Six Years Experience of Angioedema at the University Hospital of the West Indies
JA Williams-Johnson, S Hemmings, EW Williams, G Channer, AH McDonald

ABSTRACT
Angioedema (AE) is a problem that all doctors inclusive of emergency room physicians and the otolaryngologists are often asked to treat. We present a six-year experience with this disorder. In this series, angiotensin-converting enzyme inhibitors (ACEIs) were related to 60% of admissions for angioedema. Lip and tongue swelling was the most common manifestation. The discontinuation of ACEI therapy and supportive management are the recommended approaches to treatment and prevention of unfavourable outcomes. The authors strongly recommend medic alert bracelets for all patients with this disorder. The use and side effects of ACEI therapy in our population which is predominantly of African descent warrants further investigations.

Seis Años de Experiencia de Angioedema en el Hospital Universitario de West Indies
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RESUMEN
El angioedema (AE) es un problema que todos los doctores – incluyendo los médicos y otolaringólogos de las salas de emergencia – se ven a menudo en la necesidad de tratar. A continuación presentamos una experiencia de seis años de enfrentamiento a esta afección. En esta serie, inhibidores de enzimas convertidoras de angiotensina (IECAs) se relacionaron con el 60% de los ingresos por angioedema. La hinchazón de los labios y la lengua fue la manifestación más común. La suspensión de la terapia con IECAs y el tratamiento de apoyo son los métodos que se recomiendan para el tratamiento así como para la prevención de resultados desfavorables. Los autores recomiendan enfáticamente brazaletes de alerta médica para todos los pacientes con esta afección. El uso y los efectos colaterales de la terapia con IECAs en nuestra población – predominantemente de ascendencia africana – merece investigación ulterior.
it is proposed to be immune mediated which is closely linked to the metabolism of bradykinin. However IgE antibodies or other specific antibodies have not been detected. The aetiology of the inherited form has been well documented by Donaldson and Evans (4) with the elucidation of the role of C-1 esterase inhibitor in the complement cascade and its related deficiency resulting in the elaboration of vasoactive products causing angioedema. Most patients especially at the urticarial stage are seen and treated in clinics and doctors’ offices.

It is estimated that > 40 million people worldwide are receiving therapy with ACEIs. This may result in an increasing number of presentations for AE (5). The clinical presentations, treatment and disposition of this group of patients over a six-year period at the University Hospital of the West Indies (UHWI) in Jamaica were examined. General recommendations regarding therapy are suggested.

SUBJECTS AND METHODS
A retrospective chart review was conducted on all patients who had been admitted to the UHWI with a diagnosis code for AE from January 1, 2000 to December 31, 2005. All patients who developed AE while on ACEI therapy were presumed to have the diagnosis of ACEI–related AE. In some cases, there were no identifiable aetiology. Demographic data and length of hospitalization of each patient were noted. The patients’ histories were also reviewed for presenting symptoms, aetiology, medical therapy and the need for aggressive airway management (Table 1). All of the patients in this study were admitted to the otolaryngology service directly from the emergency room.

RESULTS
Over the six-year period fifteen cases were reviewed. The small number of patients and retrospective nature of the study prevents statistical analysis. The patients ages ranged from 2 to 74 (mean of 50.6) years and ten patients (66%) were females. Nine cases (60%) were thought to be related to ACEI therapy. Four of these patients were noted to be on other drugs at the time of presentation but none included antibiotics (Table 1). Fourteen cases (93%) manifested angioedema in the head and neck region.

All patients were monitored for abnormalities in their vital signs and for respiratory distress. In this study, all of the patients received intravenous hydrocortisone, antihistamines, intravenous fluids and oxygen. Two patients with compromised upper airway received subcutaneous administration of a 1:1000 solution of adrenaline (0.1%). The average length of admission was three days and only one patient who was initially managed in the intensive care unit spent ten days on the ward. Being a retrospective study, it was not possible to determine the interval from the start of therapy to the development of symptoms of AE. Furthermore, it was not possible to determine any crucial or critical doses. Five patients had an undetermined aetiology. All patients responded well to supportive management. Two patients required tracheostomy. No patients re-presented for the same illness to this institution during the study interval. No fatalities were reported.

