Internal Medicine: Open Access

Bouzerda, et al., Intern Med 2018, 8:3
DOI: 10.4172/2165-8048.1000281

Case Report Open Access

LCZ 696 Induced Fatal Laryngeal Angioedema: A Case Report

Abdelmajid Bouzerda[1*], Amin Ahmindache[1], Hajar Chouaib[1], Laila Bendriss[2] and Ali Khatouri[2]

[1]*Department of cardiology, Military Hospital of Instruction Mohammed V, Rabat, Morocco*

[2]*Department of cardiology, Military Hospital of Avicenne, University Cadi ayyad, Marrakech, Morocco*

[*]**Corresponding author:** Bouzerda A, Department of cardiology, Military Hospital of Instruction Mohammed V, Rabat, Morocco, Tel: 0662854285; E-mail: abdelmaji7@hotmail.fr

Received date: June 11, 2018; **Accepted date:** June 19, 2018; **Published date:** June 22, 2018

Abstract

Although LCZ 696 (Sacubutril/valsartan) induced angioedema is rare, itshazardousness is linked to their predominant oropharyngeal localization which can be life threatening in case of upper airway obstruction due to a tongue or laryngeal swelling, we report a new case of fatal laryngeal angioedema induced by LCZ 696.

Keywords: Sacubutril/Valsartan; Laryngeal oedema; Bradykinin

Introduction

Angiotensin II receptors blockers (ARB) and neprylisin inhibitor: LCZ 696 (sacubutril/Valsartan) is currently a part of the therapeutic arsenal for heart failure with reduced ejection fraction [1]. The PARADIGM trial has shown that this association is well tolerated except in few cases of angioedema. Unlike histaminic angioedema which is most common, LCZ 696 angiodema is related to the accumulation of bradykinin. Its onset is unpredictable and is not related to the dose and duration of the treatment. Its severity is due the asphyxiation risk in case of laryngeal involvement.

Case Report

A 65 years old female, admitted in the emergency department 5 hours after a rapid onset of swelling of the face, lips and tongue (Figure 1) with speech difficulty and dyspnea, she has a 15 years history of type 2 diabetes mellitus under metformin, dipeptidyl-peptidase 4 inhibitor and Sitagliptine since 2 months and a 2 years history of heart failure with reduced heart failure (LVEF=32%) that remained symptomatic in NYHA class III under optimal medical therapy (Ramipril 10 mg per day, Nebivelol 5 mg per day, Spirinolactone 50 mg per day and Furosemide 40 mg per day) which led, one month earlier to her present visit, to the introduction of Sacubitril/valsartan 50 mg bid with respect to the prescription rules (Ramipril was stopped 36 hours earlier avoiding the potential excess risk for developing angioedema). Otherwise, she has no history of allergies.

At admission, the examination found a tensioned tongue with a protruding anterior third due to a large edema, complete dysphagia, a hypersialorrhea and a complete dysphonia followed. The patient showed no rash. CT scan of the face (Figure 2) showed significant edema of the tongue extended to the larynx. The patient received emergency 2 blouses of adrenaline, steroids and antihistamine with no response, the diagnosis of q LCZ 696 induced angioedema was raised. Faced with the severity of the respiratory distress and the failure of the orotracheal intubation, a rescue tracheostomy was performed. The evolution rapidly turned to a hypoxic cardiac arrest. A report was expedited to the pharmacovigilance center.

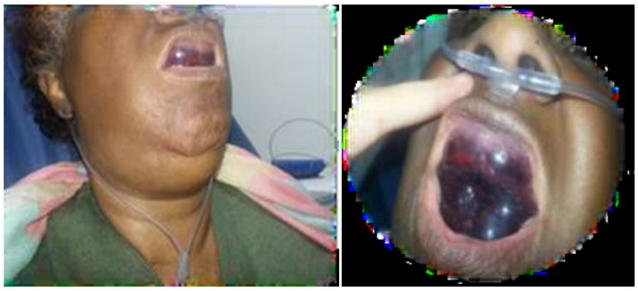

Figure 1: Large edema of the tongue and lips, extended to the neck.

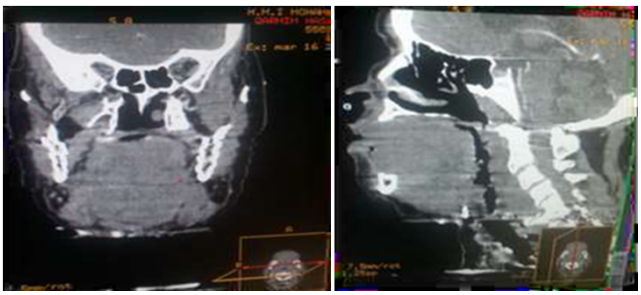

Figure 2: CT scan images showing edema of the tongue, base of the tongue and larynx.

Discussion

Heart failure is characterized by geometry and tissue remodeling and an imbalance between the two counter-regulatory systems, the natriuretic peptides and the renin-angiotensin-aldosterone system (RAAS). As heart failure progresses, sympathetic tone increases and RAAS becomes predominant over natriuretic peptides secreted in response to mechanical stretch. These peptides therefore represent a potential target in the treatment of heart failure in the same way as the RAAS [2]. The concept of LCZ 696 (Sacubutril/Valsartan) is to

combine a dual inhibition of neprilysin, to prevent the catabolism of natriuretic peptides and that of RAAS. Indeed, neprilysine is not specific for natriuretic peptides, it has a certain affinity in decreasing order for angiotensin II and I, adrenomedulin, substance P, bradykinin and endothelin, hence the need to simultaneously block its effects on other vasoactive substrates, particularly the angiotensin II, using an angiotensin II receptor antagonist [2].

