

Clinical features of angioedema induced by renin-angiotensin-aldosterone system inhibition: a retrospective analysis of 84 patients

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ABSTRACT

Background and objectives: Bradykinin-mediated angioedema (AE) induced by antihypertensive drugs primarily affect the head and neck region and may occur even after several years of uneventful treatment. Many facts about the clinical course remain unknown. Diagnosis is not easy, as the clinical appearance resembles allergic AE. No specific diagnostic markers are known and no officially approved treatment is currently available.

Methods: All patients who presented to the ORL department between 2010 and 2016 with acute AE were included. Those with a history of renin-angiotensin-aldosterone system (RAAS) blocker intake were defined as RAE and their pathophysiological characteristics and clinical course of the disease were analyzed.

Results: A total of 84 patients (median age of 71 years) with RAE was identified. The majority (80%) was on ACE inhibition. The oral cavity was most often affected. Nearly 60% were medicated for more than 1 year before AE occurred. RAE occurred more often during the morning hours. The necessity for emergency intubation and/or tracheostomy was nine times higher in patients with acute RAE compared to patients with AE due to other reasons.

Conclusions: Event-free, long-term therapy with an RAAS blocker before the first development of edema does not exclude RAE. RAE is associated with an increased risk for emergency airway management.

Abbreviations ACE: Angiotensin Converting Enzyme; ACEi AE: ACE inhibitor-induced angioedema; AE: Angioedema; ARB: Angiotensin II receptor 1 blocker; C1 INH: C1 Inhibitor; CI: Confidence Interval; CRP: C-reactive protein; DPP IV: Dipeptidyl peptidase IV; ENT: Ear, Nose and Throat; HAE: Hereditary Angioedema; ICD 10: International Statistical Classification of Diseases and Related Health Problems, 10th Edition; OR: Odds Ratio; ORL: Otorhinolaryngology; RAAS: Renin-Angiotensin-Aldosterone System; RAE: RAAS-blocker-induced angioedema

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1. Background

The first publication regarding angiotensin-converting enzyme (ACE) inhibitor-induced AE (ACEi AE) appeared approximately 40 years ago [1]. ACE inhibitors work by blocking the conversion of angiotensin I into angiotensin II and inhibiting the degradation of the vasoactive tissue hormone bradykinin. The increasing levels of bradykinin in turn lead to the development of AE without pruritus or wheals [2]. During the last 40 years, more cardiovascular drugs have been identified which may induce non-allergic AE; treatment with blockers of angiotensin II type 1 receptors (ARB) and renin inhibitors can also lead to this side effect. Almost

all AE caused by RAAS-influencing drugs, such as ACE inhibitors or ARB, are localized in the head and neck area (tongue > lips > pharynx/larynx) [2,3]. However, reports of gastrointestinal manifestations appear in the literature as well [4,5]. The risk for the development of AE increases when drugs that interfere with the degradation of bradykinin are prescribed as concomitant therapy to ACE inhibitors or ARB. Examples are dipeptidyl peptidase IV (DPP IV) inhibitors, e.g., Saxagliptin, and Neprilysin inhibitors, e.g., Sacubitril [3].

AE occurs in 0.5% of the patients with ACE inhibitor treatment [6]. According to Kostis et al., the incidence of ACEi AE is higher in women, older patients, smokers, and African Americans [7]. ACEi AE can develop at any

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Practice Points

- Angioedema induced by renin-angiotensin-aldosterone system inhibition (RAE) shares clinical features with allergic angioedema but needs a different acute treatment.
- RAE affects most often the oral cavity and can appear even after years of uneventful treatment with the renin-angiotensin-aldosterone system influencing drug.
- The risk for intubation and/or tracheostomy was nine times higher in patients with RAE in comparison to patients with acute AE due to other reasons.