DISCUSSION
The association of AE and ACEIs has received significant attention (6). These agents are routinely recommended for the treatment of hypertension, especially in the presence of left ventricular dysfunction, congestive heart failure (7), nephropathy and proteinuria.

In this series, most of the patients (60%) admitted for AE were hypertensives being treated with ACEIs. One of the remaining patients had AE related to sea-food ingestion,

Table 1: Angioedema: University Hospital of the West Indies 2000–2005

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Site of oedema</th>
<th>Intub/Trach</th>
<th>Aetiology</th>
<th>Admission (Days)</th>
<th>Other medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>62</td>
<td>Face, Tongue</td>
<td>–</td>
<td>Captopril</td>
<td>3</td>
<td>Gliclazide</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>56</td>
<td>Face</td>
<td>–</td>
<td>Lisinopril</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>5</td>
<td>Face, Extremities</td>
<td>–</td>
<td>Unclear</td>
<td>2</td>
<td>Metformin</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>2</td>
<td>Extremities</td>
<td>–</td>
<td>Unclear</td>
<td>3</td>
<td>Atenolol, Hydrochlorothiazide</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>40</td>
<td>Face</td>
<td>Trach</td>
<td>Captopril</td>
<td>10*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>60</td>
<td>Tongue</td>
<td>–</td>
<td>Unclear</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>63</td>
<td>Face</td>
<td>–</td>
<td>Ramipril</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>74</td>
<td>Subglottis</td>
<td>–</td>
<td>Captopril</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>72</td>
<td>Face</td>
<td>–</td>
<td>Lisinopril</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>60</td>
<td>Tongue</td>
<td>–</td>
<td>Unclear</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>45</td>
<td>Lip/Subglottis</td>
<td>–</td>
<td>Lisinopril</td>
<td>2</td>
<td>Aspirin, Atenolol</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>71</td>
<td>Lip</td>
<td>–</td>
<td>Enalapril</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>63</td>
<td>Face and Neck</td>
<td>–</td>
<td>Ramipril</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>45</td>
<td>Tongue</td>
<td>–</td>
<td>Sea Food</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>42</td>
<td>Face and Neck</td>
<td>Trach</td>
<td>Unclear</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Trach = Tracheostomy
*from Intensive Care Unit
while the aetiology of the AE in the remaining five patients was not determined.

The angioedema that results from patients using an ACEI is not considered an allergic reaction. It is attributed to a metabolic interference in bradykinin metabolism resulting in elevated bradykinin levels and the relative diminution of angiotension II levels caused by the ACEI (9) (Fig. 1).

Bradykinin causes vasodilation and capillary leakage into the subcutaneous tissues leading to AE. In this study, nine patients (60%) had ACEI-related AE. Some of these patients were also taking other medications and it is not clear why only a proportion of patients develop this entity while others did not. No clear predisposing risk factors for the development of AE were identified. In some reports there tends to be an increased risk of ACEI-related AE in patients of African origin (9, 10). Furthermore, it is postulated that there is a genetic deficiency of other bradykinin-metabolizing enzymes like carboxypeptidase-N and aminopeptidase-P (8). (Fig.1). These enzymes degrade bradykinin and are not affected by ACEIs. Some authors have speculated that in selected individuals angioedema may be related to a deficiency of carboxypeptidase-N (CPN) because of its parallel role with that of ACE in enzymatic inactivation of bradykinin, possible manifesting as angioedema (1,8) (Fig.1). This may also explain the general wide variation in individual response.

Manifestations of ACEI induced angioedema begins anywhere from 48 hours to 28 days after initiation of treatment but is more commonly seen in patients who have recently begun to receive ACEI therapy (1). In this retrospective study, it was not possible to determine the interval in these patients.

The most common presenting symptom was lip and tongue swelling. This was seen in almost all of the cases. Other organ systems may be involved resulting in dysphagia, abdominal pains, cough, stridor and drooling of saliva. None of the patients in this review had a previous attack or a prior history of AE and therefore this by itself could not be considered a risk factor as it were in some series (1).

