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Factors Associated with Repeated Use of Epinephrine for the Treatment of Anaphylaxis

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Abstract

Background—Studies looking at use of repeated doses of epinephrine in anaphylaxis are limited.

Objective—To determine which patients are most likely to receive repeated doses of epinephrine during anaphylaxis management.

Methods—A population-based study, with medical record review was conducted. All patients seen during the study period who met criteria for diagnosis of anaphylaxis were included.

Results—The cohort included 208 patients (55.8% female). Anaphylaxis treatment included epinephrine in 104(50%) cases. Repeated doses were used in 27(13.0%) patients (48.1% female). The median age of those who received repeated doses was 18.9 years (IQR 10-34) versus 31.1 years (IQR 15-41), p=0.065 for those who did not. The inciting agents were food (29.6%), insects (11.1%), medications (22.2%), others (7.4%) and unknown (29.6%). Patients who received repeated doses were more likely to have wheezing (p=0.028), cyanosis (p=0.001), hypotension and shock (p=0.032), stridor and laryngeal edema (p=0.007), nausea and emesis (p=0.043), arrhythmias (p<0.01) and cough and less likely to have urticaria (p=0.049). They were more likely to be admitted to hospital (48.2% vs 15.6%, p=0.0007). There was no significant difference in history of asthma between patients who received repeated doses and those who did not (p=0.168).

Conclusion—Thirteen percent of patients received repeated doses of epinephrine. Patients were younger and were more likely to present with wheezing, cyanosis, arrhythmias, hypotension and shock, stridor, laryngeal edema, cough, nausea, and emesis, and less likely to have urticaria. History of asthma did not predict use of repeated doses of epinephrine. Our results help identify high risk patients who may benefit from carrying more than one dose of epinephrine.

Introduction

Anaphylaxis is a serious systemic allergic reaction that occurs in susceptible individuals on exposure to specific antigens. The incidence of anaphylaxis appears to be increasing.1, 2 Epinephrine is the treatment of choice for anaphylaxis and has been shown to be effective when used in a timely fashion.3 The precise dose of epinephrine needed to reverse symptoms due to anaphylaxis is difficult to ascertain.

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Studies looking at the use of repeated doses of epinephrine in anaphylaxis have been limited. Further, these studies focused on patients presenting to either emergency departments (EDs) or outpatient allergy clinics. To our knowledge, this is the first population-based study to specifically evaluate patients who received more than one dose of epinephrine. The primary study objective was to determine which patients were most likely to receive repeated doses of epinephrine during the management of an anaphylactic reaction.

Methods

The resources of the Rochester Epidemiology Project organized in 1966 were used to conduct a population-based study. The Rochester Epidemiology project is a medical records linkage system that links and indexes almost all health care providers in Olmsted county. 4, 5 Virtually all residents of Olmsted County, Minnesota who presented to health care professionals with anaphylaxis from 1990 to 2000 were identified. This retrospective cohort study included patients presenting to two emergency departments (EDs) in the city of Rochester (one with approximately 70,000 ED visits per year and the other with about 19,000 ED visits per year) as well as all other healthcare providers in the city. The study was approved by the institutional review boards at both centers.

The appropriate *Hospital Adaptation of the International Classification of Diseases, Second Edition* (HICDA) codes or the *International Classification of Diseases, Ninth Revision* (ICD-9) codes were used to identify patients. Patients with a new diagnosis code related to anaphylaxis and who gave research authorization were included in our database. A review of 248 patients with codes for the following diagnoses was conducted: anaphylactic shock; anaphylactic shock due to food; anaphylactic shock not elsewhere classified; and shock, anaphylactic, following sting. Random samples of 600 patients (from 2442 potential cases with the following diagnoses) were also reviewed: 300 patients diagnosed with venom, bee sting; or toxic effect of venom; and 300 patients diagnosed with either allergy, foodstuff; adverse effect, food; dermatitis due to food taken internally; or toxic effect of specific food. All patients who met the criteria (discussed below) for diagnosis of anaphylaxis were included in the study.

Case definition

This study was started before the second symposium on the definition and management of anaphylaxis.6 The criteria used in the Yocum study to establish a diagnosis of anaphylaxis were used to identify cases of anaphylaxis.7 The criteria used in the Yocum study are very similar to those developed by the second symposium on the definition and management of anaphylaxis (shown in Table 1).6 Two-hundred and eleven cases of anaphylaxis were initially identified using the Yocum criteria. These cases were subsequently reanalyzed using the criteria proposed by the second symposium. There were only 3 cases which did not meet the criteria proposed by the second symposium and these were removed, leaving a total of 208 cases of anaphylaxis.

