J Clin Immunol (2016) 36:95–102
DOI 10.1007/s10875-015-0228-3

ORIGINAL ARTICLE

Angioedema Triggered by Medication Blocking the Renin/Angiotensin System: Retrospective Study Using the French National Pharmacovigilance Database

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Received: 7 July 2015 / Accepted: 14 December 2015 / Published online: 28 December 2015

Abstract
Introduction Bradykinin-mediated angioedema (AE) is a rare side effect of some medications, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). In France, side-effects to treatments are reported to the national pharmacovigilance database.
Methods The national MedDRA database was searched using the term "angioedema". Patients were included if they met the clinical criteria corresponding to bradykinin-mediated AE, if their C1-inhibitor levels were normal, and if they were treated with an ACEi or an ARB.
Results 7998 cases of AE were reported between 1994 and 2013. Among these, 112 met the criteria for bradykinin-mediated AE with normal C1-inhibitor levels. On the 112 drug-AE, patients were treated with an ARB in 21 % of cases (24 patients), or an ACEi in 77 % of cases (88 patients), in combination with another treatment in 17 cases (mTORi for 3 patients, iDPP-4 for 1 patient, hormonal treatment for 7 patients). ENT involvement was reported in 90 % of cases (tongue: 48.2 %, larynx: 23.2 %). The median duration of treatment before the first attack was 720 days, and the mean duration of attacks was 36.6 h. Forty-one percent (19/46) of patients relapsed after discontinuing treatment.
Conclusion Angioedema triggered by medication blocking the renin/angiotensin system is rare but potentially severe, with a high risk of recurrence despite cessation of the causative drug.

Keywords Angioedema · bradykinin · angiotensin converting enzyme inhibitor · angiotensin II antagonist

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Introduction

Angioedema (AE) is a localised subcutaneous or submucosal swelling that spontaneously regresses within a few hours or days [1, 2]. Swelling occurs due to the release of a vasodilation factor inducing an increase in capillary permeability [2].

Medication has frequently been implicated in triggering AE [3–5], and three main types of drug-induced AEs can be defined based on mechanisms causing them [4]. The most common AEs are caused by histamine release, due to allergic or non-allergic reactions [4, 6]. NSAIDs and aspirin have been shown to trigger pseudo-allergic

reactions, linked to an increased synthesis of leukotrienes [1]. Some rarer forms of AE are linked to excess bradykinin synthesis [7]. These bradykinin-mediated AEs have clinical characteristics which differentiate them somewhat from histamine-related AEs, such as absence of urticaria or itchiness and prolonged duration of attacks (more than 24 h) [8].

The main drug class known to induce bradykinin-mediated AE is angiotensin-converting enzyme inhibitors (ACEi) [9]. ACE is involved in bradykinin degradation: its inhibition therefore leads to an excess of kinins [10]. ACEi-induced AE is rare and is only thought to affect between 0.1 and 1 % of all patients treated with this class of drugs [11–13]. Nevertheless, it has been estimated that 20 to 30 million people worldwide are treated with ACEi, which results in a non-negligible incidence of ACEi-related AE [14]. These cases of AE also appear to be associated with severe manifestations, frequently involving the upper respiratory tract, thus presenting a risk of death due to asphyxiation [9].

Some drugs increase the risk of developing ACEi-induced AE. For instance, a recent meta-analysis showed that dipeptidyl peptidase 4 inhibitors (DPP-4i) increased the risk of ACEi-related AE 4.5-fold [15]. DPP-4 is an enzyme with kininase activity: its inhibition therefore has a synergic effect with ACEi, inducing an accumulation of bradykinin. Immunosuppressants, in particular inhibitors of the *mammalian target of rapamycin* (mTOR), have also been shown to increase the risk of ACEi-related AE. It has been suggested that the effect of mTOR inhibitors is linked to a reduction in expression of lymphocyte dipeptidyl peptidase 4, which could therefore produce a similar effect than that of DPP-4i [16].

AEs meeting the clinical criteria for bradykinin-mediated AE, although rarer, have also been described in patients treated with angiotensin-2 receptor antagonists or blockers (ARB) [17–19]. A recent observational, multicentre study [17] reported cumulated incidences of 1.79/1000 for ACEi against only 0.62/1000 for ARB.

Cases of AE have also been described in prostate cancer patients treated with hormone therapies. These AEs appear to occur preferentially in patients previously treated with ACEi [20], although no study has yet evaluated this risk.