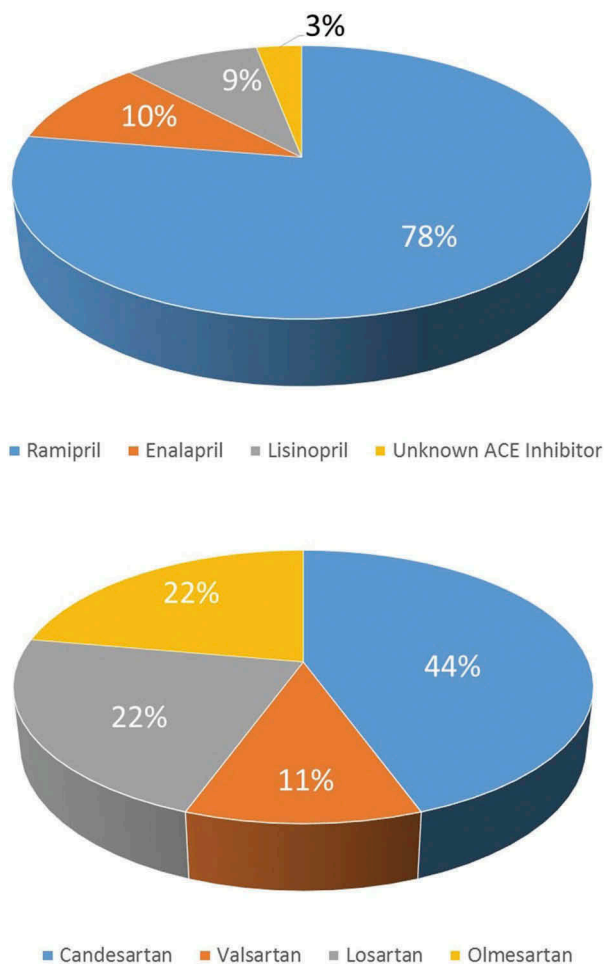


Figure 1. Percentage distribution of the regular intake of (a) ACE inhibitors (n = 67) and (b) ARB treatment (n = 9).

time during therapy with ACE inhibitors. The incidence of AE increases within the first week of treatment, but it can occur even after several years of uneventful intake of an ACE inhibitor [8,9]. ACEi AE develops due to the reduced degradation of bradykinin, which increases vascular permeability and induces vasodilation via bradykinin 2 receptor [10]. Nevertheless, the individual trigger factors that lead to the development of ACEi AE after an undefined period of time remain in most of the patients unclear. Certain circumstances were discussed to increase the risk for the development of ACEi AE: these include transplant patients, patients with immunosuppressant use and seasonal allergies [11].

No diagnostic markers for RAE are known, excepting the clinical presentation without pruritus and without wheals. However, a distinction between the different causes of AE based purely on the clinical presentation, especially in an emergency, is difficult. The cross-reactivity between ACE inhibitors and ARB concerning the risk of AE is another topic frequently discussed in the literature. A recent Danish publication found no increased incidence of AE in patients with a history of ACEi AE on ARB treatment compared with other antihypertensive drugs such as beta-adrenergic or calcium channel blockers [6].

To date, there is no officially approved treatment for ACEi AE and it is often treated as allergic AE with corticosteroids and/or antihistamines. In other bradykinin-mediated diseases, e.g., hereditary AE (HAE), this treatment has shown to be generally ineffective [12]. Due to contradictory study results, there is a roiling debate in current publications regarding the therapeutic effect of bradykinin receptor 2 blockers and C1 Inhibitor (C1 INH) concentrate in ACEi AE [2,13,14]. Both are licensed for the treatment of acute AE in HAE patients.

Although the pathophysiology of AE induced by ARB is still unknown, these drugs have been shown, in both animal and human investigations, to influence the degradation of bradykinin [3]. As with ACE, the incidence of AE induced by ARB appears to be low. In the 'Losartan Intervention For Endpoint reduction in hypertension study', an incidence rate of 0.2% was detected [15,16]. In these cases too, only off-label therapeutic options are available for acute treatment of AE. In a case series with eleven patients, the bradykinin 2 receptor blocker Icatibant was shown to be an effective therapeutic option. Full symptom recovery was achieved after 5 to 7 h, whereas symptom remission occurred between 27 and 52 in patients treated with Solu-Decortin Prednisolone/Clemastine and 24 to 54 h in untreated patients [17].

