Increasing rate of angiotensin-converting enzyme inhibitor-related upper airway angio-oedema

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ABSTRACT

INTRODUCTION: The objective of this study was to evaluate whether the increased use of angiotensin-converting enzyme inhibitors has affected the rate of upper airway angio-oedema (AE). In addition, we evaluated the presentation and treatment of patients with upper airway AE.

MATERIAL AND METHODS: This was a ten-year retrospective study of 112 patients presenting with upper airway AE at The Department of Otorhinolaryngology, Aarhus University Hospital, Denmark. Incidence, presentation and treatment in the 2000-2004-period were compared to those of the 2005-2009-period.

RESULTS: In the ten-year period, we found 112 AE patients of whom 39% were using ACEI. The relative risk of AE was 7.7 ($p < 0.0001$) among ACEI users. We found a 67% increase in AE in 2005-2009 compared with 2000-2004 which corresponds to a similar increase in ACEI use in the Danish population. The most frequent anatomic sites of involvement were the floor of the mouth and/or oropharynx including the base of the tongue. Two patients required intubation upon their arrival to the hospital. None progressed in airway obstruction requiring intubation later. None died.

CONCLUSION: We found an increasing rate of ACEI-related upper airway AE over a ten-year period corresponding to greater use of ACEI in the population. With a relative risk of 7.7 and continuously increasing ACEI consumption, this condition will certainly require future attention and resources as almost one third of patients are admitted to an intensive care unit.

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Angio-oedema (AE) is an acute, localized swelling of the deep subepithelial tissues. AE may occur anywhere on the body but has a predilection for structures in the head and neck causing potentially life-threatening airway obstruction.

Angiotensin-converting enzyme inhibitors (ACEIs), which block the conversion of angiotensin I into angiotensin II and the degradation of bradykinin, were introduced to the treatment of hypertension almost 30 years ago [1]. Whereas the pathway by which ACEIs cause AE remains controversial, the correlation of ACEIs and AE is well-established, and the reported incidence of ACEI-related AE in clinical trials ranges from 0.1% up to 1.82% in black subpopulations [2, 3]. The reaction may occur up to ten years after initiation of ACEI treatment with only a fourth of cases occurring within the first month [4, 5].

Further indications for ACEI therapy have been added over the past decade, including congestive heart failure, coronary artery disease and diabetic nephropathy. This has resulted in a dramatic growth in its use which has increased from 2.9% of the total Danish population in 2000 to 8.2% in 2009, as shown in **Figure 1** [6, 7].

In the present study, we investigated whether the increased use of ACEIs has affected the rate of upper airway AE. In addition, we evaluated the presentation and treatment of patients with upper airway AE.

MATERIAL AND METHODS

The catchment area of The Department of Otorhinolaryngology at Aarhus University Hospital, Denmark (secondary and tertiary care hospital) includes an estimated of 670,000 persons for acute referrals such as those caused by compromised upper airways.

Hospital discharge registries from the Department of Otorhinolaryngology, Aarhus University Hospital, were searched for AE (ICD-10 code T78.3) in the periods 2000-2004 and 2005-2009. A search for oedema laryngis (ICD-10 code J38.4) was added in order not to overlook miscoded AE.

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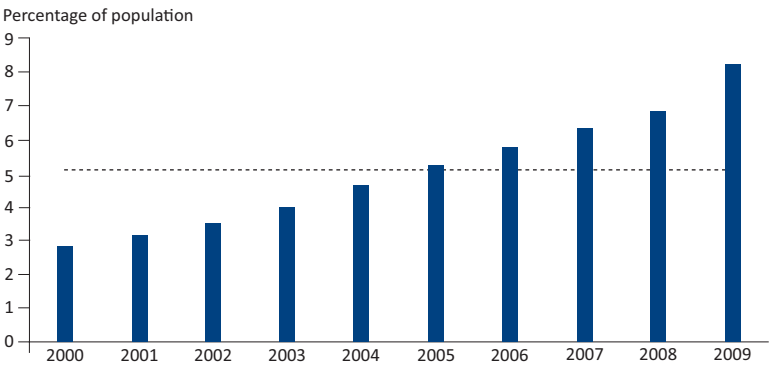
FIGURE 1

Users of angiotensin-converting enzyme inhibitors in the Danish population. The period average is 5.1% (- – -).



