CASE REPORT

Life-threatening angio-oedema after the first dose of an ACE inhibitor—not an anaphylactic reaction

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Accepted 7 May 2016

SUMMARY

We present a case of a 60-year-old Caucasian woman, with no prior history of swellings, who was admitted to a hospital due to life-threatening angio-oedema. She had, the previous day, been prescribed an ACE inhibitor for her essential hypertension. She had taken one tablet at night-time, and awoke in the morning with a swollen face progressing to involve the tongue and throat within a few hours. On arrival at her doctor's office, her voice had altered. Corticosteroids and antihistamine were administered while awaiting an ambulance. Arriving at the emergency department, she had dyspnoea due to increasingly severe angio-oedema of the upper airways. Neither adrenaline inhalations, intravenously administered corticosteroids, atropine nor furosemide were effective and the patient soon become bradycardic. A tracheotomy was performed and the patient was placed on a ventilator. She eventually made a full recovery. It was concluded that she had suffered from life-threatening angio-oedema due to her new medication.

BACKGROUND

ACE inhibitors (ACEIs) are common drugs widely used for renal and cardiovascular disorders. Acquired angio-oedema related to the use of an ACEI (ACEI-AAE) is an uncommon adverse reaction that can lead to life-threatening airway obstruction when affecting the upper airway. The sudden onset of angio-oedema is not due to a classical allergic reaction mediated by histamine, but, rather, a symptom of an increased level of the vasoactive molecule bradykinin.^{1 2} The high number of patients treated with ACEIs (in Denmark, about 9% of the population) and the potential life-threatening clinical picture of angio-oedema make it an important adverse effect to be aware of for both clinicians and patients.

The reported incidence of ACEI-AAE varies from <1% to 6%; the highest incidence was found in black males.^{2–5} In a large patient series from Tai *et al*, 367 patients presented to a hospital because of angio-oedema during a 11-year period. Of those, 168 (48.6%) were prescribed an ACEI. Twelve patients needed intubation but only one required tracheostomy.³

The resemblance of this condition to the much more common clinical picture of histamine-induced angio-oedema means that many patients have been treated as such with antihistamine, corticosteroids and adrenaline. Only after treatment failure does bradykinin-mediated angio-oedema become a valid alternative diagnosis, thereby wasting precious time

for treatment and further diagnostics.¹ In recent years, new medical treatments have been introduced in the treatment of hereditary angio-oedema (HAE), which is a genetic disease characterised by bradykinin-mediated recurrent angio-oedema. Seemingly, these drugs can also be effective in other kinds of bradykinin-mediated angio-oedema. Selective bradykinin B2 receptor antagonists and complement C1-esterase inhibitors are the most promising medical alternatives.^{6–8} Besides, there is an obvious need for a safe pharmacological alternative for angio-oedema to minimise the need for invasive airway management and admission to intensive care units.

CASE PRESENTATION

We present a case of a 60-year-old Caucasian woman who was admitted by her general practitioner (GP) to the local hospital because of acute dyspnoea. The previous day, she had been prescribed an ACEI (enalapril 10 mg once daily) to treat her known essential hypertension. The patient had been treated with an angiotensin-II antagonist for 10 eventless years but switched due to financial

Figure 1 Scar after tracheotomy.

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To cite: Krogh Nielsen T, Bygum A, Rye Rasmussen E. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214364

reasons. She had taken one tablet at night-time and awoke in the morning with a swollen face progressing to involve the tongue and throat within a few hours. She had a history of eczema and possibly urticaria, and therefore suspected an allergic reaction, took an antihistamine tablet (cetirizine 10 mg) and contacted her GP. On arrival at the doctor's office, the patient's voice was altered. The GP summoned an ambulance immediately due to airway obstruction and dyspnoea. The GP administered an injection of corticosteroids (Solu-Cortef 100 mg) and antihistamine (Tavegil 2 mg) while awaiting the ambulance. On arrival at the emergency department, the patient had breathing difficulties and her tongue continuously increased in size. She did not respond to adrenaline inhalations (2 mg in 4 mL NaCl), administered twice, nor to intravenous administered corticosteroids, atropine nor furosemide (Solu-Cortef (200 mg) once, atropine (1 mg) once, morphine (2.5 mg) once and furosemide (40 mg) once). She was therefore taken to the operation room in order to perform an acute tracheotomy (figure 1). Her swelling was extensive, so the consulting anaesthesiologist had to be summoned in order to perform the procedure. There was no department of otorhinolaryngology at the local hospital. The procedure was complicated by bradycardia, possibly caused by hypoxia since no other allergic symptoms were present.