Statistical Analysis

Distributions were calculated for each of the variables. The median and interquartile range was reported to summarize age of patients and nonparametric tests were used to compare median age in different groups. Percentages were used to summarize categorical data and percentages were compared using the chi-square test.

Based on the exploratory nature of this study, we did not correct p-values to account for testing multiple hypotheses; therefore, the probability of finding significance is not controlled at the overall nominal 0.05 level under the null hypotheses and thus considerably

more than 5% of the significant findings may be spurious. Statistical analyses were performed in JMP 7.01, SAS Institute.

Results

Overall, the cohort included 208 patients of which 116 (55.8%) were female. Ninety two percent were Caucasian, and the median age was 30.3 years (interquartile range, IQR 14- 41 years). Treatment of anaphylaxis included epinephrine in 104 cases (50%). Two or more doses of epinephrine were used in 27 patients (13.0%). The second dose of epinephrine was administered by a healthcare professional in all cases (Table 2).

The median age of those who received 2 or more doses of epinephrine was 18.9 years (IQR 10-34 years) versus 31.1 years (IQR 15-41), p=0.065 for those who received one or no doses of epinephrine. Twelve of a total of 65 children (18.5%) received 2 or more doses. Among the 27 patients who received 2 or more doses of epinephrine, 13 (48.1%) were female. The inciting agents were determined after taking into consideration the history and results of any allergy testing and were not statistically different between the two groups. Of the 27 patients who received repeated epinephrine doses, 13 (48.2%) were admitted to the hospital, compared to 15.6% of those who did not receive repeated doses of epinephrine (p=0.0007, Chi-Square). There were no case fatalities. Thirty seven percent of the patients who required repeated doses of epinephrine had a history of asthma, while 24.3% of those receiving none or one dose of epinephrine had a history of asthma (p=0.168, Chi-Square). The mean first dose of intravenous epinephrine given was 0.31 cc (1:10,000) and intramuscular epinephrine given was 0.27 mg. The mean second dose of intravenous epinephrine given was 0.28 ml cc (1:10,000) and intramuscular epinephrine given was 0.26 mg. There were 5 patients who received a first dose of > 0.5 cc (1:10,000) intravenously, and 1 patient who received >0.5mg intramuscularly.

Twenty-one of the 27 patients who received more than one dose of epinephrine did not have a prior prescription for self-injectable epinephrine (SIE). Of these 21 patients, 15 (71.4%) were prescribed self-injectable epinephrine on dismissal from ED or hospital. Of the 181 patients who did not receive more than one dose of epinephrine, 163 did not have a prior prescription for self-injectable epinephrine. Of the 163 patients, 64 (39.3%) were prescribed self-injectable epinephrine on dismissal from ED or hospital (p=0.005 for the comparison between prescription of SIE at dismissal in those that required 2 or more doses versus less than 2 doses). An allergist referral was made in 14 (51.9%) of patients who received more than one dose of epinephrine and in 73 (40.3%) in case of the patients who received less than two doses of epinephrine (p=0.28, Chi-Square). Table 3 shows demographics, inciting allergen, clinical characteristics, allergist referral and self-injectable epinephrine prescriptions for 208 anaphylactic reactions in patients receiving 0, 1 and 2 or more doses of epinephrine.

Patients who received two or more doses of epinephrine were more likely to present with wheezing (p=0.028 Chi-Square), cyanosis (p=0.001, Chi-Square), hypotension and shock (p=0.032, Chi-Square), arrhythmias (p<0.01) stridor and laryngeal edema (p=0.007, Chi-Square) and nausea and emesis (p=0.043, Chi-Square) and less likely to have urticaria (p=0.049, Chi-Square). Cough was also more likely to be common in patients who received epinephrine but was statistically significant only when patients receiving 2 or more doses of epinephrine were compared with those who did not receive epinephrine (p=0.039).

Presenting signs and symptoms after stratification based on number of doses of epinephrine are displayed in Table 4.

