

Treatment with icatibant in the management of drug induced angioedema

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Abstract. Acute, drug-induced angioedema may not respond to standard therapies, because the pathogenetic mechanism that induces the pathology is not always mediated by histamine but, in certain instances, by bradykinin. A case of angioedema is reported here, in which allergic etiology was excluded by the non-response to antihistamines. Considering the clinical history (repeated use of drugs) and the ineffectiveness of standard therapy, it was decided to administer a beta2 receptor antagonist, icatibant. After 20 minutes, the patient reported a subjective improvement. The only form of angioedema for which this type of medication is licensed is the hereditary deficiency of C1 inhibitor. The use of icatibant for the treatment of other types of angioedema (which can also be life-saving if the airway is involved) is off label. The off-label use of a drug is allowed in the absence of a viable alternative therapy, if there is scientific evidence in the literature and if the prescriber takes responsibility. The case here reported draws attention to this therapeutic problem and underlines the fact that a life-threatening emergency can justify the use of icatibant.

Key Words:

Drug induced angioedema, Icatibant, Life saving therapy.

Introduction

Acute, drug-induced angioedema is not always responsive to standard therapies, such as antihistamines, steroids and epinephrine. This could be because the pathogenetic mechanism that induces the angioedema effect of a drug is not mediated by histamine, but by bradykinin¹. The diagnosis of non-histaminergic angioedema is based on the clinical picture and on clinical suspicion: it is an angioedema that is not related to urticaria, pruritus, erythema, rash, flushing or bronchoconstriction, and is not related to food ingestion or insect stings², which breaks out and disappears more slowly than histaminergic angioedema.

There are no specific laboratory analyses that can be performed in these patients to better define the mechanism behind the drug-induced angioedema. It has also been pointed out^{3,4} that other investigations (i.e. complement fraction, trip-tase) are not performed in a routine emergency room setting.

This situation of diagnosis, unsupported by laboratory data, poses a serious problem of therapy and the clinical case reported below highlights this fact. The patient came to the Emergency Department of the Policlinico Umberto I of Rome in the spring of 2013.

Clinical Case

P.C., female, aged 72, arrived at the Emergency Room at 6.00 p.m., presenting an edema of the tongue and mouth; the condition had started at 2.00 pm and had become increasingly more serious. Only a minimal passage of air was possible and the patient could not swallow or speak. She had eupnoea, the vital signs were normal and stable (96% O₂ Sat, BP 150/70 mmHg, 70/min HR, 20/min RR); however, her condition was a cause of concern owing to the possibility of a further, rapid deterioration of respiratory function (Figure 1).

The Table I summarizes the clinical data and medical history.

The blood gas analysis, performed in ambient air, showed slight hypoxemia (PO₂ 79 mmHg) without hypercapnia, or pH changes. Other respiratory (P/F, SaO₂) and metabolic parameters (lactate and bicarbonate) were within the norm.

Antihistamine drug was administered (chlorphenamine 10 mg, i.m.), steroids (hydrocortisone 1000 mg, e.v.) and, subsequently, epinephrine (1 fl 1 mg/ml, solution 1:1000, aerosol), given the persistence of the symptoms; all without improvement.

After 45 minutes of this triple therapy, the clinical situation remained unchanged and steroid therapy was repeated to no avail. An anesthetist,



Figure 1. The figure shows the edema of tongue and mouth at access to the Emergency Room.

called in for a consultation, was prepared to perform a tracheotomy as soon as there was evidence of desaturation. It was impossible to carry out endotracheal intubation owing to the very small oral space available, which did not allow the introduction of the tube.

Meanwhile, the clinical history of the patient was reconstructed with help from relatives.

The patient was under gabapentin therapy for neuralgic amyotrophy of the brachial plexus and venlafaxine treatment for depression. In addition, she had recently suffered an infection of thoracic herpes zoster, which was mainly neurological rather than dermatologic. For these reasons, she was taking paracetamol and aciclovyr; irbesartan and also furosemide for hypertension. In her recent history, the patient took NSAIDs, occasionally, for spondylolisthesis treated by stabilization with a metal plate.

Two months before presenting at our Emergency Department there had been an episode of swelling of one half of the tongue; the swelling subsided after a few hours. A month after, there was a further episode of swelling of the entire tongue, extending under the jaw and chin, which subsided after 12 hours. The latest incident that prompted her visit to the Emergency Room was more severe than the others and was in progress for about 4 hours before hospitalization.

At this point, considering the clinical history with repeated use of drugs and given the ineffectiveness of the standard therapy, it was decided to administer a beta2 receptor antagonist, icatibant.

It was given subcutaneously at a dose of 30 mg. After 20 minutes, the patient reported a subjective improvement. This was also documented by the image (Figure 2) taken 45 minutes after administration of the drug, which showed a reduction in edema of the tongue and mouth. She was kept under observation overnight as a precaution and discharged the next morning with complete remission of the symptoms. Specific blood tests (tryptase, C3 and 4) were negative (Table II).