The renin inhibitor Aliskiren has also been implicated in the induction of acute AE, but here too the pathomechanism remains unclear. The influence on RAAS is evident, but it is not known how, if at all, bradykinin is affected. In 2015, Joseph et al. showed in vitro that renin inhibition has no effect on the rate of bradykinin degeneration in plasma, but that there has to be another unknown catalyst with influence on employing vascular endothelial cells [18]. A cohort study with more than 3 million hypertensive patients in the USA found an incidence rate of 1.71/1000 person-years for the development of acute AE in patients with Aliskiren monotherapy [19].

In the department of otorhinolaryngology (ORL) at our University Hospital, a RAAS blocker-induced AE (RAE) diagnosis is suggested for patients who present with acute AE of the upper aerodigestive tract without pruritus or wheals if allergic reactions are unlikely, there is no family history of AE, and ACE inhibitors, renin inhibitors, and/or ARB are among their regular treatment.

2. Methods

To identify patients with RAE, we searched in the electronic patient record of the department of ORL at our University Hospital with the terms 'angioedema', 'angioneurotic edema' and the ICD10 Code 'T78.3'. In our study, we included all patients who presented

an acute first-time RAE attack to the ORL department from 01.10.2010 until 31.09.2016.

We performed a retrospective analysis of the patients' clinical courses and clinical characteristics (sex, age, medication, co-medication, duration of treatment, localization of edema). Standard laboratory values were also evaluated, including C-reactive protein (CRP). In addition, we attempted to correlate the onset of AE to both the time of day and the time of year to uncover potential trigger factors and pathophysiology. Statistical analysis was performed using SPSS® Statistics Version 24. The odds ratio (OR) and 95% confidence interval (CI) were calculated with a significance level $p = 0.05$.

3. Results

Of all patients with acute first-time AE who presented to the ORL department during the period of 6 years, 41% were diagnosed with RAE (84 of 203 patients). ACEi AE was diagnosed in most of these cases (80%, 67 of 84 patients). In 11% (9 of 84 patients), AE was induced by ARB treatment, and by renin inhibitors in 2% (2 of 84 patients). Seven percent of the patients (6 of 84 patients) had more than one regular treatment which influence the RAAS: four of the patients had ACE inhibitor and DPP4 inhibitor treatment, and two patients were simultaneously treated with an ACE inhibitor and ARB.

Of the 67 patients with ACEi AE, 52 (78%) took the ACE inhibitor Ramipril as a regular medication. In two cases, the ACE inhibitor could not be specified retrospectively due to insufficient documentation. Among patients with AE due to ARB treatment, intake of Candesartan was most frequently identified (4 of 9 patients, 44%) (Figure 1).

In 34 cases (41%), we retrospectively analyzed the period of treatment of the AE-inducing drug. Twenty patients (59%) were medicated for more than 1 year before AE occurred. The median age of all patients with RAE was 71 years (43–94 years), and only six patients were younger than 50 years old. Forty patients (48%) were female and 44 patients (52%) were male.

In the majority of patients (63 of 84 patients, 74%), the oral cavity was affected. Figure 2 summarizes the affected parts of the body.

Furthermore, we analyzed whether the time of the year and/or time of day had any influence on the onset of RAE (Figure 3(a,b)). Morning was defined from 5 am to noon, midday from noon to 6 pm, evening from 6 to 11 pm and night from 11 pm to 5 am. Due to the retrospective character of the analysis and because of insufficient documentation, it was only possible to precisely identify the time of day when the first symptoms of AE occurred in 30 cases (36%).