Discussion

Epinephrine has been shown to be an effective treatment for anaphylaxis and poor outcomes are associated with receiving late epinephrine.3, 8-12

Studies regarding use of repeated doses of epinephrine are limited. Most of the studies evaluated patients presenting to outpatient allergy clinics.13-15 One study examined patients presenting to the emergency department.16 Furthermore, previous studies were limited to specific allergens or immunotherapy injections.13, 14, 16

Utilization of the resources of the Rochester Epidemiology Project permitted the collection of data on patients who received epinephrine at home, from EMS providers and in the ED. Thus, we are able to present, to date, the largest community-based cohort of patients who received repeated doses of epinephrine. To our knowledge, this is the first population-based study to evaluate risk factors for the use of repeated doses of epinephrine in patients with anaphylaxis. Furthermore, we have studied the use of repeated doses of epinephrine in patients presenting with anaphylaxis irrespective of the inciting allergen.

In this study, we found that 13.0% of the patients presenting with anaphylaxis received more than one dose of epinephrine. This is consistent with previous studies, demonstrating that it is not uncommon for patients to receive repeated doses of epinephrine.13

We found that patients receiving more than one dose of epinephrine tended to be younger. This may be because physicians were reluctant to give epinephrine to older patients who are more likely to have cardiovascular comorbidities. However, there is no data to suggest that a history of known coronary artery disease is a contraindication to epinephrine.17 Alternatively, it is possible that younger patients had more severe or persistent symptoms.

History of asthma did not significantly predict the use of repeated doses of epinephrine in our population of patients with diverse allergens. However patients with a history of asthma tended to receive more than one dose of epinephrine. A previous study of food-induced anaphylaxis in children did find that asthma was significantly associated with receiving repeated doses of epinephrine.13 Our results suggest that a history of asthma may not be present in many patients who will require repeated doses of epinephrine.

Signs involving the respiratory system such as wheezing, cyanosis and laryngeal edema and stridor had the most significant relationship to the use of repeated doses of epinephrine. These findings are comparable with a study involving children presenting with food-induced anaphylaxis in which throat closure was more common in patients receiving numerous doses of epinephrine.13

Patients who received repeated doses of epinephrine tended to be more likely to receive a prescription for self-injectable epinephrine. However, the overall prescription rates of self-injectable-epinephrine are still low, consistent with previous studies. Collaboration between allergy and emergency department personnel would likely increase prescription rates18-20

The retrospective design of this study is the primary limitation. In addition, our study population was primarily Caucasian and therefore our results may not be generalizable to minority or ethnic populations.

In conclusion, 13 percent of patients received 2 or more doses of epinephrine. The second dose of epinephrine was administered by a health care professional in all cases, and the final dose was always given by an ED physician, indicating that repeated dosing was needed to resolve the symptoms. Patients receiving repeated doses of epinephrine tended to be younger

and were more likely to present with wheezing, cyanosis, hypotension and shock, arrhythmias, stridor and laryngeal edema, cough and nausea and emesis and less likely to have urticaria.

History of asthma did not significantly predict the use of repeated doses of epinephrine. The results of this population-based study make a significant contribution to the evidence needed to identify high risk patients who may benefit from carrying more than one dose of epinephrine. Prospective studies are needed for further confirmation.

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Table 1

National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Criteria

Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue, or uvula)

AND AT LEAST ONE OF THE FOLLOWING

- **a.** Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- **b.** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- **a.** Involvement of the skin or mucosal tissue (e.g., generalized hives, itch or flush, swollen lips, tongue, or uvula)
- **b.** Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- **c.** Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
- **d.** Persistent gastrointestinal tract symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

- **a.** Infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure [a]
- **b.** Adults: systolic blood pressure <90 mm Hg or >30% decrease from that person's baseline

[a] Low systolic blood pressure for children is defined as <70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

From Sampson et al 6

Table 2

Sites of epinephrine administration during the course of anaphylactic events

Number of doses of epinephrine received	Number of patients	Place of Epinephrine Administration (Number of patients)
0	104	--
1	77	Home (3)
		EMS * (3)
		ED ± (71)
2	25	Home and ED ± (2)
		EMS * and ED ± (1)
		ED ± (22)
3	2	1 dose at Home and 2 in the ED ± (1)
		2 doses by the EMS * and 1 in the ED ± (1)

* Emergency Medical Services

± Emergency Department

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Table 3

Demographics, inciting allergen, clinical characteristics, allergist referral and self-injectable epinephrine prescriptions for 208 anaphylactic reactions in patients receiving repeated doses of epinephrine compared to those who did not receive repeated doses of epinephrine