Patient records were reviewed retrospectively for referral, known allergies, current medicine, smoking habits, symptoms, previous events, time of year, objective findings, treatment and admission time. Recurring contacts were registered as new single events. Localization of the airway swelling was based on an initial physical examination made by attending doctors from the department and were divided into three categories according to the anatomic sites of involvement as previously described by Chiu et al: Type 1; AE limited to the face and oral cavity, but not the floor of the mouth. Type 2; AE involving the floor of the mouth and/or oropharynx including the base of the tongue. Type 3; AE with oropharyngeal involvement and extension to supraglottic and glottic structures [8]. Former investigators found no patients with isolated supraglottic or glottic involvement. The time of year of the event was divided into winter or summer semester; winter was defined as the period from the beginning of October to the end of March.

Patients with an incorrect ICD-10 code, known hereditary AE or trauma were excluded. In-hospital time and in-intensive care unit (ICU) time were registered as follows: 0-24 hrs = one day, 24-48 hrs = two days, 48-72 hrs = three days and so forth.

TABLE 1

Features of patients with ACEI-related AE compared with non-ACEI-related AE from 2000 to 2009.

	ACEI AE	non-ACEI AE	RR	p value
Patients				
AE, n	44	68	–	-
Male:female, n	1.1:1	1.3:1	0.82	0.597
Age, years (range)	66 (39-84)	45 (2-92)	–	-
Known allergies, n (%)	10 (23)	26 (38)	0.60	0.086
Referral				
Other	0.07	0.07	0.93	0.915
ENT specialist	0.02	0.09	0.26	0.162
Private practitioner	0.25	0.09	2.83	0.020
Mobile emergency care unit	0.09	0.12	0.77	0.655
Emergency department	0.39	0.34	1.14	0.604
Emergency physician	0.16	0.22	0.72	0.424
Unknown	0.02	0.07	0.31	0.244
Symptoms				
Rash	0.02	0.12	0.19	0.071
Dyspnoea	0.20	0.26	0.77	0.467
Dyspnoea prior to evaluation	0.11	0.13	0.86	0.770
Change of voice	0.45	0.28	1.63	0.057
Pain	0.07	0.25	0.27	0.014
Globulus	0.41	0.50	0.82	0.346
Objective findings				
Laboured breathing	0.02	0.06	0.39	0.366
Type 1 AE	0.16	0.13	1.20	0.693
Type 2 AE	0.43	0.35	1.22	0.402
Type 3 AE	0.34	0.35	0.97	0.896
Normal on time of evaluation	0.07	0.16	0.42	0.144
Treatment				
Steriod	0.82	0.88	0.93	0.343
Antihistamin	0.84	0.76	1.10	0.330
Adrenalin inhalation	0.36	0.31	1.18	0.547
Steroid + antihistamin	0.80	0.74	1.08	0.467
Steroid + antihistamin + adrenalin	0.36	0.26	1.37	0.266
Admission to ICU	0.32	0.26	1.20	0.541

ACEI = angiotensin-converting enzyme inhibitor
AE = angio-oedema
ENT = ear-nose-throat
ICU = intensive care unit
RR = relative risk

Statistics

According to an a priori power analysis, we chose a ten-year observation period and divided it into two equal five-year periods. We calculated the frequencies of our recordings in the AE patient groups from 2000-2004 and 2005-2009, respectively. The relative risk (RR) between the two groups was then calculated and a χ^2 test was used to determine any statistically significant difference between the two groups. A two-sided p value < 0.05 was considered statistically significant. Microsoft Excel 2003 was used for all analyses.