As increasing drug-interactions lead to an accumulation of bradykinin, the prevalence of bradykinin-mediated AE is probably higher than described. A better assessment of clinical and prognostic characteristics of this disease might be helpful for physicians. Therefore, we suggest using a computerised database called *Medical Dictionary for Regulatory Activities* (MedDRA) in order to extract specific data on bradykinin-mediated AE.

Methods

This retrospective multicentre study was performed using the *French national pharmacovigilance* database. Authorisation from the regional phamacovigilance centres (RPVC) was sought before searching the computerised MedDRA database (Medical Dictionary for Regulatory Activities) using the term “angioedema”. The confidential use of this data by RPVC was approved by the National Commission on Informatics and Liberty.

In the results returned, patients combining the criteria described in Table 1 were considered as likely cases of bradykinin-related AE. The treatment triggering AE had to be one of the following drug classes: Angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor 2 blockers (ARB). The date of introduction of the treatment involved must have preceded the first episode of AE. The clinical criteria for bradykinin-mediated AE had to be met [8]: absence of urticaria, duration of the attack(s) greater than 12 h without treatment, anti-histamine and corticosteroid therapies must not have been effective during the attack. Finally, results from a weighted assay of C1-inhibitor should have been within the normal range. Among the information listed, in addition to the primary implicated treatment, the presence of another

Table 1 Inclusion criteria for this study

Patient inclusion criteria	
Drug class implicated	ACE inhibitor or ARB
Time of introduction	Prior to the occurrence of AE
Clinical symptoms of bradykinin-mediated AE	1 Duration of the attack >12 h
	2 Absence of urticaria
	3 Absence of improvement upon treatment with anti-histamines and/or corticosteroids
Biological criteria	1 Normal levels of C1-inhibitor
	2 Normal levels of functional C1-inhibitor (if measured)

treatment from the following list was taken into account: DPP-4i, mTORi, recombinant Tissue Plasminogen Activator (rTPA), oestroprogestin contraception, hormone therapy for the treatment of hormone-dependent cancers.

Whilst managing the acute episode, specific treatments were considered efficient if a relief of symptoms was reported by physicians.

All statistical analysis were performed using SPSS software (version 20.0; SPSS Inc., Chicago, Illinois). Quantitative variables were summarised by mean ± SD (standard deviation) and compared by the Student-*t*-test or Mann–Whitney *U* test when appropriate. Categorical data was summarised as count (%) and compared by Chi-Square Test ($\chi 2$) or Fisher's exact test when appropriate. Results were considered significant if the two-tailed *p* value was less than 0.05.

Results

Population Characteristics

The search performed in the *French national pharmacovigilance* database using the term "angioedema" returned 7998 patients. Among these, 7543 were excluded (Fig. 1) for one of the following reasons: no treatment implicated in triggering bradykinin-mediated AE, lack of medical history, not all the clinical criteria for bradykinin-mediated AE present. The remaining 455 patients were therefore considered to have "drug-related" bradykinin-mediated AE. Among these patients, 19 were also excluded : 12 women presented an AE while taking hormonal treatment or oestroprogestin contraception alone (without any other causative drug), one patient presented AE upon treatment with mTORi and another when treated with aliskiren alone, 4 patients had a