Variables	Patients receiving no epinephrine N=104	%	Patients receiving 1 dose of epinephrine N=77	%	Patients receiving ≥2 doses of epinephrine N=27	%
Demographics						
Race and ethnicity						
Caucasian	89	85.6	67	87	19	70.4
Black	5	2.8	0	0	1	3.7
Hispanic	1	4.8	0	0	0	0
Asian-Pacific Islander	2	1.9	4	5.2	1	3.7
Other	0	0	1	1.3	0	0
Unknown	7	6.7	5	6.5	6	22.2
Age (Years)						
Median	30.5		31.2		18.9	
Interquartile Range	15 to 43		14 to 40		10 to 34	
Female Gender	67	64.4 *	36	46.8	13	48.2
Inciting Agent						
Food	32	30.8	28	36.4	8	29.6
Insect	20	19.2	16	20.8	3	11.1
Medications	12	11.5	11	14.3	6	22.2
Other	11	10.6	6	7.8	2	7.4
Unknown	29	27.9	16	20.8	8	29.6
Hospital Admission	10	10.3 *	17	22.4 ^	13	48.2 §
History of Asthma	23	22.6	21	27.6	10	37
Prescription of SIE ±	26	28.6 ‡	38	60.3	15	71.4 ˇ
Allergist Referral	40	38.8	33	43.4	14	51.9

SIE: Self-injectable epinephrine

± Adjusted value according to prior prescription of SIE

* $0.01 \leq p \leq 0.05$ for comparison of 0 and 1 dose of epinephrine

‡ $p \leq 0.0001$ for comparison of 0 and1 dose of epinephrine

^ $0.01 \leq p \leq 0.05$ for comparison of 1 and 2 dose of epinephrine

˜ $p \leq 0.01$ for comparison of 0 and 2 doses of epinephrine

§ $p \leq 0.0001$ for comparison of 0 and 2 doses of epinephrine

Table 4

Presenting signs and symptoms of patients who received repeated doses of epinephrine compared to those who did not receive repeated doses of epinephrine.

Signs and Symptoms	Patients receiving no dose of epinephrine N=104	%	Patients receiving 1dose of epinephrine N=77	%	Patients receiving ≥2 doses of epinephrine N=27	%
Mucocutaneous symptoms						
Urticaria	71	68.3	57	74*	14	51.9
Angioedema	65	62.5	53	68.8	20	74.1
Pruritus	57	54.8	32	41.6	14	51.9
Flushing and diaphoresis	41	39.4	35	45.4	14	51.9
Conjunctivitis and Chemosis	18	17.3±	2	2.6≠	5	18.5
Cardiovascular system						
Tachycardia	33	31.7	31	40.3	11	40.7
Chest pain	14	13.5	12	15.6	5	18.5
Pre-syncope and Orthostatic hypotension	14	13.5	12	15.6	4	14.8
Hypotension and Shock	11	10.6	9	11.7	7	25.9^
Syncope	7	6.7	5	6.5	2	7.4
Arrhythmia	4	3.9	4	5.2≠	6	22.2§
Bradycardia	2	1.9	3	3.9	3	11.1
Respiratory system						
Dyspnea	44	42.3*	44	57.1	15	55.6
Tightness/fullness of throat	40	38.5	33	42.9	11	40.7
Wheezing/bronchospasm	25	24	19	24.7	12	44.4^

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Signs and Symptoms	Patients receiving no dose of epinephrine N=104	%	Patients receiving 1dose of epinephrine N=77	%	Patients receiving ≥2 doses of epinephrine N=27	%
Cough	11	10.6	13	16.9	7	25.9^
Hoarseness and Aphonia	8	7.7	12	15.6	3	11.1
Stridor and Laryngeal edema	3	2.9*	9	11.7	6	22.2§
Cyanosis	2	1.9	4	5.2≠	5	18.5§
Gastrointestinal system						
Nausea and Emesis	23	22.1	18	23.4	11	40.7^
Dysphagia	11	10.6	9	11.7	5	18.5
Abdominal pain	13	12.5	3	3.9	1	3.7
Diarrhea	8	7.7	4	5.2	2	7.4

* $p \leq 0.05$ for comparison of 0 and 1 dose of epinephrine

± $p \leq 0.01$for comparison of 0 and1 dose of epinephrine

≠ $0.01 \leq p \leq 0.05$ for comparison of 1and 2 doses of epinephrine

^ $p \leq 0.05$ for comparison of 0 and 2 doses of epinephrine

§ $p \leq 0.01$ for comparison of 0 and 2 doses of epinephrine

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