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Biphasic reactions in patients with anaphylaxis treated with corticosteroids

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ABSTRACT

Background: Although the incidence of anaphylaxis is rapidly increasing, the clinical characteristics and associated factors of a biphasic reaction are unclear.

Objective: To determine the incidence and clinical characteristics of biphasic reactions in patients with anaphylaxis treated with corticosteroids.

Methods: A total of 655 patients with anaphylaxis visiting the emergency department of a tertiary teaching hospital from January 2007 through December 2014 were analyzed. Patient characteristics, triggers, symptoms and signs, in-hospital management, and disposition were recorded. A biphasic reaction was defined as the development of anaphylaxis after complete resolution of the initial reaction without further exposure to the offending agent within 7 days. Univariate and multivariate analyses on the predictors of the biphasic reaction were performed.

Results: Of the 415 patients with anaphylaxis treated with corticosteroids, 9 patients (2.2%) developed a biphasic reaction. The mean age was 48.4 years, and 221 patients (54.4%) were women. The median time from complete resolution of initial clinical symptoms to occurrence of the biphasic reaction was 15 hours (range 1–45). History of drug anaphylaxis (odds ratio 14.3, 95% confidence interval 2.4–85.8) was a contributing factor to the development of the biphasic reaction.

Conclusion: The incidence of biphasic reactions was 2.2% in patients treated with corticosteroids and those with a history of drug anaphylaxis were at greater risk.

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Introduction

Anaphylaxis is a serious systemic allergic reaction with a sudden onset after exposure to an offending agent. Signs and symptoms can range from relatively mild to life threatening.^{1–3} Approximately 2% of the population will develop anaphylaxis during their lifetime. Common causes are food, medication, and insect stings.⁴

A biphasic reaction is a recurrent reaction or the appearance of new signs or symptoms after the initial allergy-related presentation without further exposure to the causative agent.⁵ It can be more severe than the first presentation and corticosteroids are often used to prevent it.⁶ According to current guidelines, patients with anaphylaxis are kept under observation in the

emergency department (ED) for at least 6 hours.³ The incidence of biphasic reactions varies from 1% to 20%. Very few studies have been performed to determine the risk factors of a biphasic reaction.^{7–11} Furthermore, no studies have been performed to determine the prevalence of biphasic reactions in patients receiving corticosteroids. The purpose of this study was to determine the prevalence and clinical characteristics of biphasic reactions in patients with anaphylaxis who were treated with corticosteroids.

Methods

Study Design and Population

This retrospective cohort study was conducted from January 2007 through December 2014 at a tertiary teaching hospital ED in Seoul, Korea, which cares for approximately 110,000 patients per year. Before starting the study, the institutional review board approved the review of patient data and waived the requirement for informed consent.

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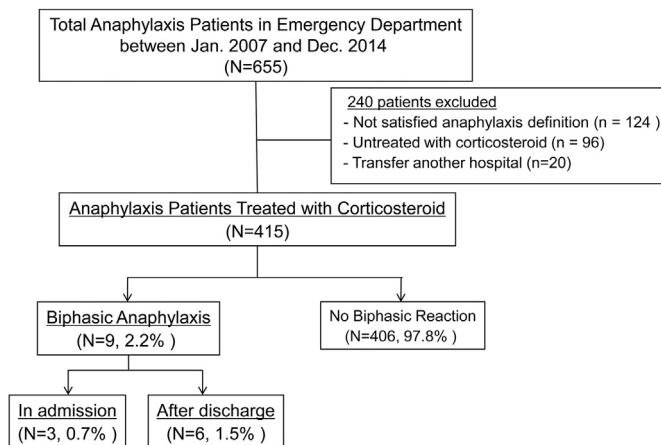


Figure 1. Flow chart for patient selection.