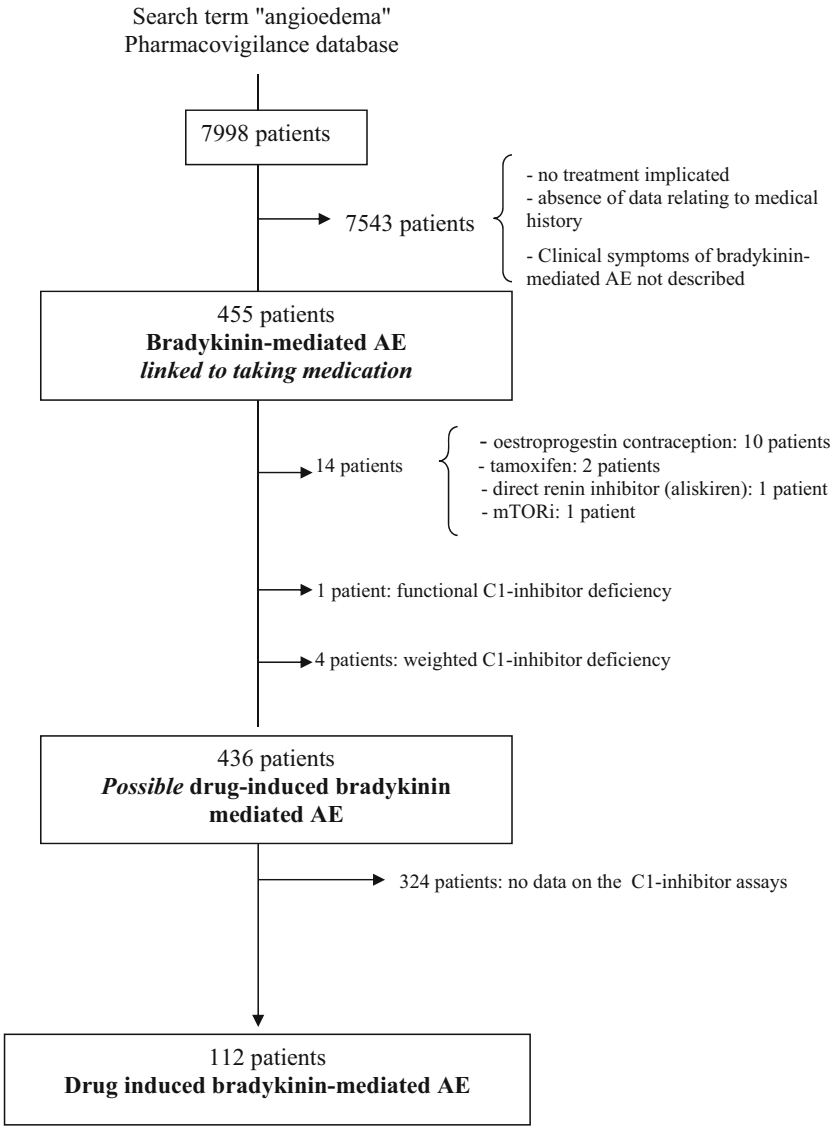


Fig. 1 Flow chart for patient inclusion

reduced C1-inhibitor antigenic level in a weighed assay, and one had a reduced functional C1-inhibitor level.

For 324 out of 436 patients, the descriptive information did not mention whether C1-inhibitor had been assayed or not; therefore these patients were also excluded.

One-hundred and twelve patients had a normal C1-inhibitor level in a weighted assay, and 71 of these patients also had a normal level of functional C1-inhibitor.

In total, 112 patients from all those listed in the database presented a probable drug-related bradykinin-mediated AE: 69 men and 43 women, with a mean age of 65 years (Table 2). Eighty-five percent of these patients had hypertension, and 19 % were diabetic. The comorbidities recorded are shown in Table 2.

Treatments Implicated (Fig. 2)

ACEi (alone or in combination) was responsible for 78.6 % of AE cases (88 patients). The main drugs involved were perindopril (27 patients), ramipril (24 patients) and enalapril (10 patients). In addition to the ACEi, 17 patients were treated with another potentially AE- triggering treatment: a second ACEi for 1 patient, an ARB for 3 patients, a DPP-4i for 1 patient, an mTORi for 3 patients (of which two were also treated with mycophenolate-mofetil (MMF), and one with ciclosporin), or another immunosuppressant (leflunomide, and ciclosporin + MMF combination) for 2 patients. Seven patients were receiving hormonal treatment at the time of the AE attack: 2 patients were taking oestroprogestin contraception (levonorgestrel + ethinyl-oestradiol), 2 patients were treated for prostate cancer with diethylstilbestrol, one with triptorelin and 2 with bicalutamide (Fig. 2).

In 21.4 % of cases (24 patients), AE had occurred with an ARB-based treatment: this was candesartan for 7 patients, valsartan for 7 patients, irbesartan for 5 patients, losartan for 3 patients, or olmesartan for 2 patients. For one patient, the ARB was taken in combination with a DPP-4i.

Location and Characteristics of Attacks

The AE attack was located in the upper respiratory tract in 89 % of cases (100 patients). A lingual location was found in 48.2 % of cases, and a laryngeal location in 23.2 %.

