Efficacy of Icatibant as Treatment for ACE Inhibitor-Induced Angioedema in Adults: A Systematic Review

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Pacific University

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Efficacy of Icatibant as Treatment for ACE Inhibitor-Induced Angioedema in Adults: A Systematic Review

Abstract

**Background:** ACE inhibitor-induced angioedema is a rare, yet potentially fatal, drug side effect. Considering nearly 40 million people are taking ACE inhibitors for their anti-hypertensive and renal-protective benefits, a significant number of patients are at risk for this drug-induced angioedema. This review was performed to evaluate the efficacy of icatibant as treatment for ACE inhibitor-induced angioedema. Strength of evidence was evaluated using the GRADE tool.

**Method:** An exhaustive search of available medical literature was conducted using Medline, PubMed, ISI Web of Science, EBM Reviews Multifile, and CINAHL. Inclusion and exclusion criteria were applied. At the time of this review, no randomized control trials were published; therefore, this review focuses on case reports.

**Results:** During the exhaustive literature search, only two case reports were found regarding the use of icatibant as treatment for ACE inhibitor-induced angioedema. Both studies included in the review showed substantial reduction in time to complete resolution of symptoms from ACE inhibitor angioedema using icatibant as compared to standard therapy. Only local-site reactions of erythema and pruritus were evident as side-effects from icatibant therapy.

**Conclusion:** Despite the small sample size of the studies, the overall Moderate GRADE outcome, and the limited statistical significance from these observational reports, icatibant appears to dramatically reduce time to: 1) first symptom improvement, and 2) complete symptom resolution of angioedema, as compared to standard therapy. Therefore, the clinical significance of icatibant as a treatment modality for ACE inhibitor angioedema is noteworthy, and should be further investigated by randomized control trials.

**Keywords:** angiotensin converting enzyme, ACE inhibitor, angioedema, icatibant, and Firazyr

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Efficacy of Icatibant as Treatment for ACE Inhibitor-Induced Angioedema in Adults: A Systematic Review

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Biography

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To my friends and family friends: Thank you for understanding how time-consuming PA school has been, and for sticking by me despite the limited time I have been able to devote to keeping in touch. True friends last a lifetime.

To my classmates: Congratulations, we did it! Through hard work, motivation, and teamwork, we reached our goal together. May we all continue along this trajectory to become successful and compassionate PAs.
ABSTRACT

**Background:** ACE inhibitor-induced angioedema is a rare, yet potentially fatal, drug side effect. Considering nearly 40 million people are taking ACE inhibitors for their anti-hypertensive and renal-protective benefits, a significant number of patients are at risk for this drug-induced angioedema. This review was performed to evaluate the efficacy of icatibant as treatment for ACE inhibitor-induced angioedema. Strength of evidence was evaluated using the GRADE tool.

**Method:** An exhaustive search of available medical literature was conducted using Medline, PubMed, ISI Web of Science, EBM Reviews Multifile, and CINAHL. Inclusion and exclusion criteria were applied. At the time of this review, no randomized control trials were published; therefore, this review focuses on case reports.

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**Conclusion:** Despite the small sample size of the studies, the overall Moderate GRADE outcome, and the limited statistical significance from these observational reports, icatibant appears to dramatically reduce time to: 1) first symptom improvement, and 2) complete symptom resolution of angioedema, as compared to standard therapy. Therefore, the clinical significance of icatibant as a treatment modality for ACE inhibitor angioedema is noteworthy, and should be further investigated by randomized control trials.

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INTRODUCTION

Background

Angiotensin converting enzyme (ACE) inhibitors are a type of medication frequently prescribed to patients for the treatment of hypertension, heart failure, and kidney disease. Through a series of complex mechanisms, ACE inhibitors help to decrease blood pressure and improve cardiac output.

Naturally occurring in our body, angiotensin converting enzyme acts to increase blood pressure and to degrade bradykinin – a potent vasodilator and inflammatory modulator (Carey, 2010). Therefore, inhibition of angiotensin converting enzyme leads to lower blood pressure and increased levels of bradykinin (Bingham, 2010). In the presence of ACE inhibition, bradykinin can accumulate and cause vasodilation, increased vascular permeability, and release of nitric oxide (Bingham, 2010). This accumulation of bradykinin, causing vascular permeability, is thought to contribute to the drug side effect of angioedema.

