

Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis

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Background: Risk factors for increased anaphylaxis severity are poorly understood. Angiotensin-converting enzyme (ACE) inhibitors have been associated with severe anaphylactic reactions in patients with hymenoptera venom allergy. Studies evaluating the association between beta-blockers and severe anaphylaxis have been conflicting.

Objective: To evaluate the association between antihypertensive medication use and increased anaphylaxis severity.

Methods: We included emergency department anaphylaxis patients aged 18 years and older. Markers of severe anaphylaxis were defined as (1) syncope, hypotension, or hypoxia; (2) signs and symptoms involving 3 or more organ systems; and (3) hospitalization. Antihypertensive medications evaluated included beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, and diuretics. Simple and multiple logistic regression analyses were conducted to estimate the association between antihypertensive medication use and markers of increased anaphylaxis severity.

Results: Among 302 patients with anaphylaxis, 55 (18%) had syncope, hypoxia, or hypotension, 57 (19%) required hospitalization, and 139 (46%) had 3 or more organ system involvement. After adjusting for age, gender, suspected trigger, and preexisting lung disease, beta-blocker, ACE-inhibitor, diuretic, or antihypertensive medication use in aggregate remained associated with both 3 or more organ system involvement and need for hospital admission. The adjusted

associations between antihypertensive medication use in aggregate and 3 or more organ system involvement yielded an odds ratio of 2.8 (95% CI, 1.5-5.2; $P = .0008$) and with hospitalization an odds ratio of 4.0 (95% CI, 1.9-8.4; $P = .0001$). **Conclusions:** In emergency department anaphylaxis patients, antihypertensive medication use is associated with increased organ system involvement and increased odds of hospital admission, independent of age, gender, suspected trigger, or preexisting lung disease. (*J Allergy Clin Immunol* 2013;131:1103-8.)

Key words: Anaphylaxis, antihypertensive medications, angiotensin-converting enzyme inhibitor, beta-blocker, risk factors, emergency department

Anaphylaxis is a systemic allergic reaction that is most commonly treated in the emergency department (ED).^{1,2} Signs and symptoms can vary from relatively mild to life-threatening.^{3,4} Brown⁴ developed a grading system linking clinical features with severity. Based on this grading system, severe anaphylaxis was defined as patients who experienced hypoxia, hypotension, or neurologic compromise, typically manifested by collapse.

Risk factors for severe anaphylaxis are poorly understood. In previous studies, ACE inhibitors have been associated with severe anaphylactic reactions in patients with hymenoptera venom allergy.⁵ There are numerous case reports of increased severity of anaphylaxis in patients taking beta-blockers.⁶⁻⁹ Beta-blocker use has been associated with an increased risk of an anaphylactic reaction to intravenous contrast, but not with an increased risk of anaphylaxis in patients receiving allergen immunotherapy injections.^{4,10,11} In multiple logistic regression analyses, however, ACE-inhibitor and beta-blocker use was not associated with severe anaphylaxis.⁴ Thus, the association of beta-blockers and ACE inhibitors with increased anaphylaxis severity has not been clearly established. Furthermore, the association of the use of diuretics or antihypertensive medications in general with anaphylaxis severity has not been reported.

We hypothesized that the use of beta-blockers, ACE inhibitors, or other antihypertensive medications including diuretics, calcium channel blockers (CCBs), and angiotensin receptor blockers is associated with markers of increased anaphylaxis severity. To test this hypothesis, we sought to estimate the association between antihypertensive medication use and markers of increased anaphylaxis severity.

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Abbreviations used

ACE:	Angiotensin-converting enzyme
CCB:	Calcium channel blocker
ED:	Emergency department
NIAID/FAAN:	National Institute of Allergy and Infectious Diseases/ Food Allergy and Anaphylaxis Network
OR:	Odds ratio
SBP:	Systolic blood pressure

METHODS**Study design and setting**

The study had a retrospective observational cohort design. Patients were consecutively included at the Saint Mary's Hospital ED, a tertiary care academic ED with 72,000 annual patient visits.

Selection of participants

Electronic medical records of ED patients aged 18 years and older were electronically queried. Records of all patients who had any ED diagnosis containing "allerg," "anaphy," or "sting" were reviewed, and those who met the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) diagnostic criteria for anaphylaxis were included. The study was conducted from April 2008 to July 2011. The Mayo Clinic institutional review board approved all study procedures.