Table 2 Demographic characteristics, comorbidities and concomitant treatments for the sub-group of patients meeting the clinical criteria for "likely bradykinin-mediated angioedema"

Gender N (%)		
Men	69/112 (61.6 %)	
Women	43/112 (38.3 %)	
Age		
< 50	20/112 (17.8 %)	
50–60	22/112 (19.6 %)	
60–70	26/112 (23.2 %)	
> 70	44/112 (39.2 %)	
Comorbidities		Causative drugs involved
AHT	85/100 (85.0 %)	ACEi: 74/85
		ARB: 11/85
Diabetes	19/101 (18.8 %)	ACEi : 16/19
		ARB : 3/19
Heart failure	22/101 (21.7 %)	ACEi : 12/22
		ARB : 10/22
Chronic renal disease	4/98 (4.0 %)	ACEi :4/4
Stroke	5/101 (4.9 %)	ACEi : 5/5
Modifiable cardiovascular risk factor	94/101 (93.0 %)	
History of cancer	14/101 (13.8 %)	
Organ transplant/ BM allograft	5/101 (4.9 %)	
Concomitant treatments		
Aldosterone antagonist	8/93 (8 %)	
Beta-blockers	28/93 (30.1 %)	
Calcium channel blocker	21/93 (22.6 %)	
Platelet aggregation inhibitors	29/93 (31.2 %)	
Statins	25/93 (26.9 %)	

AHT arterial hypertension, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker

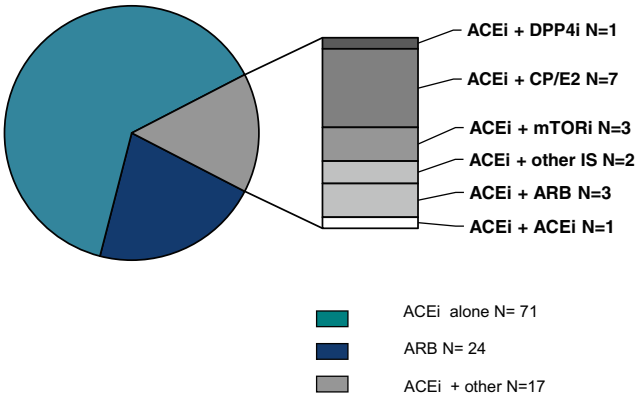


Fig. 2 Distribution of treatments implicated. *ACEi* angiotensin-converting enzyme inhibitor, *DPP4i* dipeptidyl-peptidase 4 inhibitor, *CP/E2* estrogen containing contraceptive pills/ hormone therapy, *ARB* angiotensin-2 receptor blocker

Peripheral and abdominal involvement was noted in 7 and 6 patients, respectively. A single patient presented swelling at the level of external genital organs. There was no statistical difference between drug classes in terms of location of the AE attacks. We can note that patients treated with a combination of ACEi plus oral contraception (or hormone therapy) had a laryngeal location in 42.9 % of cases, versus 21.7 % for ACEi alone. However, this difference was not found to be significant ($p=0.21$). The same analysis performed on a larger group of patients including those for whom C1-inhibitor was not assayed (438 patients) found a significantly different result: 54.5 % laryngeal involvement for the ACEi + hormone therapy combination (11 patients) against 19.4 % for ACEi alone (306 patients).

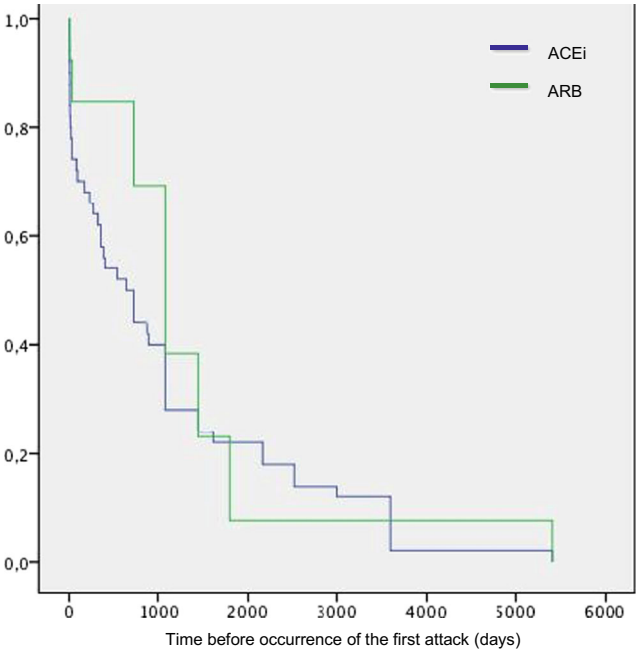
The mean duration of attacks was 36.6 h. In 65 % of cases (information available for 29 patients), symptoms had appeared at night.

