Hereditary angioedema: Experience with icatibant in severe attacks

Angioedema hereditário: Experiência com icatibant em crises graves

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ABSTRACT

Background: Hereditary angioedema (HAE) is a clinical syndrome characterized by recurrent and transient episodes of submucosal and/or subcutaneous edema. Icatibant, a selective bradykinin B2 receptor antagonist, is a new drug available for the treatment of HAE attacks. **Aim**: Description of our department's experience with icatibant use in severe HAE attacks. **Methods**: Retrospective study of patient files and telephone interviews with patients admitted from November 2009 to June 2011 to whom icatibant was administered for acute treatment of severe HAE attacks. **Results**: Nine patients (5 females; mean age 30.5 years) were treated with icatibant. Seven had HAE type II. Five patients were admitted with pharingolaryngeal attacks, one of them with associated abdominal pain, 2 due to exclusive abdominal attacks, and 2 due to exuberant mucocutaneous facial and/or lingual attacks. Laryngoscopy was performed in 7 patients by an ENT specialist, revealing upper airway edema in 3, with regression documented by laringoscopy in a second ENT evaluation 6–24 hours later. Every patient reported symptomatic relief within 2 hours of subcutaneous administration of 30 mg icatibant. The sole adverse effect mentioned by 88.9% of the patients (8/9), was a mild pain and/or burning sensation at the injection site; otherwise icatibant was well tolerated. The average time between hospital admission and icatibant's subcutaneous administration was 2.44 hours, with a median of one hour. Three patients had been previously treated with C1 inhibitor concentrate for past HAE attacks with similar symptoms. These patients reported subjective perception of a shorter time to the beginning

of action of icatibant. **Conclusions**: The authors suggest that icatibant use in acute treatment of severe HAE attacks (pharingolaryngeal, abdominal and exuberant mucocutaneous facial-lingual attacks) is effective and safe, associated to minor local, well-tolerated adverse reactions.

Keywords: bradykinin, hereditary angioedema, icatibant, severe attacks.

RESUMO

***Introdução**: O angioedema hereditário (AEH) é uma síndrome clínica caracterizada por episódios recorrentes e transitórios de edema submucoso e/ou subcutâneo. O icatibant é um novo fármaco, antagonista selectivo dos receptores B2 da bradicinina, para o tratamento das crises de AEH. **Objectivo**: Descrever a experiência do nosso Serviço com a utilização de icatibant no tratamento de crises graves de AEH. **Métodos**: Análise retrospectiva do processo clínico e entrevista telefónica aos doentes internados que receberam icatibant para tratamento de crises graves de AEH entre Novembro/2009 e Junho/2011. **Resultados**: Nove doentes (5 mulheres; média de idades: 30,5 anos) receberam icatibant. Sete tinham AEH tipo II. Cinco doentes foram internados por crise de angioedema faringo-laríngeo, um deles com queixas abdominais associadas, dois doentes internados por crise exclusivamente abdominal e dois por crise mucocutânea exuberante da face e/ou da língua. Dois dos doentes tinham antecedentes pessoais de asfixia. A laringoscopia, realizada em sete doentes, revelou edema das vias aéreas superiores em três, com documentação da sua reversão em reavaliação efectuada 6-24 horas depois. Todos os doentes reportaram alívio sintomático nas primeiras duas horas após administração subcutânea de 30 mg de icatibant. O único efeito secundário, bem tolerado, reportado por 88,9% dos doentes (8/9), foi ligeira dor e/ou sensação de queimadura no local da administração subcutânea (parede abdominal). A média de tempo entre a admissão hospitalar e a administração subcutânea de icatibant foi de 2,44 horas e a mediana de uma hora. Três doentes tinham efectuado no passado terapêutica com concentrado de C1 inibidor para crise de AEH com clínica semelhante, referindo uma percepção subjectiva de início de acção mais precoce do icatibant. **Conclusões**: Os autores sugerem que a utilização de icatibant no tratamento das crises graves de AEH (faringo-laríngeas, abdominais ou mucocutâneas faciais/linguais exuberantes) é eficaz e segura, apenas associada a reacções adversas locais, ligeiras e bem toleradas.*

***Palavras-chave:** Angioedema hereditário, bradicinina, crises graves, icatibant.*

INTRODUCTION

Clinical pictures of angioedema can be generally classified according to the mediators involved in its physiopathology. Accordingly, it may be induced by histamine release (allergic- or histamine-mediated angioedema), the most frequent types, or induced by bradykinin (bradykinin-mediated angioedema). This latter includes hereditary angioedema (HAE), acquired angioedema with deficit of C1 inhibitor, angiotensin-converting enzyme (ACE) inhibitor-induced angioedema, leukotriene--induced angioedema (non-steroidal anti-inflammatory--induced angioedema) or angioedema induced by unknown mechanisms (recurrent idiopathic angioedema)[1].