Trial registration: not relevant.

RESULTS

In the ten-year period we found 112 AE patients of whom 44 (39%) were using ACEI (**Table 1**). Comparing this proportion to the average 5.1% of the Danish population who used ACEI in the same time period (Figure 1), we calculated a RR for AE of 7.7 (p < 0.0001) among ACEI users.

As seen in **Table 2**, we found a 67% increase in AE in 2005-2009 compared with in 2000-2004. The proportion of ACEI users among patients with AE had more than doubled in the same time period corresponding to an almost doubled percentage of users in the Danish background population. We found a higher percentage of ACEI discontinuation following admission due to AE in 2005-2009 than in 2000-2004-period.

Besides a significantly lower proportion of patients with known allergies and more frequent referral via Mobile Emergency Care Unit in 2005-2009 than in 2000-2004, we found no difference in type of referral, symptoms, objective findings or treatment between the two groups. The record keeping on smoking habits was too inconsistent to allow for analysis.

The most frequent anatomic sites of involvement were AE involving the floor of the mouth and/or oropharynx including the base of the tongue as seen in **Figure 2**. In 13% of our patients, the swelling had resolved at the time of inspection. Sensation of pain seemed to be less common in ACEI patients (RR = 0.27; p = 0.014). Apart from that, we found no difference in the clinical presentation between patients with ACEI and non-ACEI-related AE (Table 1).

The most frequently used ACEIs among AE-patients were enalapril and ramipril, which corresponds with these products representing two thirds of all ACEIs sold in Denmark [7]. The time span from initiation of ACEI to AE was 1-1,825 days. We found no increased risk of AE among patients using angiotensin receptor antagonists (ARBs) (RR = 0.81; p = 0.88).

Furthermore, we found no seasonal variation between the two groups; nor a higher incidence of AE in the winter season compared with the summer season in general (p = 0.28).

Three patients had two episodes of AE during the study period. One repeat episode was due lack of ACEI discontinuation until the second episode. The median admission time was two days. 29% were admitted to an ICU. Two patients required intubation upon their arrival to the hospital. None progressed in airway obstruction in a manner that required later intubation. None died.

DISCUSSION

Upper airway AE is a rare, but severe adverse effect associated with the use of ACEI. We found a significantly increased rate of ACEI-related AE over a ten-year period in a Danish population. This increase can be explained by a corresponding increase in ACEI users in the background population.

The significantly reduced proportion of AE patients with known allergies in 2005-2009 can be explained by a dilution effect caused by the higher proportion of ACEI-related AE in this group, since the incidence is almost stable (20 versus 16 patients). This, however, only applies if ACEI users are less prone to have known allergies, which is speculative.

We confirm an earlier finding from a Danish epidemiologic study by Johnsen et al reporting an AE RR of 10.2 among ACEI users [9]. We calculated a RR of 7.7 and ascribe the small difference to differences in study design [1]. We also confirm their rejection of an association between ARBs and AE. This, however, remains a disputed topic which was most currently addressed in a recent Danish review by Suhrs and Ibsen, who state that the incidence of AE was 0.5-0.8% among ACEI users and 0.1-0.3% among ARB users [10].

In a meta-analysis, Haymore et al concluded that less than 10% of patients treated with ACEIs who developed AE would be at risk of developing AE when subsequently switched to an ARB. Since other antihypertensive agents such as diuretics, alfa-blockers and calcium-channel-blockers also carry a risk of AE, they concluded that ARB can be administered to a patient who has previously experienced ACEI-related AE if the patient is well-advised of the risk of recurrent AE. Suhrs and Ibsen concur with this conclusion [11].

The proportion of the patients using ACEI who AE varies much in international reports. Retrospectively, Zauli et al found that ACEI was the cause of AE in 7.9% of 276 patients in an Italian outpatient clinic of internal medicine. All patients were Caucasians and there were no life-threatening events [12].