Given the of the superiority of LCZ 696 on enalapril in the PARADIGM trial [3] (total mortality and CV in particular), the European Society of Cardiology ESC recommend to switch from ACE or ARB to LCZ 696 in patients with heart failure with reduced EF only if only if the patient remains symptomatic despite the association ACE, betablocker and mineralocorticoid receptor antagonist In practice, this switch requires stopping the ACE for 36 hour before introducing LCZ 696 to avoid the potential excess risk of angioedema [4]. In the PARADIGM trial, angioedema observed in the LCZ 696 group was an expected adverse effect due to the inhibition of bradykinin degradation.

The onset time of angioedema after strarting LCZ 696 is variable; the risk persists after a prolonged course of therapy. The effect is dose independent. It preferentially affects the face and the oropharyngeal area [5]. Abdominal involvement is possible with a clinical picture of a subocclusive syndrome and ascites. The LCZ 696 induced angioedema is characterized by a very deforming character unlike other types of angioedema. If the treatment is continued, relapses become more frequent with a persistent predilection for the oropharyngeal area. Edema of the face is at risk of extension to the upper airways. A history of edema of the upper airways is a risk factor for relapsing. There is no way to predict which patients are at risk of fatal laryngeal edema. The unpredictable and extensible character of the angioedemamust urges the utmost caution.

Bradykinin laryngeal angioedema results in complete obstruction within few hours and lasts for two to three days. Some cases of faster evolution with asphyxiation within minutes have been reported. Patients often accuse odynophagia first, and then dysphonia precedes acute dyspnea [6]. As in the present case, in the absence of specific treatment, death from asphyxia is possible. The diagnosis must be made quickly as it is a corticosteroid-resistant angioedema and less sensitive to adrenaline. The main differential diagnosis of bradykinin angioedema is allergic or non-allergic angioedema. Bradykinin angioedema is not accompanied by urticaria and other signs of anaphylaxis and does not respond to corticosteroids and antihistamines [6]. The risk of LCZ 696 induced angioedema increases with the combination with other drugs especially gliptins which are oral antidiabetic agents that have an anti-dipeptidyl-peptidase 4 (DPP-4) actions. Inhibitors of DPP-4 inhibit the degradation of bradykinin and potentiate the deleterious effect of LCZ 696 [7].

In severe cases, appropriate management requires a healthcare facility that has resuscitation equipment [8] and access to specific treatment. For physiological reasons, blockade of the B2 receptor of bradykinin by icatibant (Firazyr®) is the first line treatment. The dosage is 30 mg subcutaneously, which can be repeated six hours later. In case of contraindication related to hypersensitivity, the infusion of complement C1 esterase inhibitor concentrate (Berinert®) is also effective at the dose of 20 IU/kg intravenously [9].

In general terms, the risk of angioedema with sacubitril/valsartan treatment is similar to that seen with ACE inhibitors [10]. Clinicians should not be misled by the combination with valsartan considering that ARB is less likely to cause this complication. Strict vigilance in monitoring and counseling patients on the symptoms and signs of angioedema throughout the treatment with sacubitril/valsartan is strongly recommended.

Conclusion

Because of the increasing prescription of Sacubutril/valsartan as a treatment of heart failure with reduced ejection fraction, the risks of angioedema related to this combination are to be known. The diagnosis is difficult and the continuation of the treatment can be life-threatening because of the increasing intensity of recurrences. Reporting isolated cases or series of cases will strengthen the information of health professionals on this underestimated serious complication and help optimize its management.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, et al. (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37: 2129-2200.
2. DEKER M (2017) New pharmacological approaches in heart failure with altered ejection fraction. Cardiology practice.
3. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, et al. (2014) Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med 371: 993-1004.
4. ZORES F (2016) Inhibiting Neprilysin: A New Cardiovascular Priority. Practical Cardiology.
5. Beltrami L, Zanichelli A, Zingale L, Vacchinib R, Carugo S, et al. (2011) Long-term follow-up of 111 patients with angiotensin converting enzyme inhibitor-related angioedema. J Hypertens 29: 2273–2277.
6. Bouillet L (2012) Laryngeal angioedema induced by drugs interfering with the metabolism of bradykinin. French review of allergology 52: 157-159.
7. Fain O, Mekinian A, Gobert D, Khau CA, Javaud N (2015) Medicated bradykinetic angioedema (converting enzyme inhibitors and other treatments). Med Press 44: 81.
8. Braun JJ, de Blay F (2012) Laryngeal angioedema seen by the ENT. French review of allergology 52: 153-156.
9. Du-Thanh A, Raison-Peyron N, Guillot B (2011) Angioedema with bradykinin. Annals of Dermatology and Venereology 138: 328-335.
10. Owens RE, Oliphant CS (2017) Angioedema spotlight: A closer examination of sacubitril/valsartan safety results. JABFM 30: 556-557.