JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2020, VOL. 10, NO. 1, 16–18
https://doi.org/10.1080/20009666.2020.1711641

ACE inhibitor angioedema: characterization and treatment versus non-ACE angioedema in acute hospitalized patients

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ABSTRACT

Background: ACE angioedema has not been characterized in comparison with angioedema from other causes in acute hospitalized patients.

Methods: We retrospectively compared ACE-angioedema and non-ACE angioedema patients from January 2013 to May 2017.

Results: Of 855 cases screened, 575 met the inclusion criteria of angioedema diagnosis and an electronic medical record. Of these, 297 (51.7%) had ACE angioedema and 278 had angioedema from other causes, of these 31 who were taking an ACE inhibitor that was not considered to be the cause of angioedema (ACE other cause). At least 80% of cases in all groups were African American. Epinephrine was prescribed in 21% of ACE angioedema cases. One-third of patients in all groups were admitted to the ICU, and about 25% required intubation. Previous history of ACE inhibitor-induced angioedema was found in 63 of 278 non-ACE cause angioedema patients (23%) and in 23 (8%) in the ACE cause group.

Conclusion: ACE angioedema was the cause of half of angioedema admissions over a 4.5-year period. Mortality, morbidity, and treatment did not differ between the groups. Patients on ACE inhibitors were often treated with medications known not to be effective for ACE angioedema. Over one-fourth of patients not taking an ACE inhibitor had a previous history of ACE angioedema, and 31 patients taking ACE inhibitors were diagnosed with non-ACE angioedema. Regardless of the etiology of angioedema, 25% of patients required airway protection in the form of intubation.

ARTICLE HISTORY
Received 23 September 2019
Accepted 12 December 2019

KEYWORDS
Angioedema; angiotensin-converting enzyme inhibitor; ACE inhibitor; angiotensin receptor blocker; ARB

1. Introduction

Angiotensin-converting enzyme (ACE) inhibitors are effective and are widely prescribed in the treatment and prevention of complications of hypertension, diabetic small vessel disease, and heart failure[1]. Along with their proven benefit, ACE inhibitors have been associated with one-third of all hospitals visits for angioedema[2], a rare [3] but potentially life-threatening side effect [4,5]. ACE inhibitor-induced angioedema has been reported to occur more frequently in patients with specific risk factors, including African American race, those over 65, women, tobacco users, and those with a history of allergic rhinitis[6].

The distinction between ACE-induced angioedema and allergic angioedema is not always straightforward in the emergency department. Histamine-mediated angioedema responds to epinephrine, glucocorticoids, and antihistamines, whereas treatment of bradykinin-induced angioedema is discontinuation of the drug and acute airway management if indicated for both conditions [2,6].

ACE angioedema has not been characterized in comparison with angioedema from other causes. Therefore, we sought to compare patient demographics, treatment, and outcomes for ACE inhibitor-induced angioedema with angioedema from other causes in our regional health-care system.

2. Materials and methods

2.1. Selection of participants

This retrospective comparative study was approved by our institutional review board. Eligible patients were those admitted from the emergency department with angioedema or developed angioedema during the hospital course between January 2013 and May 2017 across a multisite medical system in the mid-Atlantic region including nine acute care hospitals. The electronic medical record data abstraction tool included demographics, etiology of angioedema, treatments, clinical outcomes, and intensive care unit (ICU) admission and intubation. The data abstractors used Excel for data collection and were not blinded to

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Level of evidence: Level III retrospective comparative study

the purpose of the study. The lead investigator confirmed approximately 30% of the data for internal validity. Eligible patients were identified using the ICD-10 code for angioneurotic edema (T78.3XXA) and adverse event from ACE inhibitor (T-46.4X5A) and the ICD-9 codes for angioedema (995.1) and adverse event from ACE inhibitor (E942.9). The swelling of lips, mouth, and face were confirmed in the diagnosis of angioedema in the chart. We included patients with an electronic medical record where angioedema was the index condition on ED presentation or developed during the hospital course. We classified the admission as ACE inhibitor-induced angioedema if ACE inhibitor allergy was added to the medical record. Angiotensin receptor blocker (ARB) angioedema was included in the ACE group.

2.2. Analysis

Descriptive statistics are presented using frequencies and percentages for categorical variables and using means and standard deviations for continuous variables or median and interquartile range for skewed data. Comparison of categorical variables was conducted using chi-square test or Fisher's exact test for small numbers. ANOVA or nonparametric Kruskal Wallis test for skewed data was used for continuous variables. Analysis was done using SAS 9.4.

3. Results

Of 855 patient records screened, 575 cases of angioedema as index condition and complete data were identified. Of these cases, angioedema was from ACE inhibitor use in 297 (53.7%) and from non-ACE cause in 278 (48.3%) (Table 1). Of these 278 non-ACE cases, a subgroup of 31 cases were on an ACE inhibitor but the ACE inhibitor was not considered to be the cause of angioedema. Of the 297 cases categorized as ACE inhibitor-induced, 93% were on lisinopril and 4% on an ARB (n = 12). Of 228 patients in the no ACE inhibitor group, 62 (27%) had previous history of ACE angioedema (Table 1). Age was significantly higher in the ACE cause group. African Americans made up over 80% of the study population in all groups and 45% of the total admissions in the study period. Use of epinephrine was statistically higher in the non-ACE group (Table 2). There was no identifiable cause of angioedema for most cases in the non-ACE group (Table 3). There was no difference between groups for admission to the ICU or intubation (Table 4).