The angiotensin receptor blockers (ARB) therapy was suspended and the patient, in a follow-up of 10 months, has no had any more episodes of angioedema

Discussion

A case of angioedema has been reported here, in which allergic etiology was excluded by the non-response to antihistamines, administered as standard therapy. The laboratory tests did not show any increase in tryptase, despite the lack of specificity of the results. Angioedema did not appear to be hereditary, since the crises were of recent onset in a patient of a mature age, there was no family history and the laboratory tests showed no reduction in the level of C4. Given the recent use of different drugs, it was possible to comprehend that the angioedema had been induced by such treatment. It was necessary, therefore, to identify which of the drugs taken, might have been responsible.

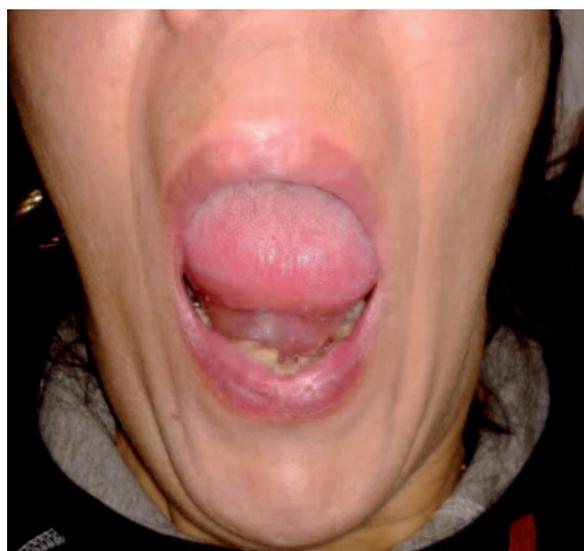


Figure 2. The figure shows a reduction of edema of tongue and mouth after administration of icatibant.

Table I. Clinical data and medical history.

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Table II. Specific blood test.

Examination	Value	Normal Range	Outcome
Trypsase	2,78 μg/L VN	< 11.4 μg/L	Negative
C3	140 mg/dL	VN 90-180 mg/dL	Negative
C4	38.70 mg/dL	VN 10-40 mg/dL	Negative

A study reported that gabapentin may induce angioedema in 0.14% of 34,020 patients followed for 6 years⁵; angioedema generally occurs within the second year of therapy, with a peak in the first month. The study stated that the population followed was not on monotherapy.

Venlafaxine can induce angioedema, as well as serotonin reuptake inhibitors. The angioedema found is described with histaminergic features (skin rash and urticaria)⁶.

Paracetamol was responsible for 8% of the reported drug-induced angioedema in our series⁷.

Acyclovir may give allergic reactions, such as urticaria, pruritus, angioedema⁸.

Extensive scientific literature shows that therapies with ACEIs and ARBs can induce angioedema as an adverse event⁹, although a lower occurrence is reported for ARBs compared with ACE -I. Trials (2002 and 2004) on angiotensin II receptor blockers (ARBs), have shown an appearance of 0.13% with the use of valsartan (Value study¹⁰) and between 0.1 and 0.2% with losartan (Life study¹¹) in a population followed for 5 years. ARBs interfere with the renin-angiotensin system, by blocking the effect of angiotensin II¹² and this can lead to an accumulation of bradykinin with vasodilatation and increased vascular permeability, (as shown by the fact that the symptoms respond to treatment with an anti-bradykinin, such as icatibant); but the mechanism of action of ARBs, is different from that the ACE – I, and may be indirect. Other mechanisms of action that do not involve the bradykinin system are less likely. It is also possible hypothesize that a drug, such as ARB, can lead to an adverse reaction such as angioedema in which other drugs, including those used by the patient, are involved. This is an interesting hypothesis, but requires demonstration. It is striking, however, is the fact that the patient who has suspended the ARB has not had any more episodes of angioedema.

There are no reports of angioedema after the use of furosemide in the literature or medical databases¹³.

In the case described above, more than one drug may be responsible for the onset of the angioedema seen and drugs together may have a synergistic action. Therefore, it is difficult to ascribe to one drug only the responsibility of having induced angioedema.

The most important point is that, in such a case of angioedema, the indication for anti-bradykinin treatment is off label. The case described here shows a clinical situation similar to that reported by Manders et al¹⁴.

The only class of drugs for which there is evidence, even though limited, for the indication to treat angioedema with bradykinin antagonists is ACE inhibitors. A number of case reports^{15,16} and a series of cases¹⁷ have appeared in the literature over the past three years (2010/12), but currently the only form of angioedema that is licensed to receive this type of medication is the hereditary deficiency of C1 inhibitor¹. The use of icatibant for the treatment of an attack of angioedema (which can also be life saving if it involves the airway) is off label. The use of an off label drug is permitted (1) in the absence of a viable alternative therapy, (2) if there is scientific evidence in the literature, (3) if the prescriber takes responsibility and (4) if there is the informed consent of the patient, as soon as the clinical condition allows. These issues are currently reported in the literature as cases of angioedema that might not be linked to the production of histamine.

Conclusions

The case reported above draws attention to the problem of having a treatment option available in such acute situations. Currently, only a life-threatening emergency can justify the use of icatibant; if, however, it expects that angioedema does not respond to standard therapy, the use of icatibant may be late.

Conflict of interest

The Authors declare that they have no conflict of interests, nor any sponsorship.

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