HAE is a clinical syndrome characterized by recurrent and transient episodes of submucosal and/or subcutaneous edema which can affect the skin, upper airway or digestive tract[2]. It was described for the first time by Milton in 1876, and it was Quincke who in 1882 introduced the expression "angioneurotic edema". Six years later Sir William Osler described the syndrome's familiar character, coining the term "hereditary angioneurotic edema"[3].

It is a disease with an incidence of 1:10 000–1:50 000, autosomal dominant, and attributed to a deficiency of the C1 inhibitor (C1 INH) caused by a mutation on the gene which codifies the C1 INH, located on chromosome 11[4]. Three types of HAE are described. Type 1 (approx. 85%) is characterized by a deficiency in quantity and function of C1 INH. Type 2 (approx. 15%) has no deficiency in quantity but in function[4]. Type 3 is rare and has no alterations in C1 INH quantity or function[5].

Clinically HAE is characterized by recurrent and transient non-itchy, non-pitting episodes of submucosal and/or subcutaneous edema, mainly affecting the limbs and genitals (95%), digestive tract (70-80%), facial structures (50%) and upper airway (48-78%)[5-8]. The most frequently seen triggers are trauma, infections, stress and medication (oestrogens, ACE inhibitors and angiotensin-converting enzyme inhibitors), although it can occur spontaneously[4,5]. Mean length of an attack is around 48–72 hours[7].

C1 INH is responsible for the regulation of proteolytic cascades generated in complement, clotting and kinin pathways[5]. In addition to inhibiting activation of the C1 fraction of the complement, C1 INH is also responsible for inactivation of the greater part of factor XIIa, which cleaves pre-kallikrein in kallikrein, which in turn cleaves to high molecular weight kininogens and leads to the excess release of several kinins, particularly bradykinin[9,10]. Bradykinin is a nanopeptide released as part of the activation of the contact pathway which induces marked increase of vascular permeability when it binds to its receptor in the vascular endothelial cells (bradykinin B2 receptor)[5]. There is an increased release of bradykinin during HAE attacks. Bradykinin is the main mediator responsible for the majority of symptoms: increased vascular permeability (which could cause edema, ascites or hypotension) and contraction of the non-vascular smooth muscle (which could cause sustained pain or colicky pain)[9].

Treatment of angioedema is well standardized in international recommendations as to three fundamental areas: 1) acute treatment for attacks; 2) long-term attacks prevention; and 3) short-term attacks prevention, ahead of surgery. The most frequently seen drugs are attenuated androgens (danazol or stanozolol), antifibrinolytics (tranexamic acid or ε-aminocaproic acid), C1 INH concentrate and icatibant[2,10-12].

In severe attacks, emergency treatment is based on use of intravenous C1 INH or subcutaneous icatibant[13]. Icatibant is a selective antagonist of bradykinin B2 receptors available in Portugal since November 2009, and which reverses increased vascular permeability. Two randomised, double blind and multicentre phase 3 studies, FAST (For Angioedema Subcutaneous Treatment), FAST-1 (icatibant *vs.* placebo) and FAST-2 (icatibant *vs.* tranexamic acid), have shown icatibant's efficacy in HAE attacks, particularly in the reduced time taken to obtain relief from symptoms[13,14].

We report our experience with using icatibant in treatment of severe HAE attacks in the Immunoallergology Department of the Hospital de Santa Maria, Centro Hospitalar Lisboa Norte (HSM) since the drug's introduction in Portugal.

MATERIAL AND METHODS

This was a retrospective analysis of the clinical files of and telephone interview with patients who had received icatibant for treatment of acute HEA attacks

November 2009–June 2011, with subsequent hospital admission in the HSM Immunoallergology Department.

We evaluated age, gender, race, HAE classification, characterization of HAE attack (clinical examination, evaluation by Ear, Nose and Throat (ENT) specialist, ancillary exams), treatment taken previously (for prior attacks and maintenance) and response to icatibant (dose, time until symptoms improved, adverse effects and in patients who had taken C1 INH previously, comparison of time to symptomatic improvement). Time from hospital admission until subcutaneous administration of icatibant was also evaluated.

The descriptive statistical values for the different variables (mean, median, minimum and maximum) was performed, calculated using Microsoft Excel® 2007 software.

RESULTS

Over the twenty-month period studied, 9 patients received icatibant for treatment of severe HAE attacks. In terms of demographics, 5 patients were female, 7 Caucasian (2 black) and mean age was 30.5 years old (median 30, minimum 25 and maximum 37). In terms of HAE classification, 7 (78%) had HAE type 2 and 2 patients (22%) type 1. Two of the HAE type 2 patients were members of the same family (they were brothers) with the remaining patients having no kin connection whatsoever.

