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Retrospective Evaluation of Patients with Angioedema Treated with C1 Inhibitors in an Emergency Department

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Aim: We aimed first to investigate patients who received C1 inhibitor therapy in the ED. The patients' complaints, examination findings, length of stay in the ED and whether the patients were treated with anything other than C1 inhibitor were investigated. Secondly, we aimed the response of patients who received C1 inhibitor therapy in the presence of Angiotensin Converting Enzyme Inhibitor (ACEI) -induced angioedema.
Materials and Methods: A retrospective descriptive study was designed. Patients who received C1 inhibitor therapy between January 2011 and February 2018 were reviewed using the hospital's records on file.
Results: Data were evaluated for 62 admissions in 23 different patients. The diagnosis of hereditary angioedema (HAE) was present in 65.2% (n=15) of the patients, and 85.5% (n=53) of the admissions were related to acute HAE episodes. The main complaints of these patients were nausea, vomiting and abdominal pain and swelling of the face, lips, throat and extremities. It was determined that C1 inhibitor treatment was given to 8% (n=5) of admissions due to ACEI-induced angioedema. The complaints of these patients (5 admissions for 4 patients) were swelling of the tongue (n=3), lip (n=1) and face (n=1). Clinical improvement was observed in admission symptoms after treatment of C1 inhibitor in all patients with angioedema induced by HAE episodes or ACEIs.
Conclusion: C1 inhibitor treatment is effective in treating acute HAE episodes. Although more evidence is needed for treatment of ACEI-induced angioedema attacks, C1 inhibitor therapy may be considered in patients who do not respond to classical treatment.

Keywords: Hereditary angioedema, C1 inhibitor, angiotensin converting enzyme inhibitor, histamine, bradykinin, emergency medicine.
Short Title in English: C1 Inhibitor Treatment in Emergency Department

Introduction

Angioedema is characterized by edema in the subcutaneous and submucosal areas such as the tongue, lips, facial region, extremities, upper airway and gastrointestinal tract. Life-threatening laryngeal attacks may occur as a result of upper airway obstruction. Additionally, acute abdominal pain may occur due to gastrointestinal involvement (1).

Acquired, hereditary and idiopathic causes lead to angioedema. Acquired causes of angioedema occur as allergic (histaminergic), non-allergic (non-histaminergic), drug-related (particularly for angiotensin-converting enzyme inhibitor [ACEI] and non-steroidal anti-inflammatory drugs) or complement-mediated (acquired C1 inhibitor deficiency). Hereditary angioedema (HAE) is often caused by a C1 inhibitor deficiency (type 1) due to a C1 inhibitor gene mutation or functional inhibition despite normal C1 inhibitor levels (type 2). In rare cases, HAE is related to a factor 12 mutation or oestrogen effects (type 3) (2-4).

Angioedema develops through mechanisms of histamines and bradykinin. Since the treatment approach is different, it is important to know which mediator caused the angioedema. Histamine-induced angioedema, also known as allergic angioedema, releases histamines through immunoglobulin E-mediated mast cell degranulation after allergen (food, drug, insect etc.) contact, after which rapid onset angioedema develops as a result. This type of angioedema responds to antihistaminic, glucocorticoid and adrenaline treatments. Bradykinin-induced angioedema is the most common cause of nonallergic angioedema. It is associated with HAE, non-histaminergic acquired angioedema and ACEI-induced angioedema (5).

The C1 inhibitor is the regulator of the complement system and also has effects on quinine, coagulation, fibrinolytic and contact systems. The C1 inhibitor plays an important role in the inactivation of factor 12, which plays a key role in the conversion of prekallikrein to kallikrein. In addition, the C1 inhibitor inhibits the formation of bradykinin from high molecular weight plasma kininogen by means of kallikrein. Bradykinin is an important vasodilator and acts on vascular permeability and smooth muscle contraction. Patients with HAE and acquired C1 deficiency are exposed to bradykinin through these mechanisms (3,6). Angiotensin-converting enzyme (ACE) is involved in the breakdown of bradykinin. ACEI-induced angioedema is thought to be a result of preventing this breakdown (7).

The US Food and Drug Administration has confirmed that plasma-derived C1 inhibitor concentrates can be used to treat patients with acute episodes of HAE. However, there is no confirmation that these drugs can be used in the presence of ACEI-induced angioedema. There are data in the literature that patients with ACEI-induced angioedema may be discharged from the emergency department (ED) earlier with drugs that act on the bradykinin pathway (8).

In this study, we aimed first to investigate patients who received C1 inhibitor therapy in the ED. The patients' complaints, examination findings, length of stay in the ED and hospital and whether the patients were treated with anything other than a C1 inhibitor were investigated.

Secondly, we aimed to contribute to the literature by investigating the response of patients who received C1 inhibitor therapy in the presence of ACEI-induced angioedema.