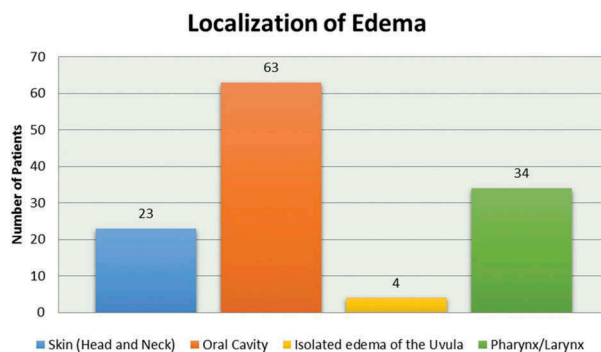


Figure 2. The affected body region of RAE; total amount exceeds 100% due to the possibility of edema affecting more than one area; $n = 84$.

In our ORL department, regular working hours are from 7:30 am to 4:45 pm. In 81 cases, it was retrospectively possible to determine the exact time of arrival in our ORL department. Almost 60% of the patients with acute RAE (48 patients) presented outside the regular working hours.

We focused on the patients' CRP levels at the time of acute RAE. In eleven cases (13%), the CRP value remained unclear. Of the remaining 73 patients (87%), 50 patients (69%) were abnormally elevated (above 5 mg/l). Figure 4 summarizes the results.

In 71 patients with RAE (85%), the therapy consisted of corticosteroids (mostly Prednisolone-21-hydrogen-succinate, Solu-Decortin®H 250–500 mg i.v.), antihistamines (in most cases, Dimetindene 4 mg and Ranitidine 50 mg i.v.), and inhaled Epinephrine. This treatment complies with the standard anti-allergic therapeutic concept of the department. Eleven patients (13%) were treated with C1 INH i.v. or the bradykinin 2 receptor blocker Icatibant s.c. in addition to the anti-allergic medication.

The decision to treat with specific antibodykinin medication was a lack of symptom improvement [20]. In six patients (7%), intubation was required, and three patients (4%) received a temporary tracheostomy due to upper airway stenosis. The risk for intubation and/or tracheostomy was 9 times higher in patients with RAE in comparison to patients who presented to our department with acute AE due to other reasons (OR 9,077; 95%-CI: 1,072–76,859).

4. Discussion

The importance of analyzing the clinical course and pathogenic mechanisms of RAE results from the need to identify predictive markers and characteristics to improve the diagnosis of and therapy for this potentially life-threatening side effect. As ACEi AE has the highest incidence among RAE, research into this side effect has proceeded further than ARB-induced AE or AE due to Renin inhibition. Therefore, the focus of the following discussion is ACEi AE.