ACE inhibitor (ACEi)-associated angioedema is a rare, yet potentially life-threatening, side effect of treatment with ACE inhibitors (Byrd, Adam, & Brown, 2006). Reactions range from mild to severe swelling of the face, lips, tongue, mouth, larynx, pharynx, soft palate, and subglottic tissue, which can make it difficult to breathe or swallow (Bingham, 2010). ACE inhibitor-induced angioedema occurs in 0.1% to 2.2% of patients, and accounts for 20 to 30% of all angioedema cases presenting to emergency departments in both community and tertiary-care settings (Carey, 2010; Bingham, 2010). The risk for angioedema is greatest in the first month of treatment with an ACE inhibitor; but interestingly, the majority of cases
occur after 1 month of treatment – nearly 1/3 of angioedema cases present more than 6 months after initiation of ACE inhibitor therapy, and some patients have experienced angioedema occurring up to 10 years post-initiation of treatment (Byrd et al., 2006).

The pathophysiology of ACE inhibitor-induced angioedema is similar to that of hereditary angioedema (HAE) in the aspect that they are both mediated by bradykinin (Bas et al., 2010). Studies have shown icatibant – a bradykinin type 2 receptor antagonist – to be effective in the treatment of hereditary angioedema (Byrd et al., 2006). Icatibant has been approved by the European Medicines Agency for the treatment of HAE: 30mg of subcutaneous icatibant demonstrated rapid and stable relief from symptoms in cutaneous, abdominal or laryngeal HAE attacks (Gras, 2009). Since the bradykinin-induced etiology is responsible for most of the symptoms relating to both HAE and ACE inhibitor-induced angioedema, it might be speculated that icatibant could also potentially be effective for ACEi angioedema. However, no randomized control studies have been performed to test the efficacy of icatibant as treatment for ACE inhibitor-induced angioedema.

Currently, no specific or designated treatment regimens exist for ACE inhibitor-induced angioedema. Treatment modalities utilized for ACEi angioedema thus far, include airway support, antihistamines, steroids, and in more severe cases, epinephrine (Byrd et al., 2006). Unfortunately, these treatment options have not always been effective, at times requiring patients to undergo intubation, tracheotomy or cricothyroidotomy (Bas et al., 2010). This risk profile is frightening,
especially considering that these procedures are invasive, and require patients to undergo general anesthesia, which can implicate a host of new complications.

ACE inhibitor angioedema is often overlooked or misdiagnosed, yet it is an important medical emergency because, if untreated, it may develop into a serious life-threatening condition (Bas et al., 2010). Considering that there are nearly 40 million people taking ACE inhibitors (Byrd et al., 2006), many of whom have an increased risk of a potentially fatal drug-induced angioedema, the discovery of a definitive, safe, evidence-based treatment for ACEi angioedema is essential. Icatibant may be the effective, therapeutic solution for ACEi angioedema that physicians need.

Purpose of the Study

The purpose of this paper is to perform a systematic review of the literature regarding the use of icatibant as treatment for ACE inhibitor-induced angioedema using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, developed by the GRADE working group, in order to grade the strength of recommendation (Guyatt et al., 2008).

METHOD

An extensive literature search was performed using Medline, PubMed, ISI Web of Science, EBM Reviews Multifile, and CINAHL databases. These databases were accessed through the Pacific University Library system. The following keywords were searched individually and in combination: “angiotensin converting enzyme”, “ACE inhibitor”, “angioedema”, “icatibant” and “Firazyr”. “Angioedema” was also searched in a title field. The search was limited to human subjects, the
English language, full text articles, and to articles published since the year 2000. The initial search results included two references from Medline, six from PubMed, five from ISI Web of Science, one from EBM Reviews Multifile, and zero from CINAHL. Relevant articles were selected and cross-referenced for additional materials. A total of 14 articles were yielded from these search results. Duplication articles and articles that did not investigate icatibant or Firazyr as treatment modalities for ACE-inhibitor-associated angioedema were then excluded. Limited research is available on this topic. At the time of this review, there were no published randomized control studies. Therefore, this systematic review included the only two studies which were relevant. One study was a case series and one was a case study.

RESULTS

After the exhaustive literature search and application of inclusion and exclusion criteria, only two case report articles remained which met the search criteria. The outcomes of these two case reports included: 1) time to first improvement of symptoms, and 2) time to complete symptom resolution. A total of nine patients were reviewed. In both case reports, all patients were adults, were taking ACE-inhibitors, and had an acute angioedema attack of the head or neck (tongue, larynx, and/or pharynx) of less than 10 hours duration. Angioedema of etiologies other than ACE inhibitor-induced were excluded from the diagnosis. In addition, all nine patients stopped taking their prescribed ACE inhibitors (either ramipril, enalapril, or fosinopril) once this etiology was identified as the cause of angioedema.
Time to First Improvement of Symptoms

Bas et al. (2010) conducted a case series report using eight patients with acute ACEi-induced angioedema, treated with a single, subcutaneous injection of 30mg icatibant. The authors reported that the average time to first symptom improvement of the eight patients after icatibant administration was 50.6 minutes, with a standard deviation of 21 minutes. No other additional interventions were used for these patients. Based on these findings, the authors concluded that administration of 30mg subcutaneous icatibant quickly and reliably reduced time to first improvement of symptoms without necessitating any other interventions.