Materials and Methods

Our study was planned as a retrospective descriptive study. Patients admitted to a tertiary hospital where 200,000 patients are accepted each year were evaluated. After obtaining approval from the local ethics committee (Record number and date: 18-7.1/55, 27.06.2018) patients who received C1 inhibitor therapy between January 2011 and February 2018 were reviewed using the hospital's records on file. The age, gender, complaints and physical examination findings of the patients were recorded. The presence of a HAE diagnosis, a history of drug use that may lead to angioedema, medical therapies given in the ED (antihistamines, corticosteroids, fresh frozen plasma, adrenaline etc.), airway interventions, length of stay in the ED, and the elapsed time to start C1 inhibitor treatment were investigated.

Descriptive statistics were applied to the demographic data. Discontinuous and ordinal variables were given using frequencies and percentages. Mean and standard deviations were used for continuous variables showing normal distribution. Data were evaluated using SPSS 18.0.(SPSS Inc.Chicago, IL).

Results

Eighty-one ED admissions were examined in 25 different patients. Nineteen admissions related to treatment with a prophylactic C1 inhibitor were excluded from the study. In total, data were evaluated for 62 admissions in 23 different patients. Sixty-five percent (N=15) of the patients were female. The mean age was 41.3 years old (minimum 18; maximum 76; standard deviation 17.3).

The diagnosis of HAE was present in 65.2% (N=15) of the patients, and 85.5% (N=53) of the admissions were related to acute HAE episodes. The main complaints of these patients were nausea, vomiting and abdominal pain and swelling of the face, lips, throat and extremities. The complaints and physical examination findings of the patients are shown in Tables 1 and 2. Airway intervention was required in 2 patients. Tracheostomy was performed in 1 patient, and an oropharyngeal airway was inserted in 1 patient. The patients who were treated with airway interventions had no HAE diagnosis. Patients were given either 1000 IU Cetor (Sanquin, Amsterdam, Netherlands) or 1000 IU Cinryze (Sanquin, Amsterdam, Netherlands) as the C1 inhibitor treatment. The other medical treatments initiated in the ED are shown in Table 3. The mean starting time of C1 inhibitor therapy for patients with acute HAE episodes was 77.5 ±59.9 min. The mean ED stay of patients was 5.2 ±4.4 hours. It was determined that 6.5% (n=4) of

the admissions were hospitalized. Two patients were admitted to the Immunology Unit, 1 was admitted to the Dermatology Unit and 1 was admitted to the Intensive Care Unit.

It was determined that C1 inhibitor treatment was given to 8% (N=5) of admissions due to ACE inhibitor-induced angioedema. The complaints of these patients (5 admissions and 4 patients) were swelling of the tongue (n=3), lip swelling (n=1) and swelling of the face (n=1). It was determined that C1 inhibitor treatment was started on these patients when there was no response to antihistaminic and corticosteroid treatment. In one patient, it was determined that fresh frozen plasma was used. The mean starting time of C1 inhibitor therapy for these patients was 186 ±122 minutes, and the mean ED stay was 30.9 ±24.8 hours.

The complaints of patients with an unknown aetiology of angioedema (4 patients, 4 admissions) were respiratory arrest (n=1), lip swelling (n=2) and extremity swelling (n=1). In these patients, C1 inhibitor treatment was started when there was no response to antihistamine or corticosteroid therapy. Clinical improvement was not observed in the patient with respiratory arrest after C1 inhibitor treatment, but the symptoms of the other 3 patients improved. The mean starting time of C1 inhibitor therapy for these patients was 740 ±949 minutes, and the mean ED stay was 20.5 ±15.1 hours.

Discussion

Angioedema is a relatively rare but important reason for emergency admissions. It may be difficult to differentiate the mechanism that led to angioedema at the time of admission for the emergency physicians (EPs), and there is no valid rapid diagnostic test for this condition. Patient history and physical examination findings may help in finding this distinction. For example, urticaria occurs in approximately 30% of histamine-mediated angioedema attacks (9). Histamine-associated angioedema can also be caused by insect bites as well as some foods, beverages and medications, and it shows a rapid clinical onset. Bradykinin-associated angioedema has a slower onset. As a prodromal symptom, a tingling sensation may be present in the area where the acute episode will begin. Itching and urticaria do not occur. The diagnosis of HAE needs to be reviewed in the presence of urticaria (3,5). Similarly, in our study, there were no signs of pruritus or urticaria in patients who were evaluated for acute episodes of HAE and treated with C1 inhibitor therapy. In addition, acute episodes were not associated with any allergen contact.

Abdominal pain accounts for 10% of all ED admissions, but the aetiology may not be detected in 40% of patients who present with abdominal pain in the ED (10). Although swelling of the face and extremities is the most common complaint associated with acute HAE episodes, abdominal pain is reported to be associated with 50% of acute episodes (11). In our study, when

all of the admissions were considered, it was determined that the most common presenting complaint was abdominal pain, nausea and vomiting for acute HAE episodes. Therefore, emergency physicians should question whether these symptoms are recurrent, especially in patients with undiagnosed abdominal pain. Additionally, the presence of a history of HAE in the family and angioedema-like symptoms in the skin and mucous membranes should be questioned when taking patient histories.