Time to Onset of the First Attack

Overall, the median duration of treatment before occurrence of the first attacks was 720 days [1–5400], and the mean duration 1119 days+/− 1304 (individual and combined treatments). In addition, 30 % of patients (23/77) presented their first attack within the first 3 months of introducing the treatment. For patients taking ACEi or ARB (excluding any combination therapy with DPP-4i, mTORi, rTPA and oestroprogestin contraception) there was no statistical difference in terms of the mean time duration of treatment before occurrence of the first attack, according to the log-rank test ($p=0.688$, Graphs 1).

Description of Patients Hospitalised

Forty-five patients had to be admitted to hospital, of which 20 to intensive care units. Swelling was located in the upper



Graph 1 Comparison of the time before occurrence of the first attack for patients treated with ACE inhibitors and patients treated with ARB. The Y-axis shows the percentage of patients who have not yet had an attack of angioedema

airway in 95.6 % of patients admitted to hospital. This was not statistically more frequent than with patients not admitted to hospital (93.3 %; $p=0.732$). Similarly, for other attack locations there was no statistical difference between patients admitted to the hospital and those not admitted.

Eighty percent of patients admitted to hospital were being treated with ACEi, and in 27.7 % of cases, this was associated with another treatment. Patients admitted to ICU frequently had swelling of the larynx (10/20, 50 %) in comparison with other patients (4/26, 15.4 %; $p=0.011$).

Risk Factors and Factors Precipitating Attacks

In 12 % of cases (14 patients), a triggering factor for the AE attack was identified. These triggering factors are as follows: dental treatment (4 patients), orotracheal intubation (1 patient), "other" local stimulation (4 patients: gastroscopy, cauterisation/nosebleed, antiseptic mouthwash, gastro-oesophageal reflux), broncho-pulmonary infection (5 patients).

Management of the Attack

During the episode declared, all patients stopped taking the involved treatment, except for one for whom diagnosis was not made immediately. Forty eight patients were treated with anti-histamines, and 61 with corticosteroids; 11 patients were given parenteral adrenalin.

Only 47 out of 112 patients benefitted from a specific treatment of their bradykinin-mediated angioedema. Among 71 patients treated after 2008 (date at which icatibant was made available in France), 23 (32.3 %) were treated with icatibant. Six patients received C1-inhibitor concentrate, and 18 were given tranexamic acid (Table 3). An emergency tracheotomy had to be performed on two patients.

Of the 23 patients treated with icatibant, 91 % experienced swelling of the upper airway: lingual for 13 patients (59 %), laryngeal for 7 patients (32 %) and the lips for one patient. Two patients were treated with icatibant for abdominal swelling.

Six patients were treated with C1-inhibitor concentrates (Berinert®), all six due to upper airway angioedema (1 for laryngeal involvement, 3 for lingual involvement and 2 for swelling of the lips).

Tranexamic acid was used to treat 18 patients: 88 % presented an upper airway swelling, with laryngeal involvement for 9 of these (50 %), and lingual involvement for 10 (55 %).

Efficacy data was available for 22 patients treated with icatibant, 5 with C1-inhibitor concentrates, and 15 with tranexamic acid. The efficacy of specific treatments (symptom regression) was 100 % for icatibant (22/22 patients), C1-inhibitor concentrates (5/5 patients) and tranexamic acid (15/15 patients). No justification was available concerning the choice of one drug class over another for the management of the acute episode.

Recurrence of Angioedema After Discontinuation of the Treatment

Information was available for 56 patients on their status after discontinuing their treatment: 46 because they had a follow-up consultation and 10 others because they were admitted to hospital for a subsequent attack. Among patients who had a systematic follow-up consultation (46 patients), 27 were treated with ACEi alone (excluding any combination with DPP-4i, mTORi, rTPA or oestroprogestin contraception) and 13 with ARB alone. Among the 27 patients treated with ACEi, 8 had a subsequent attack (29.6 %) while 9 of the 13 patients treated with ARB relapsed (69.2 %). This difference was statistically significant according to the log-rank test ($p = 0.018$, Graph 2).

With ACEi, the recurrence of an attack occurred on average 208.8 days after discontinuation of the treatment (almost 7 months later). 58 % (7/12) had a recurring attack within 3 months and 41 % (5/12) during the first month.