Mahoney el al, on the other hand, reports 63% ACEI-related AEs in their five-year retrospective study of 182 patients evaluated by otolaryngologists at the Boston Medical Center. 70% were black patients, and this subpopulation was over three times more likely to have AE due to ACEI than all other groups [13].

Indeed, the settings and the population seem to

TABLE 2

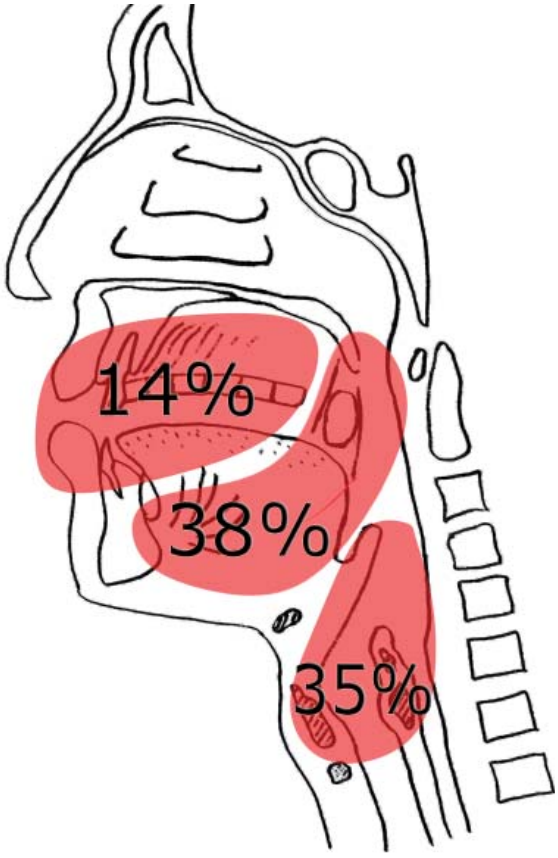
Features of angio-oedema patients from 2000-2004 compared with 2005-2009.

	2000-2004	2005-2009	RR	p
Patients				
AE, n	42	70	1.67	0.008
Male:female, n	1:1	1.4:1	1.18	0.353
Age, years (range)	47 (2-92)	56 (12-84)	–	-
Known allergies, n (%)	20 (48)	16 (23)	0.48	0.007
ACEI, n (%)	10 (24)	34 (49)	2.04	0.009
ACEI users in Denmark,%	4	6	1.78	< 0.001
ACEI discontinued, n (%)	6 (60)	32 (94)	1.57	0.006
Referral				
Other	0.07	0.09	1.20	0.788
ENT specialist	0.02	0.09	3.60	0.190
Private practitioner	0.17	0.14	0.86	0.734
Mobile emergency care unit	0.02	0.16	6.60	0.027
Emergency department	0.40	0.30	0.74	0.257
Emergency physician	0.26	0.16	0.60	0.177
Unknown	0.05	0.07	1.50	0.614
Symptoms				
Rash	0.05	0.09	1.80	0.449
Dyspnoea	0.26	0.23	0.87	0.690
Dyspnoea prior to evaluation	0.17	0.10	0.60	0.302
Change of voice	0.36	0.34	0.96	0.878
Pain	0.26	0.13	0.49	0.074
Globulus	0.45	0.47	1.04	0.845
Objective findings				
Laboured breathing	0.05	0.04	0.90	0.906
Type 1 AE	0.12	0.16	1.32	0.577
Type 2 AE	0.36	0.40	1.12	0.652
Type 3 AE	0.38	0.33	0.86	0.573
Normal on time of evaluation	0.14	0.11	0.80	0.658
Treatment				
Steriod	0.79	0.89	1.13	0.153
Antihistamin	0.76	0.80	1.05	0.634
Adrenalin inhalation	0.24	0.39	1.62	0.108
Steroid + antihistamin	0.67	0.80	1.20	0.115
Steroid + antihistamin + adrenalin	0.21	0.36	1.67	0.111
Admission to ICU	0.26	0.30	1.15	0.666

ACEI = angiotensin-converting enzyme inhibitor
AE = angio-oedema
ENT = ear-nose-throat
ICU = intensive care unit
RR = relative risk

FIGURE 2

Localisation of the angio-oedema.