INVESTIGATIONS

Chest X-ray was clear. Complement analysis showed a normal total concentration of C1INH 0.35 g/L, functionality 1.78 akt/n (0.70–1.30 akt/n), C1q 0.36 μ mol/L (0.29–0.60 μ mol/L) and C4c 0.48 g/L (0.1–0.4 g/L). Standard blood tests all came out normal (kidney and liver function, electrolytes, C reactive protein, white cell count).

DIFFERENTIAL DIAGNOSIS

Anaphylactic reaction: no other allergic symptoms were present, such as bronchospasm, abdominal pain, vomiting, urticaria or hypotension.

Hereditary angio-oedema: there was no history of prior swelling episodes. It would be highly unlikely that a patient suffering from hereditary angio-oedema would present with a first attack

at the age of 60 years. The family history was also negative for swelling tendencies, but 25% of patients are carriers of new mutations. Complement tests were normal.

Acquired complement C1-esterase inhibitor deficiency: The patient did not suffer from premalignant nor malignant disease, which can predispose to an increased degradation of complement C1-inhibitor. The complement tests were normal. No further swelling episode has presented after the ACEI was discontinued.

OUTCOME AND FOLLOW-UP

The tracheostomy tube was removed after <8 hours, and the patient made a full recovery.

Subsequently, the patient was referred to the department of dermatology and allergy centre, to rule out complement C1-esterase inhibitor deficiency. The patient was also tested for specific IgE sensitisation, using a standard panel. Owing to the short half-life of bradykinin (about 16 ns), it is difficult to measure and thus no tests have been developed. There is furthermore no specific test to determine ACEI-AAE. ACE activity was not measured because of the test's inability to prove a causal link between ACE-inhibition and angio-oedema. During ACEI treatment, ACE levels will always be low. Coupled with no further incidents and no family history, it was concluded that this patient had suffered from life-threatening ACEI-AAE. Total follow-up was 361 weeks. The patient has shown no evidence of other disease.

DISCUSSION

The development of ACEI-AAE can present itself within a few hours of the first ACEI intake, as in our case, and as late as after 20 years of regular use.^{9 10} With corticosteroid and antihistamine treatment, the mean time until complete resolution is 27.1 hours, and with the use of icatibant (a specific bradykinin receptor antagonist), 8.0 hours.⁶ Few case reports of fatal or near-fatal incidences related to laryngeal or oral ACEI-AAE can be found in the literature.^{2 3 11}

The exact mechanism of ACEI-AAE has not yet been fully revealed, although the nanopeptide bradykinin and possibly

Figure 2 Different points of attack in the bradykinin pathway and relevant pharmaceuticals. C1INH: complement C1-inhibitor concentrate (Berinert, Cinryze and Ruconest). Icatibant (Firazyr). Ecaltantide (Kalbitor, not available in the European Union). Tranexamic acid (Cyklokapron). Attenuated androgens (Danazol, Stanozolol). HK, high molecular weight kininogens; LK, low molecular weight kininogens.

substance P seem to be involved.¹² ACE facilitates the breakdown of bradykinin and substance P, thereby lowering their vasoactive effects (vasodilation, mainly). ACEI therapy thereby causes a rise in bradykinin levels leading to the increased risk of angio-oedema.^{6 13 14}

ACEI-AAE is reported more frequently in individuals of African descent and less frequently in those of Asian ancestry. Researchers have looked for possible predisposing mutations or polymorphisms in genes encoding proteins involved in bradykinin production or degradation. ACE gene polymorphism does not seem to influence the risk of ACEI-AAE.¹³ Low dipeptidyl peptidase-IV antigen concentration and enzyme activity are reported in patients with ACEI-AAE.¹⁵ In black males, two specific mutations of the gene encoding aminopeptidase P and neprilysin have been associated with ACEI-AAE. Seemingly, the genetic predisposition is more of a complex trait. Also, female gender, smoking, age over 65 years and even seasonal allergies, have been identified as risk factors for ACEI-AAE suggesting that the pathogenesis is both genetic and environmental.^{4 16}

The proper treatment of ACEI-AAE is still being debated. Owing to the non-histaminergic reaction in ACEI-AAE, traditional treatment with corticosteroids and antihistamine has limited or no effect. As a result of the involvement of bradykinin in the pathophysiology, it is logical to speculate that drugs developed for treatment of HAE could be effective in ACEI-AAE as well.¹²

A recent phase 2 study concluded that the duration of ACEI-AAE of the upper airways was significantly shorter when patients received icatibant (Firazyr), a selective bradykinin B2 receptor antagonist, than corticosteroids and antihistamine.⁶ Administration of Berinert, a complement C1-esterase inhibitor concentrate, has also shown a treatment potential in early trials, however, a randomised double-blind phase 3 study is ongoing and awaited with great interest (NCT01843530).^{7 8} Ecallantide (Kalbitor), a kallikrein inhibitor, was not found effective in ACEI-AAE.¹⁷ The main obstruction in order to implement new treatment options might be the high economic burden of these drugs. Tranexamic acid and attenuated androgens are drugs used for hereditary angio-oedema, but no studies have been

conducted regarding the efficacy in ACEI-AAE (figure 2). In the Western world, these two drugs are no longer widely used due to more effective treatment regimens as described above, and due to possibly severe side effects of attenuated androgens (liver carcinoma). Further research into the correct medical treatment of life-threatening ACEI-AAE is needed.