For ARB, the mean time until relapse was 96.1 days. 75 % of patients (6/8) had a recurrence over the first 3 months, and 37.5 % (3/8) during the first month. There was no significant difference between times to recurrence for patients treated with ACEi and those treated with ARB ($p = 0.518$).

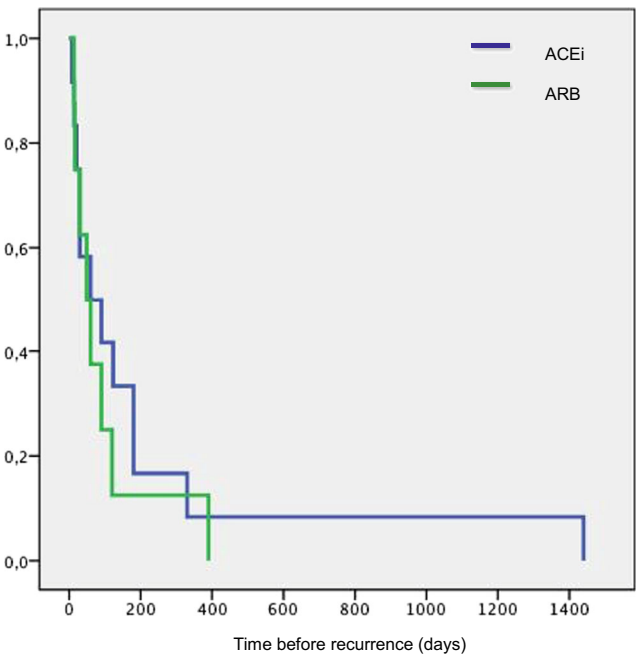
The subsequent AE attacks were milder (57 %) or equally severe (43 %) than the first attack.

Table 3 Management of angioedema attacks

Management of the acute attack	
Hospitalisation	45/57 (78.9 %)
Intensive care unit	20/45 (44.4 %)
Discontinuation of the treatment implicated	110/111 (99.0 %)
Non-specific treatments	
Anti-histamines	49/90 (54.2 %)
Corticotherapy	61/90 (67,7 %)
Adrenalin	11/90 (12,2 %)
IOT/tracheotomy	2
Specific treatments	
Icatibant (after 2008)	23/71 (32.3 %)
C1-inhibitor concentrates	6/90 (6.6 %)
Tranexamic acid	18/90 (20.0 %)

Discussion

Angiotensin converting enzyme inhibitors (ACEi) have been known to cause bradykinin-mediated AE since they were first released on the market (1981 for captopril) [21]. Following this, other inhibitors of the renin-angiotensin-aldosterone system, including antagonists of the receptor for angiotensin 2 (ARB) were also involved. In 2012, two studies highlighted the low risk of AE when using ARB. In Makani's meta-analysis [22] (35,479 patients followed prospectively), the incidence was 0.11 versus 0.07 % for



Graph 2 Comparison of the time to recurrence for patients treated with ACE inhibitors and patients treated with ARB, who relapsed despite cessation of treatment. The Y-axis shows the percentage of patients who have not yet had a recurrence of their angioedema

the placebo (the difference was not significant). In the series presented by Toh et al. [17] (retrospective study involving 467,313 patients) the relative risk was 1.16 compared to beta-blockers. The rarity of ARB-triggered angioedema could nevertheless explain the lack of significance for these results. In this series, the presence of a normal C1-inhibitor antigenic level was required to retain the diagnosis of drug-related bradykinin-mediated AE. This criterion allows us to eliminate undiagnosed acquired forms of angioedema, due to blood diseases or autoimmune diseases [22], as well as hereditary forms of C1-inhibitor-related. Our study confirms the preferential involvement of the upper airway in drug-related bradykinin-mediated AE - with 90 % of cases (101 patients) showing swelling of this area (48.2 % presented with lingual swelling, and 23.2 % had laryngeal involvement). This data supports those of other series concerning AE induced by ACEi [23, 24]. Angioedemas induced by ACEi have been suggested to be more severe than those induced by ARB [18]. In our study, patients treated with ARB presented a similar clinical picture to those treated with ACEi. Laryngeal involvement in particular, was no less frequent. AE induced upon treatment with anti-androgens has previously been described [25]. In the specific example of prostate cancers, several cases of AE due to oestrogen-derived hormone therapy (such as diethystilbestrol or estramustine) have previously been reported, in particular when this treatment is combined with ACEi [20]. In this study, patients treated with a combination of ACEi and oral contraception (or hormone therapy) had a laryngeal swelling in 42.9 % of cases versus 21.7 % for ACEi alone. However, this difference was not significant ($p = 0.21$). Data relating to management during the acute phase of attacks of drug-related AE are currently available from case reports and small retrospective series. In our series, we note that the majority of patients were given non-specific treatments in the initial stages: corticosteroids and anti-histamines in 80.2 and 74.2 % of cases, respectively. Prescription of these treatments can be explained by the difficulties in distinguishing this disease from histamine-related AE.