Type 1 (14%): angio-oedema limited to the face and oral cavity, but not the floor of the mouth.
Type 2 (38%): angio-oedema involving the floor of mouth and/or oropharynx including the base of the tongue.
Type 3 (35%): angio-oedema with oro-pharyngeal involvement and extension to supraglottic and glottic structures.13% had normal findings at the time of inspection.

have much impact on the proportion of ACEI-related AE with non-outpatient-settings and black background population tending to increase the proportion. Our data correspond well with these facts and with international reports.

The Department of Otorhinolaryngology at Aarhus University Hospital primarily serves as a tertiary care unit, and it therefore receives only severe cases of upper airway AE. This explains our low incidence of type 1 AE (14%) compared with 57-64% in other studies including patients from emergency departments [2]. In 13% of our patients, the swelling had already resolved at the time of inspection. This finding underlines the wide variation in AE reactions and raises the question of the amount of patients who seek no treatment for smaller reactions.

The OCTAVE study (Omapatril Cardiovascular TreAtment Versus Enalapril) was a randomized, double-blinded clinical trial including 12,557 persons with hypertension treated with Enalapril (ACEI) in which an incidence rate of 0.68% AE was found over 24 weeks of follow-up [3, 14]. The AE was self-limiting in 51% of the patients, and only 0.02% were admitted to hospital. No patients required intubation, none died.

In a retrospective study with 64 patients and 22% ACEI-related AE, Malde et al found no refractory or progressive incidents of AE. No patients required intubation, none died [5]. They all received steroid and antihistamine in the emergency department, which was also the case for most of our patients. Two of our patients were intubated upon arrival to the hospital. None of the remaining patients progressed to a respiratory state demanding intubation.

Fatalities from ACEI-related AE are extremely rare, with only isolated case reports in the literature mainly involving black people [15]. Despite this, almost one third of all patients presenting with AE in our department are admitted to the ICU. This was only the case for 11% of the patients in a study by Banerji et al [16].

The higher rate of ICU admissions in our study can be explained by the higher proportion of severe (type 2 and 3) AE among our patients due to the causes mentioned above.

The significantly higher percentage of ACEI discontinuation following admission due to AE in 2005-2009 than in 2000-2004 corresponds to an increasing knowledge of the association among clinicians, and the grade of (correct) discontinuation in our study is considerably higher than that reported by Roberts et al, who found only 57% of patients with ACEI-related AE to have the association noted in the medical record [17]. They also report physician error to contribute to 12 out of 23 cases (52%) of recurrent ACEI-related AE. This was only the case in one of three cases (33%) in our study.

To our knowledge, the only study dealing with change of ACEI-related AE over time is a retrospective study by Banerji et al., who found no significant change in the proportion of ACEI-related AE from 2003-2005 in 586 patients presenting with AE in an emergency department [16]. However, no data on background population ACEI-usage was provided, and the shorter time span may possibly explain the insignificant findings.

There are limitations to the present study that should be acknowledged. Because of its retrospective nature, there is a risk of bias due to identification and selection of patients. In addition, the link between ACEIs and AE development is based on the clinical findings including patient history because there is no objective test that can be administered to directly link ACEI use to AE.

CONCLUSION

We found an increased rate of ACEI-related upper air-

way AE corresponding to greater use of ACEI in the population. With a relative risk of 7.7 and a continuously increasing ACEI consumption, this condition will certainly require future attention and resources as almost one third of patients are admitted to an ICU. Fortunately, most doctors have recognized the relation between AE and ACEI as 94% of ACEI prescriptions were discontinued following AE in 2005-2009. ARBs seem to be a safe substitute.

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