Schmidt, Hirschl, and Trautinger (2010) described how one adult patient, taking the ACE inhibitor fosinopril, was admitted to the emergency unit with acute ACEi-induced angioedema. Since this patient’s angioedema was refractory to initial treatment with intravenous methylprednisolone, intravenous diphenhydramine, inhaled epinephrine, and infusion of C1 esterase inhibitor concentrate, he was ultimately given a dose of 30mg subcutaneous icatibant. The authors explained that emergency tracheotomy was considered for this patient, but was avoided, because 10 to 15 minutes after the administration of 30mg subcutaneous icatibant, the “situation began to improve” (Schmidt et al., 2010, p.913). The authors concluded that treatment with antihistamines, corticosteroids, and epinephrine is often ineffective in treating ACE inhibitor-induced angioedema. Furthermore, the authors recommend further investigation of icatibant in clinical trials, especially considering that a single dose of 30mg icatibant resulted in rapid symptom improvement and helped to prevent tracheotomy on this patient.
Time to Complete Symptom Resolution

In the case series performed by Bas et al. (2010), complete symptom resolution was assessed by a physician. This study defines complete symptom resolution as the complete recovery from all symptoms of angioedema, and associated with the discharge of the patient from the hospital, with no further drug treatment related to angioedema. Bas et al. (2010) reported that the average time to complete symptom resolution of the eight patients after administration of 30mg subcutaneous icatibant was 4.4 hours, with a standard deviation of 0.8 hours. No other additional interventions were used for these patients.

Also evaluated by Bas et al. (2010) was a historical group of 47 patients, similarly diagnosed with ACEi-induced angioedema, and treated during the previous seven years with methylprednisolone and clemastine. The authors considered these 47 patients to be the control group. In this group of patients, the mean time to complete symptom resolution was 33 hours, with a standard deviation of 19.4 hours. Some of these patients underwent tracheotomy, were intubated, or received a second administration of corticosteroids (250-500mg methylprednisolone) due to symptom persistence or worsening. The authors concluded that administration of 30mg subcutaneous icatibant resulted in quicker time to complete symptom resolution than standard therapy. Thus, for a more effective achievement of complete symptom resolution from ACEi-induced angioedema, the authors recommend 30mg subcutaneous icatibant.

Schmidt et al. (2010) explain in their case report that the one adult patient with acute ACEi-induced angioedema due to fosinopril experienced complete
resolution of airway obstruction within 10-15 minutes after injection of 30mg subcutaneous icatibant. The authors concluded that, a single dose of 30mg subcutaneous icatibant results in rapid and complete symptom resolution, and should be investigated further in clinical trials as a treatment modality for ACE inhibitor-induced angioedema.

Additional Study Information

Bas et al. (2010)

For all ACEi-induced angioedema patients, the authors found no sign of inflammation such as increased leukocyte count or increased body temperature, and there were no signs of infection during hospitalization.

All patients in this study who were treated with icatibant developed mild, local injection-site reactions of erythema and pruritus; yet these local reactions resolved spontaneously within approximately two hours. A 3-6 month follow-up stage after the study’s completion revealed no systemic or serious adverse events. Unfortunately, no records were kept as to how and when follow-up was conducted.

In all patients in this case study, including the historical group, a flexible trans-nasal fiber-optic laryngoscopy was performed hourly to monitor edematous mucosa until symptom relief was achieved.

Schmidt et al. (2010)

This study focused on one 42-year-old caucasian male taking the ACE inhibitor fosinopril. Normal levels of C4 in this patient ruled out hereditary angioedema, and no other etiology of angioedema was elucidated, except for the ACE inhibitor. The patient’s angioedema was refractory to treatment with
antihistamines, corticosteroids, and epinephrine. Although the patient’s angioedema was responsive to 30mg subcutaneous icatibant, the authors did not address any adverse drug reactions or side-effects of icatibant therapy. No follow-up was mentioned at all for the patient in this study. The authors did not assess signs of inflammation, infection, or use a laryngoscope to monitor edematous mucosa, as compared to Bas et al. (2010).

DISCUSSION

ACE inhibitor-induced angioedema is a rare, yet potentially fatal, side effect of taking a commonly prescribed anti-hypertensive medication. Bas et al. (2010) demonstrated that in all eight patients with ACEi-induced angioedema, a simple subcutaneous injection of 30mg icatibant resulted in an average time to first improvement of symptoms within 50.6 minutes, and an average time to complete resolution of symptoms within 4.4 hours. Comparatively, time to complete resolution of symptoms in the historical control group in this study, who had been prescribed standard treatment modalities of methylprednisolone and clemastine, had an average time to complete resolution of 33 hours. Therefore, patients who received 30mg subcutaneous icatibant injection in this study experienced complete symptom resolution 7.5 times faster compared to standard therapy. This dramatic difference in time to complete symptom resolution can equate to an issue of life versus death for a patient.