Of the 575 cases of angioedema, 538 were unique patients. In the ACE inhibitor group, 12 of 291 patients had a second incidence of angioedema, 6 after re-exposure to lisinopril and 6 from non-ACE cause. One patient with ACE angioedema returned within 6 months, suggesting possible delayed response to the original exposure.

3.1. Discussion

In this study, ACE inhibitor-induced angioedema represented half of angioedema admissions over the 4.5-year study period. About a third of cases in all groups required an ICU bed, and roughly a quarter of patients required intubation. Despite expected differences in demographics, the treatment and outcomes of ACE inhibitor-induced angioedema were similar to those in non-ACE angioedema. However, ICU admission for the specific indication of angioedema was statistically more common in the ACE-group.

Table 2. Medications prescribed for angioedema.

	No. (%) prescribed			
		Non-ACE inhibitor induced		
Drug	ACE inhibitor	No ACE inhibitor	On ACE inhibitor	P value
Steroids	281/292 (96)	234/243 (96)	29/30 (97)	1.00
H1 blocker	272/293 (93)	226/243 (93)	28/31 (90)	0.77
H2 blocker	251/293 (86)	190/241 (79)	24/30 (80)	0.11
Epinephrine	60/293 (21)	72/242 (30)	9/31 (29)	0.041

Table 3. Angioedema in non-ACE inhibitor cause cases.

Cause of angioedema	Incidence, n (%) (N = 266)
Unknown	110 (41)
Drug	100 (38)
Antibiotic	37/100 (40)
Alteplase	15/100 (15)
Amlodipine	7/100 (7)
Food	36/266 (14)
Miscellaneous	20 (8)

*Includes insect stings, hair dyes, latex allergy, and hereditary angioedema (one patient).

Table 1. Patient demographics.

	Angioedema case data			
		Non-ACE inhibitor induced (n = 278)		
Factor	ACE inhibitor (n = 297)	No ACE inhibitor (n = 247)	On ACE inhibitor (n = 31)	P value
Age at admission, mean (SD)	62.78 (13.23)	58.63 (17.17)	59.06 (11.04)	0.004
Female sex, n (%)	168/297 (57)	168/247 (68)	14/31 (45)	0.004
Black race, n (%)	245/296 (83)	202/243 (83)	25/31 (81)	0.86
Active smoking history, n (%)	111/259 (43)	48/198 (24)	11/26 (42)	<0.001
Urticaria documented, n (%)	11/297 (3.7)	46/246 (19)	5/31 (16)	<0.001
Previous history of ACE inhibitor angioedema, n (%)	23/296 (8)	62/228 (27)	1/31 (3)	<0.001

Table 4. Patient outcomes.

	Angioedema group data, no. (%)			
		Non-ACE inhibitor induced		
Factor	ACE inhibitor	No ACE inhibitor cause	On ACE inhibitor	P value
ICU LOS	1 (2–2)	1 (2.25–2.25)	0 (2–2)	0.41
Total LOS	2 (5–5)	3 (6–6)	3 (5.5–5.5)	0.014
ICU admission	129/297 (43)	89/247 (36)	10/31 (32)	0.15
ICU admission for angioedema	125/129 (97)	75/89 (84)	8/10 (80)	0.001
Intubation	76/297 (26)	55/247 (22)	7/31 (23)	0.092
Intubation for angioedema	75/76 (99)	49/55 (89)	7/7 (100)	0.092
Tracheostomy or cricothyrotomy	10/297 (3)	3/247 (1)	0/31 (0)	0.28
Mortality	4/297 (1)	3/246 (1)	1/31 (3)	0.46

LOS, length of stay.

In this study, physicians often prescribed medications that are known not to be effective for treating ACE-induced angioedema. This finding may suggest that the difficulty of making a definitive diagnosis and limited time to act leads providers to over-treat for ACE-induced angioedema.

Our study was not designed to evaluate the incidence of angioedema among African Americans. However, blacks made up a substantially higher percentage in all groups compared to the overall population. In this study, over 95% of the documented indications for ACE inhibitors were for hypertension. Although ACE angioedema is rare, this finding supports consideration of alternate medications such as angiotensin receptor blockers to avoid the potential for angioedema from ACE inhibitors, especially in high-risk patients[7].

There are inherent limitations in using ICD-9 and ICD-10 codes to find all angioedema cases[5]. Abstractors were not blinded to the study question, but criteria were strictly defined to avoid subjective interpretation. Also, lisinopril was used almost exclusively in the ACE inhibitor patients. Therefore, the findings may not be generalizable to other ACE inhibitors.

In conclusion, ACE angioedema was the cause of half of angioedema admissions over a 4.5-year period. Mortality, morbidity, and treatment did not differ between the groups. Physicians treated ACE inhibitor-induced angioedema like angioedema from other causes, showing the difficulty of distinguishing between the two conditions. Although ACE inhibitor-induced angioedema is rare, alternative equivalent treatment for hypertension should be considered, especially in groups at greater risk for angioedema. The current data suggest that angioedema poses a significant risk to patients regardless of the etiology in that 25% of patients required airway protection in the form of intubation.

Acknowledgments

We thank the Summer Research Project, Georgetown University School of Medicine, for the support of this study.

Author contributions

Conceived study: DW
Supervised study and data collection: DW, SP
Collected data: NA, MB, MQ, DW, SP
Managed data and provided quality control: DW, SP
Advised on study design and provided statistical analysis: SD, AK
Developed interpretation: DW, LC, SD
Wrote manuscript and all authors contributed substantially to revision: DW, LC
Takes responsibility for the paper as a whole: DW

Author roles

All authors had access to the data and a role in writing the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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