Data Collection and Patient Management

All electronic medical records of consecutive adult patients (>18 years) with anaphylaxis presenting to the ED from January 2007 through December 2014 were collected. The records of all patients with an ED diagnosis containing the words *anaphylaxis*, *anaphylactic*, or *anaphylactoid* were reviewed. Any of the following 3 diagnostic criteria for anaphylaxis had to be met³:

- The following 2 criteria had to be met:
 - Skin or mucosal tissue involvement
 - One of the following:
 - Respiratory compromise
 - Systolic blood pressure <90 mmHg or syncope
- Two of the following criteria had to be met after exposure to a likely antigen:
 - Skin or mucosal tissue involvement
 - Respiratory compromise
 - Systolic blood pressure <90 mmHg or syncope
 - Gastrointestinal symptoms
- Systolic blood pressure <90 mmHg after exposure to a known allergen

Skin involvement was defined as urticaria, rash, pruritus, and swelling of the face or ears. Localized pruritus or rash deemed secondary to trauma or an obvious insect bite was not considered as fulfilling the definition of “skin involvement.”

Mucosal tissue involvement was defined as swelling of lips, tongue, or pharynx.

Respiratory compromise was defined as wheeze or stridor on auscultation, hypoxemia (oxygen saturation <95%), or a respiratory rate faster than 22 breaths/min.

Gastrointestinal symptoms were defined as abdominal pain or vomiting present in the ED.

Patients were excluded if they did not meet the definition of anaphylaxis, if they had been transferred from another hospital or to another hospital, or if they did not receive corticosteroid treatment. A biphasic anaphylactic reaction was defined as the development of anaphylaxis after complete resolution of the initial reaction without further exposure to the offending agent within 7 days. Almost all patients with anaphylaxis were given outpatient care within 7 days of discharge from the ED or another unit of the hospital. In cases in which outpatient care was not possible, a phone call was made by patients at the time of the onset of the biphasic reaction.

The clinical and demographic characteristics of all patients, including their age, sex, medical history, suspected triggers,

Table 1

Characteristics of all anaphylactic reactions^a

	Overall (n = 415)	No biphasic reaction (n = 406)	Biphasic reaction (n = 9)	P value
Demographics				
Age (y)	48.4 ± 15.7	48.6 ± 15.7	41.0 ± 11.9	.15
Women	228 (54.9)	221 (54.4)	7 (77.8)	.19
Medical history				
History of allergies				
Food	89 (21.4)	88 (21.7)	1 (11.1)	.69
Drug	52 (12.5)	50 (12.3)	2 (22.2)	.29
Contact	10 (2.4)	10 (2.5)	0 (0.0)	1.00
Hymenoptera venoms	4 (1.0)	4 (1.0)	0 (0.0)	1.00
History of anaphylaxis				
Food	22 (5.3)	21 (5.2)	1 (11.1)	.39
Drug	13 (3.1)	11 (2.7)	2 (22.2)	.03
Hymenoptera venoms	0 (0.0)	0 (0.0)	0 (0.0)	
Idiopathic	11 (2.7)	11 (2.7)	0 (0.0)	1.00
History of asthma	5 (1.2)	4 (1.0)	1 (11.1)	.10
Triggers				
Drugs	187 (45.1)	183 (45.1)	4 (44.4)	1.00
Foods	117 (28.2)	114 (28.1)	3 (33.3)	.72
Hymenoptera venoms	28 (6.7)	28 (6.9)	0 (0.0)	1.00
Others	4 (1.0)	4 (1.0)	0 (0.0)	1.00
Unknown	72 (17.3)	70 (17.2)	2 (22.2)	.66
Symptoms and signs				
Rash or urticaria	250 (60.2)	245 (60.3)	5 (55.6)	.75
Mucosal involvement	138 (33.3)	134 (33.0)	4 (44.4)	.49
Hypoxemia	100 (24.1)	99 (24.4)	1 (11.1)	.69
Wheezing	42 (10.1)	39 (9.6)	3 (33.3)	.05
Hypotension	190 (45.8)	186 (45.8)	4 (44.4)	1.00
Tachycardia	31 (7.5)	30 (7.4)	1 (11.1)	.51
Abdominal pain	49 (11.8)	48 (11.8)	1 (11.1)	1.00
Vomiting	53 (12.8)	53 (13.1)	0 (0.0)	.61
Syncope	43 (10.4)	42 (10.3)	1 (11.1)	1.00
Dizziness	91 (21.9)	90 (22.2)	1 (11.1)	.69
Time interval				
Trigger to onset ^b	30 (10–50)	30 (10–60)	45 (23–45)	.51
Trigger to ED ^b	60 (30–102)	60 (30–101)	127 (34–158)	.42

Abbreviation: ED, emergency department.