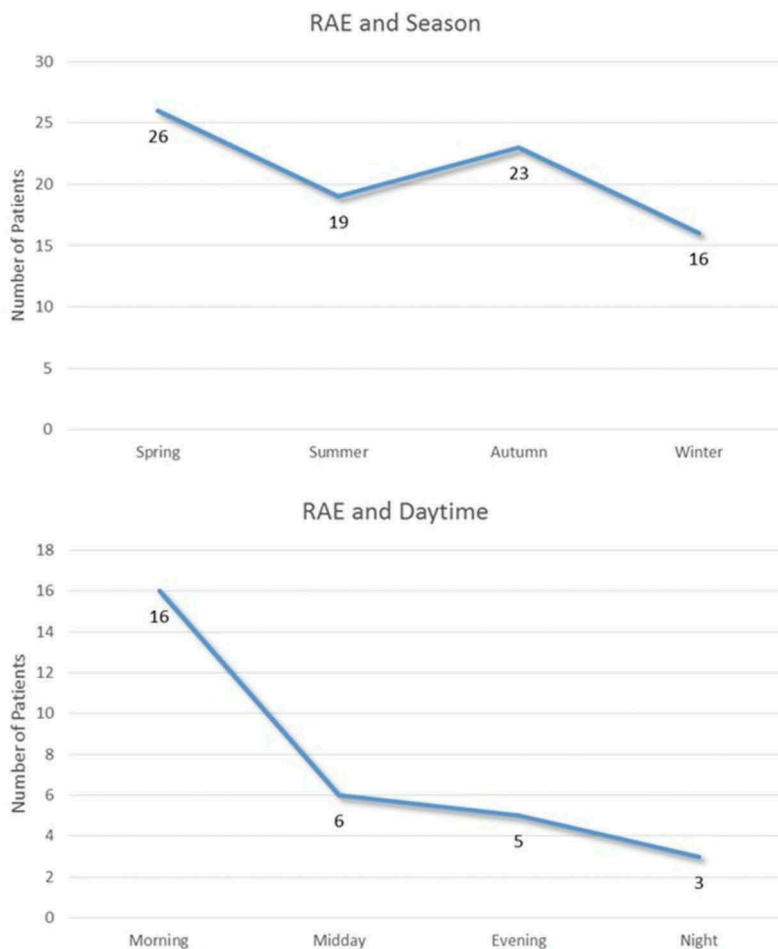


Figure 3. The influence on the onset of RAE concerning the time of the year (a) and time of day (b).

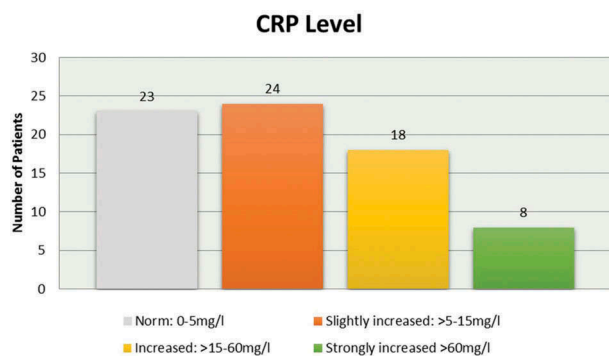


Figure 4. CRP levels at the time of acute RAE, n = 73.

Although ACEi AE is a very rare side effect of ACE inhibitors, it is the most common cause of AE seen in the emergency department, accounting for almost one-third of patients with acute AE in a US medical record review with five emergency departments [21]. In our analysis, the number of ACEi AE was comparable (33% of all acute AE; 67 of 203 patients). When discussing the significance of ACEi AE it is important to consider, despite the low incidence of less than 1%, that ACE inhibitors are still taken regularly by millions of patients [22].

In the present study, more than three-quarters (78%, 52 of 67 patients) of patients with ACEi AE took Ramipril

as a regular medication. Concerning the most commonly prescribed ACE inhibitor, fundamental differences are found between different regions. We want to clarify in this context, that our result does not indicate, that the intake of Ramipril results in a higher incidence of AE in comparison to other ACE inhibitors. In one of the largest studies regarding the incidence of ACEi AE among those initiating ACE inhibitors – a national study of 195,192 veterans receiving health care from the US veterans affairs health-care system – the mainly prescribed ACE inhibitor was Lisinopril (72%), followed by Fosinopril (22%), and Captopril (6%). The relative risk was elevated for all three ACE agents individually (Lisinopril: 3.63, CI 2.34–5.48; Fosinopril: 3.45, CI 2.06–5.46; Captopril: 2.20, CI 1.08–3.95). The risk appeared to be comparatively lower for Captopril, but the differences were not statistically significant [23].

ACEi AE can develop at any time during the treatment course. It has been stated in the literature that the onset of AE is most common soon after the initiation of ACE inhibitor therapy. In a Swedish analysis with 36 Swedish patients, 77% experienced acute ACEi AE within 3 weeks after the first intake of the drug [24]. The results of other studies were somewhat lower with approximately 60% of the patients experiencing ACEi AE within the first week of

treatment [25]. Banerji et al. discussed this matter recently; in a large retrospective cohort study with 134,945 patients treated with the ACE inhibitor, 0.7% developed ACEi AE during the first 5 years of intake. Only 10% of the patients developed ACEi AE within the first month and the annual rate after the first year of ACE inhibitor prescription was largely stable [26]. Comparable to our results – more than half of the patients were treated with an ACE inhibitor for more than 1 year before AE occurred – the data indicates that ACEi AE is a potential diagnosis even after years of uneventful treatment [8].