Eight patients were admitted through the Emergency Department and one through our Immunoallergology day

Table I. Patients' clinical characterisation

ID / gender / age	PMM / F / 31	MAC / F / 29	LMN / M / 35	MLV / F / 25	OLV / M / 23	JMO / M / 37	CSS / M / 37	SMR / F / 30	LIL / F / 28
HAE classification	1	1	2	2	2	2	2	2	2
Personal history	---	---	MV (x2)	---	---	---	---	appendectomy	MV
Clinical presentation	oropharyngeal grasp, feeling of cervical edema	laryngeal grasp, dysphonia	laryngeal grasp, dysphonia	odynophagia, oropharyngeal grasp, dysphonia, dysphagia, dyspnea	dysphonia, abdominal pain, vomiting	AE of the face, edema of the tongue	Exuberant AE of the face and edema of the oropharynx	Colic-like abdominal pain, nausea, vomiting	abdominal pain, nausea, vomiting; AE of the left foot
Abdominal scan/CT	---	---	---	---	---	---	---	ascitis, thickening of the gastric and intestinal walls, edema of the intestinal wall	---
Time from admission (A&E/outpatients) to icatibant	0,75 h	0,25 h	2,5 h	4,25 h	2 h	0, 75	1 h	10 h	0,5 h
Time from icatibant to ENT exam	1 h	1,5 h	2 h	1 h	3 h	2 h	1,5 h	---	---
ENT exam	normal IL	normal IL	edema of the arytenoid	edema of the uvula, aryepiglottic and arytenoid folds	omega-shaped epiglottis with mild edema	normal IL	normal IL	---	---

HAE – hereditary angioedema; AE – angioedema; MV – mechanical ventilation; ENT – ear, nose and throat; IL – indirect laryngoscopy; CT – computerised tomography; A&E – Emmergency Department; --- Not performed/Not relevant.

hospital with pharingolaryngeal attacks (4), pharingolaryngeal and abdominal attacks (1), abdominal attacks (2) and mucocutaneous facial or lingual attacks (2). Table I shows patients' clinical profiles.

In terms of patient histories we mention asphyxia with need for mechanical ventilation in two (one with pharingolaryngeal presentation at the time and one with abdominal attack at the time) and "non-appendicitis appendectomy" in one of the patients with abdominal presentation. All patients with pharingolaryngeal attacks or involvement of the face and/or tongue (7 patients) were seen by an ENT specialist. Given the urgent nature of the treatment, icatibant was administered initially in all cases and patients were afterwards seen in ENT (a mean 1.7 hours after icatibant administration; median 1.5 hours, minimum 1 hour and maximum 3 hours). Only 3 of these 7 patients presented abnormalities in the indirect laryngoscopy, absent in the ENT re-evaluation performed 6-24 hours later.

Table II shows patients' treatment profiles. Mean time from hospital admission (Emmergency Department/Outpatients) to subcutaneous icatibant administration was 2.44 hours (median 1 hour, minimum 0.25 and maximum 10 hours). The longest timelag seen (10 hours) was an exclusively abdominal angioedema attack which onset during dawn and partly responded to treatment with stronger androgen dose (which the patient took under his own initiative at home) and intravenous antifibrinolytics at Emmergency Department, with the patient inclusively being

Table II. Patients' treatment profiles

ID / gender / age	PMM / F / 31	MAC / F / 29	LMN / M / 35	MLV / F / 25	OLV / M / 23	JMO / M / 37	CSS / M / 37	SMR / F / 30	LIL / F / 28
Icatibant	30 mg/sc	30 mg/sc	30 mg/sc	30 mg/sc	30 mg/sc	30 mg/sc	30 mg/sc	30 mg/sc	30 mg/sc
ENT re-evaluation	---	---	Improvement in edema of the larynx (4h)	no edema (24h)	no edema (24h)	---	---	---	---
Relief of symptoms with icatibant	yes (30 min)	yes (60 min)	yes (30 min)	yes (60 min)	yes (120 min)	yes (80 min)	yes (90 min)	yes (60 min)	yes (10 min)
Icatibant adverse effects	none	mild pain / burning feeling in the abdominal wall	mild pain / burning feeling in the abdominal wall	mild pain / burning feeling in the abdominal wall	mild pain / burning feeling in the abdominal wall	mild pain / burning feeling in the abdominal wall	mild pain / burning feeling in the abdominal wall	mild pain / burning feeling in the abdominal wall	mild pain in the abdominal wall
Treatment given in earlier attacks	corticosteroids antihistamines	androgens, antifibrinolytics, C1 INH	androgens, antifibrinolytics, C1 INH	androgens	none	androgens, antifibrinolytics	androgens, antifibrinolytics	androgens, antifibrinolytics, C1 INH	androgens, antifibrinolytics, C1 INH
Self-report (icatibant vs. C1 INH)	(no C1 INH)	No recall	icatibant quicker and more effective	(no C1 INH)	(no C1 INH)	(no C1 INH)	(no C1 INH)	icatibant quicker and more effective	icatibant quicker and more effective
Earlier maintainance treatment	none	none	Stanozolol (4mg/day)	Stanozolol (2mg/day)	none	Danatrol (200 mg/day)	Danatrol (200 mg/day)	Stanozolol (6 mg/day)	Danatrol (200 mg/days alternating)