It is a clear recommendation that ACEIs should not be considered for treatment in patients with a history of previous ACEI-related angioedema. Furthermore, it is even suggested in several reports that even angiotensin receptor blockers (ARB’s) are not considered safe or as an alternative in patients with a history of ACEI-related AE (11, 12). Hereditary angioedema (HAE) is relatively uncommon. In one series of 146 patients with AE only one case of HAE was identified (1). Patients with HAE usually have recurrent episodes on a background of a strong family history of AE. Hereditary angioedema is associated with a genetic autosomal dominant trait in which the production or function of C-1 esterase inhibitor enzyme is reduced. This results in the elevation of C-1 esterase activity which activates the complement cascade. Some of the increased complement cascade products have potent vasoactive qualities which lead to increased vascular dilatation and permeability with leakage of fluid into the extravascular spaces resulting in tissue oedema. Family history is critically important in all angioedema patients. If the patient has a personal or family history of AE, then HAE must be considered. No such patient was reported in this study and C-1 esterase inhibitor enzyme levels or functions are not routinely done at this institution. These assays should be reserved for those who fit the clinical picture of HAE.

The approach to the management of patients with ACEIs associated AE generally includes discontinuation of the suspected initiating agent along with close monitoring and supportive care. Airway management is paramount and crucial. The roles of the otolaryngologist and anaesthetist are crucial. The decision on when to intubate should be made on standard physiologic criteria with an early awareness of a difficult airway. Two of the patients in this study required emergency tracheostomy as they presented with significant facial and neck oedema and had failed endotracheal intubation. These patients also received epinephrine (0.1%) subcutaneously. The early administration of subcutaneous adrenaline is critical in alleviating severe symptoms such as reversing the severity of laryngeal oedema. Severe cases may present with hypotension as a result of significant extravasation of large amounts of fluid into extravascular spaces as in an anaphylactic reaction. Here intravenous crystalloids are ideal. Most of the patients in this report received treatment with intravenous steroids and anti-histamines. It is recommended that this approach should be initiated as a true allergic reaction cannot be excluded. However, no controlled studies have been done to document efficacy of these agents in ACEI-related AE (1). Although the role of the above agents is controversial, they can be safely used for symptomatic relief until the aetiological agent is identified and discontinued.

All of the patients in this study were admitted to the otorhinolaryngology service. Once the AE was resolved, they were safely discharged home without therapy. A work-up diagnosis for HAE should be performed in patients who
do not respond to supportive therapy. In this small study there was no clear evidence for a dose-dependent relation or preponderance of any gender in this disease. The average length of admission was three days.

A high index of suspicion, communication between specialties and close monitoring of the airway are mandatory in the case of patients with angioedema of the head and neck. In the event of airway involvement, intubation under direct visualization or via flexible bronchoscopy should be considered prior to tracheostomy (13).

Laryngeal angioedema is a relatively rare but potentially life-threatening side effect of ACEI therapy. At this time, identification of individuals at risk of this adverse effect is not possible.

Besides ACEI-associated angioedema, many other causes of AE exist which includes food allergies and hypersensitivity to hymenoptera venom (bees, wasps). However, despite detailed history taking, many AE patients still have to be classified as being “idiopathic” as were some of our cases. With the increasing use of ACEIs, AE may become more frequent. Clinicians should exercise caution in prescribing ACE inhibitors for patients with prior idiopathic episodes of sudden swelling of the skin, throat or mouth. Proper history taking is crucial. The discontinuation of therapy with ACEIs and supportive management are the recommended approaches to therapy and to prevent unfavourable outcomes. The more severe patients should consider carrying a kit of self-administerable adrenaline (Epi-Pen). These kits are not available locally but can be obtained in the United States of America. Patient education including advice for future attacks of AE is important. The authors strongly recommend medic alert bracelets for all patients with this disorder. The use and side effects of ACEI therapy in our population which is predominantly of African descent warrants further investigation.

REFERENCES