In this context, the pathomechanism, molecular markers and potential trigger factors for the development of RAE are crucial but to date are not known, respectively, understood. Bas et al. found increased CRP levels in a retrospective cohort study of 25 patients with ACEi AE. At the symptomatic stage, all patients with ACEi AE had significantly increased CRP plasma levels and fibrinogen in comparison to normal values found in patients with AE of unknown cause. In addition, the differences disappeared after successful treatment of the AE [27]. In our retrospective analysis, 69% of the patients (50 of 73) were found to have abnormal CRP levels, so it remains conceivable that inflammatory stimuli can lead to or support the development of ACEi AE in some patients. Based on a murine study which showed that inflammatory stimuli can induce the release of kininogens and CRP from the submandibular gland, Bas et al. presumed that pharyngeal CRP release can accelerate the local inflammation and subsequently lead to AE [27,28]. This may also partially explain why ACEi AE is almost exclusively located in the upper aerodigestive region. According to previous studies, more than half of the patients in our analysis had involvement of the oral cavity [29,30]. As previously mentioned, several case reports exist regarding ACEi AE located in the gastrointestinal tract [4,5]. It still appears to be a very rare manifestation of ACEi AE and it remains unclear why AE in HAE patients, which is also mediated by the tissue hormone bradykinin, is predominantly localized in the abdomen and extremities [31]. In our study, gastrointestinal manifestation of ACEi AE did not play a role, as exclusively patients who presented to the ORL department were analyzed.

It is also important to discuss the diagnosis of patients with isolated edema of the uvula. Acute AE that affects only the uvula is often snoring induced but can also be triggered by drugs or an allergic reaction [32,33]. In these cases, the diagnosis is challenging and cannot be definitively proven. To date, there is still no method to distinguish RAE from snoring-induced AE. Based on the patient's anamnesis (presence of snoring, obstructive sleep apnea, allergies, etc.), the treating physician establishes the most probable diagnosis.

To identify potential trigger factors of RAE, we analyzed the timing of occurrence. To our knowledge, this is manuscript belongs to the first works to correlate RAE with the time of the year and time of day. No correlation between the time of the year and the onset of RAE could be determined, but there was a tendency toward increased incidence of the first symptoms in the morning hours (5 to 12 am). Further research is required to determine whether hormonal factors and/or the time of medication intake may influence the onset of RAE. Limitations resulting from the retrospective setting of our study prevent further clarification of these points at this time.

The current therapeutic options of RAE are insufficient and unsatisfying as only off-label therapy options are available and previous study results are incongruent [2,13,14,34].

Our results show that almost 60% of the patients with acute RAE (48 patients) presented outside of regular working hours (7:30 am to 4:45 pm). Therefore, it is of utmost importance that physicians who work in emergency departments are familiar with the clinical presentation of RAE. For our department, we developed an algorithm as a first, strategic, therapeutic approach [20].

5. Conclusions

The incidence of RAE tends to be higher in the morning hours and inflammatory stimuli might trigger the development of AE. The oral cavity is most often affected. The differentiation between mechanically initiated edema isolated to the uvula and drug-induced AE of the uvula is challenging. Event-free, long-term therapy with an RAAS blocker before the first development of edema does not exclude a diagnosis of RAE. Since intubation and tracheostomy are required in some patients with RAE due to acute stenosis of the upper airways, the development of guidelines with strategic approaches for rapid diagnostic and targeted therapeutic management is crucial.

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Competing interests

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Declarations

- Ethics approval and consent to participate: The local ethic committee of the University approved the study.
- Consent for publication: Not applicable.
- Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Disclosure statement

No potential conflict of interest was reported by the authors.

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