^aValues are expressed as mean ± SD, median (interquartile range), or number (percentage). Biphasic anaphylactic reaction was defined as the development of anaphylaxis after complete resolution of the initial reaction without further exposure to the offending agent within 7 days.

^bBy Mann-Whitney test.

symptoms, signs, ED management, disposition, and clinical outcomes, were retrieved from the hospital's electronic records. All patients were treated with corticosteroids. The time from the resolution of initial anaphylaxis symptoms to the onset of the biphasic reaction also was reviewed. The decision to give epinephrine and other drugs was at the discretion of the individual treating physicians.

Statistical Analysis

Data in this study are presented as mean ± SD or median with interquartile range for continuous variables and as absolute or relative frequency for categorical variables. Patients who developed a biphasic reaction were compared with those who did not. The Student *t* test or Mann-Whitney *U* test was used to compare continuous variables depending on the distribution of data and expressed as mean ± SD or median and interquartile range, respectively. The χ^2 test was used for categorical variables. Univariate and multivariate analyses to identify risk factors for the occurrence of the biphasic reaction were conducted. A *P* value less than or equal to .05 was considered statistically significant. All

Table 2
Emergency department treatment of initial anaphylaxis^a

	Overall (n = 415)	No biphasic reaction (n = 406)	Biphasic reaction (n = 9)	P value
Epinephrine				
Administered	241 (58.1)	235 (57.9)	6 (66.7)	.74
Route of administration				
Intramuscular	200 (48.2)	195 (48.0)	5 (55.6)	.74
Intravenous	33 (8.0)	32 (7.9)	1 (11.1)	.53
Others	8 (2.0)	8 (2.0)	0 (0.0)	1.00
Time from symptoms to epinephrine administration (min)	30 (20–60)	30 (20–60)	70 (20–570)	.52
Total dose (mg)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	1.00
Corticosteroid ^b				
Administered ^b	415 (100.0)	406 (100.0)	9 (100.0)	1.00
Category				
Methylprednisolone	362 (87.2)	353 (86.9)	9 (100.0)	.61
Total dose (mg) ^b	62.5 (62.5–120.0)	62.5 (62.5–120.0)	62.5 (62.5–125.0)	.79
Hydrocortisone	53 (12.8)	53 (13.1)	0 (0.0)	.61
Total dose (mg)	200.0 (100.0–300.0)	200.0 (100.0–300.0)	NA	NA
H ₁ antihistamines (chlorpheniramine)				
Administered ^b	393 (94.7)	385 (94.8)	8 (88.9)	.39
Total dose (mg) ^b	4.0 (4.0–4.0)	4.0 (4.0–4.0)	4.0 (4.0–4.0)	1.00
H ₂ blocker				
Administered	280 (67.5)	273 (67.2)	7 (77.8)	.72
Category				
Famotidine	125 (30.1)	120 (29.6)	5 (55.6)	.14
Ranitidine	142 (34.2)	139 (34.2)	3 (33.3)	1.00
Cimetidine	13 (3.1)	12 (3.0)	1 (11.1)	.25

Abbreviations: H₁ blocker, histamine-1 receptor blocker; H₂ blocker, histamine-2 receptor blocker; NA, nonapplicable.

^aValues are expressed as mean $\pm$ SD, median (interquartile range), or number (percentage). Biphasic anaphylactic reaction was defined as the development of anaphylaxis after complete resolution of the initial reaction without further exposure to the offending agent within 7 days.

^bBy Mann-Whitney test.

statistical analyses were performed using SPSS 18.0 for Windows (SPSS, Inc, Chicago, Illinois).