Schmidt et al. (2010) described how one adult male with ACEi-induced angioedema had tried all initial standard treatment modalities including corticosteroids, antihistamines, epinephrine, and a C1 esterase inhibitor, and he
was about to undergo emergency tracheotomy, when one subcutaneous injection of 30mg icatibant resolved his symptoms within 10-15 minutes. Quicker symptom resolution not only means improved quality of life, but also reduces the chances of patients needing to undergo surgical operations or general anesthesia, which can increase morbidity, extend hospitalization, increase chances of infection, and increase healthcare cost.

One of course must consider the possible side effects of drug intervention. Indeed, icatibant has been shown to have side effects. Fortunately, these drug reactions appear to be minimal and brief, and include only local-site reactions of erythema and pruritus, which are extremely tolerable, considering the alternative of ultimate tracheal intubation or tracheostomy. No serious adverse events were associated with administration of icatibant.

Limitations

Limitations in these studies do exist. In particular, the limited patient population (sample size) results in a low power and low probability of statistical significance. The results of observational studies, such as these case reports, do not meet the level of rigor that randomized control trials contain. Unfortunately, no randomized control trials regarding icatibant as treatment for ACE inhibitor-induced angioedema were elucidated from the extensive literature search. Additionally, the only ACE inhibitors that patients were taking in these case reports were ramipril, enalapril, and fosinopril. Further research should be performed to delineate whether icatibant is effective at treating any type of ACE inhibitor-induced angioedema, regardless of which ACE inhibitor is prescribed. An additional
limitation includes the fact that there was no specificity with regard to the follow-up of patients. Bas et al. (2010) mentioned a follow-up period of 3-6 months after the study’s completion, but failed to specify how this was conducted; and Schmidt et al. (2010) did not address any follow-up protocol. These points should be considered if a prospective, randomized control trial is performed.

GRADE

To grade quality of evidence and strength of recommendation, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool, developed by the GRADE working group, was used (Guyatt et al., 2008). The comparison was icatibant versus standard therapy for treatment of ACE inhibitor-induced angioedema (Appendix: Table 1). GRADE was applied to two outcomes: 1) time to first improvement of symptoms, and 2) time to complete symptom resolution.

Time to first improvement of symptoms

Using the first outcome of time to first improvement of symptoms, two case studies were used. Based on the study design of observational studies, which are inherently categorized as low quality of evidence, the two case reports used for this systematic review were evaluated with a starting grade of “Low.” As defined by the GRADE working group, “Low” quality of evidence means: “further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate” (Guyatt et al., 2008, p. 926). Only outcomes with the initial GRADE of high can be down-graded based on study quality, consistency, directness, precision or publication bias. Outcomes with an initial GRADE of low
can be upgraded. No increase in GRADE was awarded further for dose-response or confounders; however, based on large magnitude of clinical significance, the GRADE was updated to “Moderate”, which is defined as: “
further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate” (Guyatt et al., 2008, p. 926).

Time to complete symptom resolution

Using the second outcome of time to complete symptom resolution, the same two case studies were examined. Similarly, based on study design, the two case reports were evaluated with a starting grade of “Low.” No increase in GRADE was awarded further for dose-response or confounders. Nevertheless, the GRADE was updated to “Moderate” based on large magnitude of clinical significance.

Based on criteria established by GRADE working group, the overall GRADE of evidence of the systematic review, across all outcomes, was “Moderate”.

Conclusion and Implications for Practice

Despite the limitations and the overall Moderate GRADE outcome, the clinical significance of this review is remarkable and noteworthy. If one single, subcutaneous injection of 30mg icatibant can substantially reduce the time of complete symptom resolution from 33 hours to 4.4 hours, eliminate the need for surgical intervention or general anesthesia, decrease morbidity and mortality for patients, and cause no systemic or serious adverse events, then this drug should certainly be evaluated for approval to be used as first-line treatment for ACE inhibitor-induced angioedema. A prospective, randomized control trial should be performed to confirm the findings of these observational studies.
REFERENCES


# APPENDIX

## Table 1: GRADE Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Starting grade</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Grade of Evidence for Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icatibant vs. standard therapy for ACE inhibitor-induced angioedema</td>
<td>Time to first improvement of symptoms</td>
<td>2 case reports</td>
<td>Positive</td>
<td>Low</td>
<td>0 0 0 0 0</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Time to complete symptom resolution</td>
<td>2 case reports</td>
<td>Positive</td>
<td>Low</td>
<td>0 0 0 0 0</td>
<td>+1</td>
<td>0</td>
</tr>
</tbody>
</table>

Overall GRADE of Evidence: **Moderate**