Angioedema of Head and Neck Complicating the Use of ACE Inhibitors

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Objective: To study the clinical manifestations and to assess our management of cases of angioedema of head and neck precipitated by the use of Angiotensin – Converting enzyme (ACE) inhibitors.

Design and setting: This is a retrospective analysis of 42 consecutive cases with angioedema of head and neck seen and managed at the teaching hospitals of the University of Ottawa, between 1991 and 1995. Twenty four cases were associated with the use of ACE inhibitors.

Subjects: Female patients constituted 69% and males 31%. There was a male to female ratio of 1.0:2.2. The mean age of the patients was 64 years. More than two thirds of the patients (62%) presented as a first episode. The tongue was most commonly affected. Other affected areas included the lips, oro-pharynx, supraglottis and soft palate.

Results: ACE’s were used in 24 (57%) cases. All cases treated medically responded to therapy which included the use of anti-histamine, steroids and sometimes subcutaneous epinephrine. Admission to intensive care unit (ICU) were required in 12 (28.6%) patients and endotracheal intubation was required in 3 (7%) cases. Fiberoptic Nasolaryngoscopy (FNLS) was utilized in the assessment of 21 patients (50%). No mortality was recorded.

Conclusion: Angiotensin – Converting Enzyme (ACE) inhibitors are relatively common cause of angioedema of head and neck. Treatment to keep the airway open during the acute phase is essential to prevent death.


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Angioedema is a disorder characterized by localized swellings of sudden onset, which subside during the course of 24 to 48 hours\textsuperscript{1}. Sometimes it presents as a life threatening disease that affects the deep layers of dermis, subcutaneous tissues and mucosa. It has been classified into hereditary (a rare autosomal dominant disorder) and acquired type depending upon the level and functional activity of C1-inhibitor which physiologically regulate complement system activation.

Since 1980's, Angiotensin converting enzyme (ACE) inhibitors have been widely used as effective treatment for many cardiovascular disorders including hypertension and chronic congestive heart failure. Generally, these drugs have a relatively good clinical safety margin. But numerous side effects have been reported. One of its dangerous idiosyncratic side effects is the development of angioneurotic oedema, which sometimes causes acute upper airway obstruction. This serious side effect is estimated to occur in 0.1–0.7 % of cases receiving ACE inhibitors\textsuperscript{2,3}.

In this study we are reporting 42 patients with angioedema related to head and neck who required admission to the hospital. Twenty four patients are thought to be associated with ACE inhibitors use.

The purpose of this paper is to study the clinical manifestations of this condition and to assess their management.

METHODS

In four-year period, between 1991 and 1995 we retrospectively studied 42 consecutive cases of angioedema related to head and neck, which presented to the emergency department, and required hospitalization at the teaching hospitals of the University of Ottawa.

The following data were collected from the hospital chart: demographic data, clinical presentation profile, which includes specifically questions about the presence or absence of dyspnea, dysphagia, odynophagia and dysphonia, history of medication use specifically ACE inhibitors (their type and duration), number and locations of angioedema episodes (tongue, lips, oropharynx, soft palate and supraglottis).

Investigation results included routine blood work, we looked specifically to the result of the complement system factors levels (C1, C3 and C4), other investigations included the use of the fiberoptic flexible nasolaryngoscope to assess the base of the tongue, glottis and supraglottic regions for the presence of mucosal edema.

Methods of management were recorded which include observation in the emergency room, the use of medical treatment (antihistamines and steroids either alone or with subcutaneous epinephrine when indicated), requirements for endotracheal intubation and ICU admission.
RESULTS

Females constituted 69%, males 31%, male to female ratio of 1.0: 2.2. The mean age of the group was 64 years and the range was 20-97 years. More than two thirds presented as a first episode, 26 (62%) patients. Location of angioedema varied, tongue was the primary site in the majority of cases (71.4%). Other locations included lips, oropharynx, supraglottis and soft palate as shown in Table 1.

Table 1. Angioedema of Head and Neck Complicating the use of ACE Inhibitors: clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage(number)</th>
</tr>
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<tbody>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31%(13)</td>
</tr>
<tr>
<td>Female</td>
<td>69%(29)</td>
</tr>
<tr>
<td>Number of episodes:</td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td>62%(26)</td>
</tr>
<tr>
<td>Second episode</td>
<td>23.8%(10)</td>
</tr>
<tr>
<td>Multiple episodes</td>
<td>14.3%(6)</td>
</tr>
<tr>
<td>Locations of angioedema:</td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>71.4%(30)</td>
</tr>
<tr>
<td>Lips</td>
<td>9.5%(4)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>9.5%(4)</td>
</tr>
<tr>
<td>Supraglottis &amp; soft palate</td>
<td>9.5%(4)</td>
</tr>
<tr>
<td>Type of ACE inhibitors:</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>41.7%(10)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>37.5%(9)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>12.5%(3)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>8.3%(2)</td>
</tr>
</tbody>
</table>

ACE inhibitors were used in 24 (57%) cases. The type of ACE inhibitor responsible are shown in Table 1. Hypertension was the main indication for ACE inhibitors use (83% of the cases). Duration between starting ACE inhibitor’s and angioedema development varied. The shortest was one hour with Captopril and the longest was 5 years with Enalapril.