Data collection and outcome measures

Data were collected by using a standardized data abstraction form. We collected data on daily medication use, medical history, suspected triggers of the anaphylaxis episode (based on documented trigger at the time of the ED evaluation), clinical signs and symptoms, ED management, and disposition. Markers of increased anaphylaxis severity included the following: (1) signs and symptoms of syncope, hypotension, or hypoxia; (2) signs and symptoms involving 3 or more organ systems; and (3) hospital admission. Hypotension was defined according to the NIAID/FAAN criteria as a 30% drop in systolic blood pressure (SBP) from baseline; or: SBP less than 70 mm Hg for children 1 month to 1 year, or less than (70 mm Hg + [2 × age]) for children 1 to 10 years, or less than 90 mm Hg for children 11 to 17 years and adults.

Statistical analysis

We present all continuous data as medians with interquartile range as appropriate for the distribution of the data. Categorical data are presented as percent frequency of occurrence. Simple (univariate) and multiple (multivariable) logistic regression models were fit to estimate the association between antihypertensive medication use and markers of increased severity of anaphylaxis. Because previous studies demonstrated potential associations between age, gender, the suspected trigger of the reaction, and underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and anaphylaxis severity, we adjusted for these confounders in multiple logistic regression analyses. Cardiovascular disease was highly correlated with antihypertensive medication use and was therefore dropped from the multiple logistic regression analysis to avoid the problem of collinearity.

Odds ratios (ORs) with corresponding 95% CIs were calculated for each association. *P* values represent 2-sided hypothesis testing unless otherwise noted, and *P* value of .05 or less was considered statistically significant. Statistical analyses were performed by using JMP software, version 9.0 (SAS Institute, Inc, Cary, NC).

RESULTS

From April 2008 to July 2011, we included 302 adults who met NIAID/FAAN diagnostic criteria for anaphylaxis. Baseline characteristics, suspected triggers of anaphylaxis, underlying lung disease, and outcomes of the study cohort are summarized in

TABLE I. Patient characteristics and outcomes in 302 ED patients with anaphylaxis

Variable	Finding, n (%)
Females	204 (68)
Age (y)	
Median (IQR)	44.3 (32-58)
Race	
White	274 (91)
Hispanic	0
Black	9 (3)
Asian/Pacific islander	4 (1)
Other	13 (4)
Unknown	2 (1)
Inciting allergen	
Food	82 (27)
Medication	78 (26)
Venom	29 (10)
Latex	2 (1)
Contrast	17 (6)
Other	14 (5)
Unknown	80 (27)
Lung disease	
Asthma	75 (25)
COPD	9 (3)
Antihypertensive agents	
Beta-blockers	49 (16)
ACE inhibitors	34 (11)
CCBs	22 (7)
ARBs	8 (3)
Diuretics	45 (15)
Any antihypertensive	87 (29)
Outcomes	
Intubation	8 (3)
Syncope, hypotension, hypoxia	55 (18)
≥3 Organ system involvement	139 (46)
Hospital admission	57 (19)

ARBs, Angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table I. Median age of the study sample was 44.3 years (interquartile range, 31.5-58.0). Two hundred four patients (68%) were female, and 91% were white, reflecting the relatively small proportion of minorities in the community. Eighty-seven (29%) patients were on at least 1 antihypertensive medication, 49 (16%) were on beta-blockers, 34 (11%) were on ACE inhibitors, 22 (7%) were on CCBs, 8 (3%) were on angiotensin receptor blockers, and 45 (15%) were on diuretics.

Fifty-five patients (18%) had signs or symptoms of syncope, hypoxia, or hypotension. One hundred thirty-nine patients (46%) had 3 or more organ system involvement, and 57 (19%) patients required hospital admission, including 27 to the intensive care unit and 30 to the ward. To establish the association between hospital admission and anaphylaxis severity, we analyzed the association between hospital admission and symptom severity (presence of syncope, hypoxia, hypotension) as well as the association between hospital admission and the administration of more than 1 dose of epinephrine by performing multiple logistic regression analysis. We found (after adjusting for age, gender, trigger, and underlying cardiovascular or lung disease) that both the presence of syncope, hypotension, or hypoxia (OR, 4.5; 95% CI, 2.2-9.2; *P* < .0001) and the administration of more than 1 dose of epinephrine (OR, 17.3; 95% CI, 7.0-46.4; *P* < .0001) were associated with hospital

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