BRIEF OBSERVATION

THE AMERICAN JOURNAL of MEDICINE®

Angiotensin-converting Enzyme Inhibitor Angioedema Requiring Admission to an Intensive Care Unit

Guy W. Soo Hoo, MD, MPH,[a] Henry K. Lin, MD,[b] Imran Junaid, MD,[b] William B. Klaustermeyer, MD[b]

[a]Pulmonary and Critical Care Section and [b]Allergy and Immunology Section, Department of Medicine, Veterans Affairs Greater Los Angeles Healthcare System and David Geffen School of Medicine, University of California, Los Angeles.

ABSTRACT

OBJECTIVE: The purpose of this study was to review consecutive cases of angiotensin-converting enzyme (ACE) inhibitor angioedema admitted to an intensive care unit.

METHODS: Fifty subjects with ACE-inhibitor angioedema admitted from 1998-2011 were reviewed.

RESULTS: All 50 subjects were men, 62.8 ± 8.4 years of age, 76% African Americans. Fifteen (30%) required ventilatory support and 2 (4%) required tracheostomy. Over half (56%) had taken ACE inhibitors for over a year. Logistic regression identified dyspnea and tongue involvement with the need for ventilatory support ($P < .01$). Hypercapnia ($PaCO_2 = 45.2 \pm 6.7$; $P = 0.046$) also identified patients needing ventilatory support.

CONCLUSIONS: Ventilatory support was provided for about one-third of those with ACE inhibitor-associated angioedema. Angioedema can occur even after extended use. Dyspnea and tongue involvement identified patients requiring ventilatory support.

Published by Elsevier Inc. • The American Journal of Medicine (2015) 128, 785-789

KEYWORDS: Angioedema; Angiotensin-converting enzyme inhibitor; Respiratory failure

Angioedema is a well-recognized adverse effect associated with angiotensin-converting enzyme (ACE) inhibitors.[1] Given its frequent use, it is not surprising that ACE-inhibitor angioedema is the most common hospitalized adverse reaction (5.4/100,000 hospitalizations).[1,2] ACE-inhibitor angioedema in the US is estimated at 0.2% (2/1000 persons) of those starting treatment.[3,4] ACE inhibitors cause one-third to two-thirds of the angioedema seen in emergency departments.[5,6] However, the incidence has been increasing, especially among African Americans who experience a threefold greater risk.[7-10]

The pathogenesis of ACE inhibitor-induced angioedema is mediated by the vasodilator bradykinin.[11] Angiotensin II produces bradykinin breakdown, and ACE inhibitors decrease angiotensin II. This produces vasodilation and increased permeability of fluid. Angioedema of the upper airway and potential respiratory compromise is of the greatest concern.

Prior reviews have reported a wide spectrum of clinical severity ranging from asymptomatic to respiratory failure.[12-15] We have focused on patients with the greatest risk for respiratory failure and report our experience in patients with severe angioedema requiring intensive care unit (ICU) admission.

METHODS

Patients with ACE inhibitor-induced angioedema and ICU admission between January 1998 and December 2011 were identified from our local ICU patient database. Patients were cross-referenced with the pharmacy adverse drug effects database for secondary confirmation. This retrospective

Funding: None.

Conflict of Interest: None of the authors have any conflicts of interest to disclose.

Authorship: All authors had access to the data and contributed to preparation, review and completion of the manuscript.

Requests for reprints should be addressed to Guy W. Soo Hoo, MD, MPH, Pulmonary and Critical Care Section, Veterans Affairs Greater Los Angeles Healthcare System, 11301 Wilshire Blvd. (W111Q), Los Angeles, CA 90073.

E-mail address: guy.soohoo@va.gov

0002-9343/$ -see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2015.02.006

study was approved by our Institutional Review Board, which waived the need for patient consent given its minimal risk.

Each patient was reviewed using the electronic medical record, Computerized Patient Record System (CPRS, version 1.0.28.24) by at least 2 investigators using a structured case report form. Data were abstracted and compiled in an Excel spreadsheet (Microsoft Corporation, Redmond, WA). Statistical analysis was performed using a statistical software program, MedCalc, version 12.6 (MedCalc Software, Ostend, Belgium).