Because the mechanisms leading to angioedema are different, the drugs selected for treatment should be related to the mediator and its effects. The ED medical treatment approach in the presence of angioedema classically includes antihistamines, glucocorticoids and adrenaline. However, this approach is not effective for the treatment of bradykinin-induced HAE episodes (12). As the current medical approach, plasma-derived and recombinant C1 inhibitors, plasma kallikrein inhibitors and bradykinin-2 receptor antagonists are recommended for the treatment of acute episodes of HAE (5,13). If these treatments are not available, fresh frozen plasma may be used as second-line treatment (14). In our study, it was determined that C1 inhibitors were given to patients presenting with acute HAE episodes. All of the patients' symptoms were resolved after treatment, and these patients were discharged from the ED earlier than patients without HAE diagnoses. No airway intervention was needed for HAE-diagnosed patients. However, approximately 20% of the patients were given antihistaminic and glucocorticoid therapy, suggesting that some physicians did not have sufficient information about the treatment of acute HAE episodes.

ACEIs are the most commonly used antihypertensive drugs. ACEIs constitute 40% of the patients admitted to the ED with drug-induced angioedema (15). Angioedema due to ACEI can be seen in patients who have just started treatment or in patients who have been using these drugs for many years (16). ACEIs prevent the conversion of bradykinin to inactive metabolites and cause angioedema. Most cases are characterized by edema of the face, lips, tongue and

airway but rarely occur with episodes of abdominal-visceral angioedema (17,18). There is no approved drug therapy for ACEI-induced angioedema attacks. Since there are no randomized controlled studies on the subject, it is not known whether C1 inhibitor treatment will work in the presence of ACE inhibitor-induced angioedema or for what symptoms it will be beneficial in patients admitted to the ED. Although cases with a response to classical angioedema treatment are reported in current case reports, there are also cases that did not benefit from this treatment and whose symptoms improved after C1 inhibitor treatment (19,20). Also, it has been reported that symptoms are controlled more quickly and there is no need for airway intervention in patients receiving C1 inhibitor treatment (21). In our study, it was determined that 5 patients receiving C1 inhibitor therapy had symptoms that were thought to be associated with ACEI-induced angioedema. All patients were treated with C1 inhibitors because of an inadequate response to conventional angioedema treatment. It was determined that the symptoms of patients diminished after this treatment, and no airway intervention was needed to manage the patients.

There are some limitations in our study. Descriptive data such as the onset time of symptoms and presence of accompanying prodromal findings could not be accessed in patients with HAE. The causes triggering the acute episodes of HAE could not be determined. The onset of drug action in the patients who benefited from C1 inhibitor treatment could not be determined. The data of 3 patients who had no diagnosis of HAE and presented with angioedema-like findings and benefited from C1 inhibitor treatment could not be obtained for the diagnosis of HAE in the outpatient follow-up. The physician's clinical experience was considered because there is no test showing the exact diagnosis of ACEI-induced angioedema.

Conclusion

C1 inhibitor treatment is effective in treating acute HAE episodes. EPs should consider the diagnosis of HAE as a differential diagnosis in patients with undiagnosed abdominal pain in the context of a comprehensive history. Although more evidence is needed for treatment of ACEI-induced angioedema attacks, C1 inhibitor therapy may be considered in patients who do not respond to classical treatment.

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Table 1 Complaints of Patients

	Patients with HAE **n(%)**	**Patients without HAE** **n(%)**
Nausea-vomiting-abdominal pain	24 (%45,3)	0
Face swelling	7 (%13,2)	1 (11,1)
Lip swelling	7 (%13,2)	3 (33,3)
Throat swelling	6 (11,3)	0
Extremity swelling	5 (9,4)	1 (11,1)
Shortness of breath	1 (1,9)	0
Tongue swelling	1 (1,9)	3 (33,3)
Testicular edema	1 (1,9)	-
Rashes & itching	0	1 (1,6)
Chest pain	1 (1,9)	0

Table 2 Physical Examination Findings of Patients

	Patients with HAE **n(%)**	**Patients without HAE** **n(%)**
Edema around the face and mouth	15 (28,3)	3 (33,3)
Edema of the lips	13 (24,5)	6 (66,7)
Edema of the tongue	2 (3,8)	4 (44,4)
Uvula edema	10 (18,9)	4 (44,4)
Edema of the larynx	1 (1,9)	2 (22,2)
Dyspnea	3 (5,7)	3 (33,3)
Abdominal tenderness	24 (45,3)	0
Subcutaneous edema of the extremities	7 (13,2)	2 (22,2)
Urticaria	0	1 (11,1)

Table 3 Treatments in the Emergency Department

	Patients with HAE **n(%)**	**Patients without HAE** **n(%)**
H1 receptor antagonist	11 (20,8)	8 (88,9)

H2 receptor antagonist	9 (16,9)	4 (44,4)
Corticosteroids	10 (18,9)	9 (100)
Adrenalin	0	2 (22,2)
Fresh frozen plasma	2 (3,8)	1 (11,1)