Patients receiving these treatments presented upper respiratory tract involvement in 80 to 100 % of cases. Icatibant was systematically effective (22 patients), as was C1-inhibitor concentrates (5 patients) and tranexamic acid (15 patients). It should be noted that the efficacy of specific treatments in our study was judged on the regression of AE symptoms, irrespectively of the time until onset of relief. The apparent efficacy of tranexamic acid or C1-inhibitor concentrates has to be interpreted with caution. Indeed, no placebo-controlled trial evaluated the therapeutic effect of C1-inhibitor concentrates or tranexamic acid in this indication.

In France, the expert consensus recommends first-line treatments with icatibant when there is airway or facial involvement or severe painful abdominal attacks [26]. This is because facial swelling can progress to the larynx in an unpredictable manner, and thus justifies rapid and specific treatment [27]. The choice of icatibant as a first-line therapy is currently based on the data of a double blind phase 2 study in which the median time to the onset of symptom relief was significantly shorter with icatibant than with standard therapy [28].

ACEi-induced AE have the specificity of being able to recur sometime after stopping the treatment. This risk is maximal over the first 4 weeks and appears to persist up to 1 year [29]. In our study, 46 patients were seen for a systematic follow-up appointment after discontinuing the causative drug. Follow-up consultations took place on average 1 year after the attack. Of the 27 patients treated with ACEi, 8 had a recurring attack (29.6 %). This proportion appears to be lower than that in Beltrami's series [29] (111 patients), in which 46 % of patients had a relapse over a similar follow-up period. In 41 % of cases, the recurrence occurred in the first 30 days after stopping treatment with the ACEi. In comparison, in Beltrami's series, 88 % of patients relapsed during the first month. This difference could partially be explained by the difference in cohort sizes between the two studies (111 patients for Beltrami, and 27 patients in this study). To our knowledge, this work is the first to report a risk of recurring attacks after an AE triggered by ARB. It must be underlined that the risk of relapse appears significantly greater for patients whose AE is triggered by ARB than for patients with angioedemas triggered by ACEi (69.2 versus 29.6 %, $p = 0.018$). Given these results, patients who develop angioedema upon treatment with ARB should be clearly informed of the risk of recurrence, and should be closely monitored, similarly to patients whose AE is triggered by ACEi.

A potential bias in our study is that of over-diagnosis of drug-related bradykinin-mediated AE, whether in terms of diagnosis or relapse. Indeed, the distinction between histamine-related AE and bradykinin-mediated AE is mainly clinical: histamine-related AEs are much more frequent, and can sometimes be misdiagnosed as bradykinin-mediated AE.

Given that hereditary angioedema with normal C1-inhibitor (C1inh-HAE) is only described since the 2000s whereas the patients of this study were included from 1991, it is not excluded that some C1inh-HAE patients may have been included in this study, their angioedema attack being triggered by an ACEi intake. Nevertheless, the rarity of this disease makes this risk very low [30].

As there is currently no specific diagnostic test, only medical history and careful clinical examination will allow the practitioner to make the correct diagnosis. Furthermore, limits inherent to the retrospective nature of the study *ie* incomplete data from the database, the lack of standard definition of efficacy may be addressed in this study.

Conclusion

Drug-induced bradykinin-mediated AE is rare but potentially severe, and can lead to a risk of death. A formal biological diagnostic is still needed and would be a prerequisite to establish sound recommandations for the management of ACEi-induced AE. As a result, diagnosis is currently based on a combination of symptoms. Data in this study argues in favour of icatibant efficacy in this indication. The potential therapeutic role of C1-inhibitor concentrates or tranexamic acid has to be clarified. Patients' education is a key element of disease management seeing as there is a high risk of recurrence despite cessation of the causative drug.

Acknowledgments We thank the French National Network of Pharmacovigilance Centers.

Compliance with Ethical Standards

Conflict of Interest The authors declare no commercial or financial conflict of interest.

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