Results

During the study period, 655 patients with anaphylaxis came to the ED. Excluded were 124 patients who did not meet the criteria for anaphylaxis, 96 patients who were not treated with corticosteroids, and 20 patients transferred from another hospital or to another hospital. Therefore, 415 patients with anaphylaxis were included in the final analysis (Fig 1). All patients were treated with corticosteroids. The mean age was 48.4 ± 15.7 years and 54.4% of patients were women. Biphasic reactions were observed in 9 of 415 patients, with an overall incidence of 2.2% (Table 1). In these patients, a history of food allergy was most common, followed by drug- and contact-induced allergy. In patients who developed a biphasic reaction, the proportion with a drug-induced anaphylaxis history was significantly larger. The

most common cause of anaphylaxis was drugs (45.1%), followed by food, unknown causes, and hymenoptera venoms. Rashes and urticaria were most commonly reported (60.2%). Hypotension was observed in 190 patients (45.8%), followed by mucosal involvement (33.3%) and hypoxemia (24.1%). Other clinical signs and symptoms are presented in Table 1. ED management using epinephrine and histamine-1 receptor blocker (H₁ antihistamines) did not differ between the 2 groups (Table 2). Multivariate analysis showed that patients with a history of drug anaphylaxis (odds ratio 14.3, 95% confidence interval 2.4–85.8) had a significantly greater chance of developing of a biphasic reaction ($P = .03$).

Detailed clinical characteristics and management of the 9 patients who developed a biphasic anaphylactic reaction are presented in Table 3. Of these patients, 2 were men (22.2%) and 7 were women (77.8%). The median age of these patients was 41 years (range 24–60). No mortality from anaphylaxis was observed during the study period. The median time from complete

Table 3
Characteristics and management of patients with biphasic reactions^a

Age (y)/sex	Trigger	Asthma history	Allergy history	Anaphylaxis history	Time onset (h)	Location	Initial signs and symptoms	Biphasic signs and symptoms
41/F	food (clam)	no	no	no	15	home	MC + PLM	MC + PLM
60/F	food (vegetable)	no	yes (plant)	yes (plant)	41	home	MC + CV	MC + CV
25/M	drug	no	no	no	1	home	MC + PLM	MC + PLM
24/F	food (sea food)	yes	no	no	2	ICU	MC + CV	MC + PLM
48/F	food (herb)	no	no	no	15	home	MC + CV	MC + CV
53/F	drug (cephalosporin)	no	no	no	45	GW	MC + PLM	MC + PLM
36/F	drug (lidocaine)	no	yes (drug)	yes (drug)	26	GW	MC + PLM	MC + PLM
43/F	drug (NSAIDs)	no	no	no	1	home	MC + CV	MC + CV
39/M	drug (pyrin)	no	yes (drug)	yes (drug)	28	home	MC + PLM	MC + PLM

Abbreviations: CV, cardiovascular; F, female; GW, general ward; ICU, intensive care unit; M, male; MC, mucocutaneous; NSAIDs, nonsteroidal anti-inflammatory drugs; PLM, pulmonary.

^aBiphasic anaphylactic reaction was defined as the development of anaphylaxis after complete resolution of the initial reaction without further exposure to the offending agent within 7 days.

resolution of initial clinical symptoms to the occurrence of the biphasic reaction was 15 hours (range 1–45). For 3 patients, the biphasic reaction occurred during hospital admission, and 6 patients developed the biphasic reaction after hospital discharge and thus were readmitted to the ED (Table 3). Initial and subsequent clinical features did not differ. Skin and mucosal involvement were observed in all biphasic reactions, whereas no gastrointestinal symptoms or signs occurred.

Discussion

To the authors' knowledge, this is the first study to evaluate the occurrence of anaphylactic biphasic reactions in patients treated with corticosteroids in the ED. There was a 2.2% incidence of anaphylactic biphasic reactions in 415 patients treated with corticosteroids. The median time from the resolution of initial clinical symptoms to the occurrence of the anaphylactic biphasic reaction was 15 hours (range 1–45). The biphasic reaction was associated with a history of drug anaphylaxis.