Fiberoptic nasolaryngoscopy (FNLS) was utilized in 21 (50%) patients usually because of symptoms or signs suggested the upper airway obstruction. FNLS groups presented with dyspnoea, dysphagia, dysphonia or odynophagia. Symptoms occurred in 21 (100%) cases of FNLS group compared to 5 (24%) cases in the group who didn’t have FNLS. The glottis was abnormally swollen and oedematous in 3 (14.3%) cases of the FNLS group. Endotracheal intubation was required in 3 (14.3%) cases of FNLS group but was not used in the non-FNLS group, ICU admissions were required in 10 (48%) cases of FNLS group and 2 (9.5%) cases for non-FNLS group.
Laboratory investigations included routine blood work (i.e. CBC, electrolytes, urea and creatinine) for all patients, and complement factors level (C1-inhibitor, C3 and C4) for 13 (31%) patients. Only one patient showed low level of C1-inhibitor. This patient was a twenty years old female, with no family history of angioedema who had three episodes of angioedema attacks. This case was considered as a case of hereditary angioedema according to the diagnostic criteria which include: recurrent episodes of non-inflammatory angioedema in the first four decades of life with or without family history of angioedema.

Management

In terms of management, 30 (93%) cases were treated medically with antihistamines and steroids. Subcutaneous epinephrine was added to steroid and antihistamine in 18 (43%) patients, while racemic epinephrine was added to steroid and antihistamine in only one (2.4%) patient.

Endotracheal intubation was required in 3 (7%) cases to protect the airway. The group who required intubation presented to the emergency room earlier within 3.3 hours of the attack. Those who didn’t require intubation presented 9 hours after the attack. FNLS was performed in all cases prior to intubation and performed only in 18 (46%) cases of the non-intubated group. FNLS showed abnormal glottis swelling and edema in all intubated patients (3 cases) while it was normal in all the cases in the non-intubated group who had FNLS performed (18 cases).

No tracheotomy was performed in any of the cases and there was no mortality related to angioedema. All the cases treated medically did not show any progressive obstructive signs or symptoms. Admissions to the intensive care unit were required in 12 (28.6%) patients. FNLS showed abnormal glottis swelling in 8 (80%) cases of the ICU group while it was normal in all (11 cases) of the non-ICU group who had FNLS.

DISCUSSION

The mechanism by which ACE inhibitors precipitate angioedema is unknown; however, it is likely to be biochemical rather than immunological related, through both the Renin-Angiotensin and the Kallikrin-Bradykinin systems. ACE inhibitors prevent the breakdown of bradykinin, which is a potent vasodilator and this increases the vascular permeability and produces tissue edema. At the same time ACE inhibitors reduce the production of Angiotensin II which is a potent vasoconstrictor thereby causing a net vasodilatory effect, which may potentiate the formation of angioedema.

Suggested predisposing risk factors, which identify patients at risk for this side effect are black American race and patients with pre-existing narrowing of the oropharyngeal space. In this study according to the diagnostic criteria of Cicardi and Agostoni, we have only one case of hereditary angioedema. We found ACE inhibitors to be very commonly associated with angioedema (57%).
When symptoms and signs of upper airway involvement are present, FNLS is a very useful tool to evaluate upper airway involvement in patients with angioedema, and can be utilized to identify the patient requiring close monitoring, intubation and ICU admission. Generally no specific laboratory test is necessary in angioedema cases, unless indicated for other medical reason. It is only those cases thought to be hereditary, who will need to be investigated for complement factor levels. These are people having recurrent episodes of non-inflammatory angioedema in the first four decades, with or without family history.

Most of the angioedema cases resolved with medical treatment mainly comprising of antihistamines and steroids. In few cases epinephrine may be indicated. It is only those cases with clinical symptoms and signs indicating upper airway involvement and abnormal FNLS findings who need intubation to secure their airways in their early presentations.

Most of the cases stayed in the hospital less than 48 hours, and the cases that required an ICU admission spent an average of 27 hours in ICU. We believe ICU admission should be reserved for those cases with clinical presentation suggesting upper airway obstruction and confirmed by flexible scopy.

Replacement of ACE inhibitors with Angiotensin two blockers has been recommended because the initial reports suggested its safety regarding the angioedema hazard. Specific investigations (mainly the complement factor levels) should be reserved for the cases with clinical presentation suggesting a hereditary angioedema. Other investigators have suggested that certain clinical factors including odynophagia and tongue swelling at the time of presentation are predictors for adverse prognosis and a useful guide for diagnostic intervention and admission to the hospital.

**CONCLUSION**

ACE Inhibitors are relatively common cause of angioedema of head and neck. All cases with angioedema related to head and neck region should be carefully evaluated regarding symptoms and signs of upper airway involvement, and flexible nasolaryngoscopy performed if clinically indicated. This will help in identifying high risk patients who may need admission to intensive care unit.

**REFERENCES**