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Acknowledgements The authors would like to thank consulting anaesthesiologist Lyng Kirkegaard for critical review of the case. The authors also thank Shire and CLS Behring for their continuous support for research within the field of HAE.

Contributors TKN contributed the idea, writing, correspondence with the patient, and found references. AB contributed in critical review and assessment of the patient. ERR contributed in writing of the case, critical review and found references.

Competing interests AB and ERR have received research grants from CLS Behring, Shire and Viropharma. Furthermore they have received payment for lectures from MSD Norway and Shire. TKN has no conflicts of interests.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cicardi M, Aberer W, Banerji A, *et al.* Classification, diagnosis, and approach to treatment for angioedema: consensus report from the hereditary angioedema international working group. *Allergy* 2014;69:602–16.
- 2 Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J* 2007;97:244–5.
- 3 Tai S, Mascaro M, Goldstein NA. Angioedema: a review of 367 episodes presenting to three tertiary care hospitals. *Ann Otol Rhinol Laryngol* 2010;119:836–41.
- 4 Pare G, Kubo M, Byrd JB, *et al.* Genetic variants associated with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet Genomics* 2013;23:470–8.
- 5 Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2006;26:725–37.
- 6 Baş M, Greve J, Stelter K, *et al.* A randomized trial of icatibant in ACE-Inhibitor–induced angioedema. *N Engl J Med* 2015;372:418–25.
- 7 Nielsen EW, Gramstad S. Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. *Acta Anaesthesiol Scand* 2006;50:120–2.
- 8 Greve J, Bas M, Hoffmann TK, *et al.* Effect of C1-Esterase-inhibitor in angiotensin-converting enzyme inhibitor-induced angioedema. *Laryngoscope* 2015;125:E198–202.
- 9 Norman JL, Holmes WL, Bell WA, *et al.* Life-threatening ACE inhibitor-induced angioedema after eleven years on lisinopril. *J Pharm Pract* 2013;26:382–8.
- 10 Chan NJ, Soliman AMS. Angiotensin converting enzyme inhibitor-related angioedema: onset, presentation, and management. *Ann Otol Rhinol Laryngol* 2015;124:89–96.
- 11 Beltrami L, Zingale LC, Carugo S, *et al.* Angiotensin-converting enzyme inhibitor-related angioedema: how to deal with it. *Expert Opin Drug Saf* 2006;5:643–9.
- 12 Rasmussen ER, Mey K, Bygum A. Angiotensin-converting enzyme inhibitor-induced angioedema—a dangerous new epidemic. *Acta Derm Venereol* 2014;94:260–4.
- 13 Gulec M, Caliskaner Z, Tunca Y, *et al.* The role of ace gene polymorphism in the development of angioedema secondary to angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. *Allergol Immunopathol (Madr)* 2008;36:134–40.
- 14 Nussberger J, Cugno M, Amstutz C, *et al.* Plasma bradykinin in angio-oedema. *Lancet* 1998;351:1693–7.
- 15 Byrd JB, Touzin K, Sile S, *et al.* Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. *Hypertension* 2008;51:141–7.
- 16 Woodard-Grice AV, Lucisano AC, Byrd JB, *et al.* Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet Genomics* 2010;20:532–6.
- 17 Lewis LM, Graffeo C, Crosley P, *et al.* Ecallantide for the acute treatment of angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter, randomized, controlled trial. *Ann Emerg Med* 2015;65:204–13.

Learning points

- The high number of patients treated with ACE inhibitors (ACEI) and the potential life-threatening clinical picture of angio-oedema, make it an important adverse effect to be aware of for both clinicians and patients.
- Dealing with ACEI-acquired angio-oedema, traditional anti-allergic treatment with corticosteroids and antihistamines have limited or no effect.
- The ability to master a difficult intubation and the surgical skill to perform an acute tracheotomy are therefore still the life-saving requirements if all else fails.
- Selective bradykinin B2 receptor antagonists and complement C1-esterase inhibitor concentrate are the most promising medical alternatives.

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