Little is known about the incidence of biphasic reactions or the timeframe in which they occur. Previous ED studies have reported an incidence ranging from 0.2% to 19.4%. Ellis and Day¹² reviewed 103 cases of anaphylaxis and reported that 20 were biphasic reactions (19.4%). Vezir et al¹³ reported 5.2% biphasic reactions in 91 patients. A 4-year observational study conducted in Thailand identified 13 biphasic reactions (6.3%) in 208 cases of anaphylaxis.¹⁴ However, 2 large retrospective observational studies have recently reported that the biphasic incidence is lower than previously thought. Rohacek et al¹⁵ reviewed 532 cases of anaphylaxis and observed only 25 biphasic reactions (4.5%), whereas Lee et al¹⁶ reported a 4.0% incidence of biphasic reactions in 541 cases. Compared with recently published studies, the present incidence of 2.2% is relatively low. Although a Cochrane review failed to determine the effectiveness of treatment with corticosteroids on clinical outcomes, including mortality, biphasic reactions, adverse events, and cost effectiveness, it might explain the association between corticosteroid treatment and the prevention of biphasic reactions.¹⁷ However, further studies are necessary to clarify this issue.

Previous studies have reported a wide range of results for the time from the resolution of initial symptoms to the occurrence of biphasic reactions.¹⁶ In the present study, the median time was 15 hours (range 1–45), whereas Rohacek et al¹⁵ reported a median time of 12 hours. The median times of the 2 studies appear similar. In contrast, another study reported a median time of only 7 hours,¹⁶ but it included patients of all ages instead of adults only.

The present study differs from other studies on biphasic reactions in that drugs were the most common cause of anaphylaxis, whereas previous studies have reported food as the main trigger. A possible explanation for this is that contrast agents were included in the drugs category (17.6%). Cardiovascular symptoms and signs, especially hypotension, were more prevalent than in previous studies.¹⁶ This also seems to be because of contrast agents. In fact, cardiovascular symptoms were more common in patients who were given contrast agents than in those who were not ($P = .00$).

In this study, a history of drug-induced anaphylaxis was associated with the occurrence of anaphylactic biphasic reactions. In contrast, Lee et al¹⁶ found that although a history of anaphylaxis was associated with biphasic reactions, it was not limited to drug-induced anaphylaxis. The present study did not find an association between overall history of anaphylaxis and the occurrence of biphasic reaction except for a history of only drug-induced anaphylaxis. Other studies have not observed an association between a history of anaphylaxis or allergy and the occurrence of

biphasic reactions,^{12,18,19} so there is a need for larger studies on this controversial issue.

In the meantime, compliance with the guidelines on epinephrine administration in anaphylaxis treatment is not enough.²⁰ In this study, epinephrine was administered to 58.1% of patients, which was higher than in previous studies where it ranged from 12% to 54%.^{5,16,17,21,22} Several studies have reported that delayed administration of epinephrine could relate to the occurrence of biphasic reactions.^{10,14} However, in the present study, no association was observed between the timing of epinephrine and the occurrence of biphasic reactions ($P = .52$; Table 2).

A major limitation of this study was its retrospective nature, which could have compromised the validity of the data. In addition, all data were collected from a single center, making it difficult to generalize. Although most patients received an outpatient follow-up, a small proportion did not (although they were tracked by phone), so some cases of biphasic reactions might not have been identified. Time-related variables, such as the time from anaphylaxis to the onset of the biphasic reaction, might be inaccurate, because these values were derived mainly from the patient's memory. In this study, H₁ antihistamines were frequently used in the 2 groups, so it might be inappropriate to uncover an association between H₁ antihistamines usage and biphasic reactions. Also, corticosteroids were used in all patients, so it could be difficult to identify an association between corticosteroid usage and biphasic reactions.

To conclude, the incidence of biphasic reactions was 2.2% in patients treated with corticosteroids, which is lower than that previously reported. Further studies are needed to clarify whether corticosteroid treatment decreases the occurrence of biphasic reactions in anaphylaxis. It appears that patients with a history of drug anaphylaxis are at an increased risk of biphasic reaction occurrence.

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