CLINICAL SIGNIFICANCE

- Angiotensin-converting enzyme (ACE) inhibitor angioedema is increasing due to increasing use of these agents, with >150 million prescriptions annually, estimated at 0.2%, which translates to 40,000 cases a year.
- ACE-inhibitor angioedema can occur after prolonged use of these agents.
- Recognition of presenting features such as dyspnea, tongue involvement, longer duration of use, and hypercapnia may identify those at risk for upper airway compromise requiring advanced airway management.

RESULTS

Fifty consecutive ICU patients with ACE-inhibitor angioedema were reviewed. All were male, and 76% were African American; additional details are in Table 1. Only 13 (26%) had been taking the ACE inhibitor for 3 months or less, with 28 (56%) taking the ACE inhibitor for a year or longer.

Table 2 provides a summary of symptoms, diagnostic studies, location of angioedema, and treatment rendered. Dysarthria was the commonly reported symptom in 42%. The diagnosis of angioedema was made with bedside clinical examination in all patients. Lips and tongue were the most commonly affected areas. Corticosteroids were administered to all except one with isolated lip angioedema treated with antihistamines, given concern for a possible allergic reaction. Bradykinin receptor antagonists were not available for use at our institution when these episodes occurred. Concern for incipient or impending airway obstruction and respiratory failure were the main indications for ICU admission.

Table 3 outlines treatment. Fifteen (30%) required either noninvasive or invasive ventilatory support. Of 5 patients treated with noninvasive ventilation, 3 required intubation. Of 13 intubated patients, 2 required tracheostomy. Therefore, 13/15 (87%) were intubated, with only 2 patients able to avert intubation. Arterial blood gases were obtained in 12, 6 who were eventually intubated, with $PaCO_2$ significantly higher in those requiring intubation. Of these 15 patients, angioedema involved the tongue in 12 (75%).

The duration of intubation was 5.23 ± 4.46 days, but most (64%) were intubated for 3 days or less. Almost half (44%) required a day or less in the ICU; 70% were hospitalized for 3 days or less. The average ICU length of stay was 3.42 ± 5.47 days; the average hospitalization was 7.6 ± 13.2 days. One patient died, but not from angioedema, which had resolved at the time of death.

Several logistic regression models were generated and outlined in Table 4. No clinical parameters involving concomitant medications or conditions were predictive of the need for ventilatory support. Dyspnea, but not dysphonia, dysarthria, or dysphagia was associated with the need for ventilatory support ($P < .002$). With respect to the location of angioedema, tongue involvement was the sole parameter associated with ventilatory support ($P = 0.04$). Isolated involvement of the lips was noted in 7 (14%), and none of these patients had progression of their angioedema or respiratory failure. In one model, the duration of ACE inhibitor, dyspnea, and tongue involvement were associated with the need for ventilatory support. Complement studies obtained in 31 (62%) were all normal.

DISCUSSION

ACE inhibitors are the fifth most prescribed agent, with almost 169 million prescriptions written in 2010.[16] While ACE inhibitor-induced angioedema remains relatively rare, the sheer volume of patients transforms an unusual event into a frequent event. A conservative estimate of 20 million patients with 0.2% incidence of angioedema represents 40,000 cases annually. The number of cases of ACE-inhibitor angioedema has been increasing, coinciding with increasing use of these medications.[2] This adverse reaction also may cause unexpected death.[17] Whereas previous investigators have included all patients with angioedema, this study represents the largest series of ICU patients with angioedema.

The typical patient was a middle-aged man of African American ethnicity. Most had been on ACE-inhibitor therapy for over a year. Of 50 patients admitted to the ICU, 15 required some form of ventilatory support. This represents 30% of those with ACE-inhibitor angioedema, and 13 (26%) were eventually intubated. The $PaCO_2$ was significantly higher in those eventually intubated, and relative hypercapnia is another finding that may predict the need for ventilatory support. Those who did not require intubation had a relative respiratory alkalosis on blood gas analysis, which would be consistent with initial hyperventilation associated with upper airway compromise. The 30% intubation rate is a much higher percentage of patients requiring ventilatory support than previously reported, where intubation was <10%.[5,10,12,18] Table 5 provides a comparison of other reported series. No other study reported blood gas data,