reaction has been quite consistent. It should be noted that the definition of severity used in previous studies is inconsistent and mainly based on severe clinical manifestations such as hypotension or required therapeutic interventions such as multiple epinephrine treatments.[21] A summary of the studies that described this link is provided in Tables I and II.

To date, one of the most robust reports demonstrating a "dose-response" effect of disease severity by incorporating a clinical severity scoring was published by Brown et al.[19] In their prospective cohort study of adults with anaphylaxis, delayed anaphylaxis was associated with the severity of the initial reaction. Hypotension was also identified as a predictor of biphasic anaphylaxis in a recent metanalysis.[42] The largest pediatric study on biphasic anaphylaxis to date showed similar findings. Children with biphasic reactions had a higher triage acuity score, had manifestation of anaphylactic shock with wide pulse pressure, needed multiple epinephrine treatments for their initial reaction, and had significant respiratory distress that required treatment with inhaled β-agonists compared with those with uniphasic reactions.[21] Among children who had double-blind, placebo-controlled food challenge, the risk of late reactions was significantly higher in children with initially severe reactions after the challenge (Table I).[45]

Impact of epinephrine treatment. Epinephrine is the first-line therapy, and the single most important agent in anaphylaxis treatment. Timely epinephrine administration plays a significant role in the prevention of severe and fatal anaphylaxis.[50-53] Prospective data from the Cross-Canada Anaphylaxis REgistry found that epinephrine administration before arrival to the ED was the only