C1 INH – C1 inhibitor concentrate; sc – subcutaneous route; --- Not performed/Not relevant.

able to sleep through this. It was decided to administer icatibant the following morning in face of the persistent abdominal pain, of significant intensity.

All patients needed only one 30 mg subcutaneous dose of icatibant to manage their attacks. In the telephone interview all patients reported (retrospectively) significant relief from symptoms within 120 minutes (mean 60 minutes; median 60 minutes, minimum 10 and maximum 120 minutes). Eight patients associated administration of icatibant with adverse local effects such as mild pain and burning feeling in the abdominal wall (Table II), which they felt were tolerable.

In terms of past treatment for severe HAE attacks, 6 patients had taken androgens, 5 antifibrinolytics, one had received corticosteroids and antihistamines and 4 patients C1 INH concentrate, for clinically similar attacks. Three of these last 4 patients stated in terms of a subjective and retrospective comparison between the 2 drugs that they perceived icatibant started working quicker. The fourth patient could not recall when C1 INH started working, making it impossible to draw any comparison with icatibant here.

In terms of earlier maintenance treatment, 6 patients had been prescribed regular treatment with androgens (stanozolol – 3; danazol – 3). The remaining 3 patients were not taking any maintenance treatment. One had suspended treatment a month earlier due to the lack of attacks and the other 2 patients had no maintenance treatment as they had a low rate of attacks. At hospital discharge, all patients were medicated with daily androgen treatment.

DISCUSSION

Here we describe our experience with using icatibant to treat 9 severe HAE attacks (5 pharingolaryngeal, one with associated abdominal complaints, 2 abdominal and 2 mucocutaneous of the face and tongue) in patients admitted to HSM's Immunoallergology Department.

One of the interesting points about this study is that it is the first description in Portugal of a series of patients medicated with icatibant in severe HAE attacks. We add that a further point of interest is the attempt to define a comparative self-assessment, albeit subjective and retrospective, with prior administrations of C1 INH: we have found no other published studies in the literature comparing in any way the efficacy of these two drugs. The main flaws of this study are the small sample size and that it is a non-controlled and non-randomised retrospective study.

We evaluated 9 patients with severe HAE attacks, the majority of whom had HAE type 2. To our knowledge there is no relationship between type of HAE and severity of presentation or attacks, leading us to believe this over-representation of type II patients might be explained by the high rate (40%) of type 2 cases we find in patients followed in our Department. Factors contributing to this are the existence of two large families, multiple members of whom are affected.

While early descriptions state females might have a more severe version of the disease due to the effect of the endogenous and, possibly, exogenous hormone (contraception)[15], we found no significant predominance of females. The majority of patients were caucasian, probably a result of the higher rate of Caucasians in the region in question, there being no difference between races or ethnic groups described[5].

All HAE attacks of patients in this study showed indication, in line with the 2010 international recommendations[10], for treatment with icatibant. They were severe attacks, the greater part pharingolaryngeal (55.5%), which can lead to asphyxia, which could be responsible for a mortality rate of 30–50% in undiagnosed patients[2,8]. The

severe attacks were cases of edema of the face, tongue, pharynx, larynx and upper airway (constituting a risk of edema of the larynx) and painful abdominal edema (visual analogue pain scale > 5), and cases associated with hypovolemic shock[2].

Edema of the upper airway, seen in indirect laryngoscopy, occurred in 42.8% of cases (3/7 of the patients in whom indirect laryngoscopy was performed). This is similar to the 49.6% seen by Bork[16]. The two patients with pharingolaryngeal complaints who did not present ENT abnormalities were those who had received an early icatibant injection (15–45 minutes), however. That the ENT examination only occurred after administration of icatibant might have contributed to the normal parameters found in this exam.

In view of the good response seen to past treatment with C1 INH concentrate, and patient severity, 2 of them with history of asphyxia, the option to switch to a new drug might occasion some patient or physician fear, particularly fear that the new drug might not be as effective. This study, however, confirmed the efficacy of icatibant in these situations of severe HAE attacks.

The literature does not contain many studies evaluating icatibant in pharingolaryngeal HAE attacks, adequately documented. We found only four studies in the literature dealing explicitly with evaluating icatibant in treating pharingolaryngeal edema. In the first, Bas *et al.* reported in the use of icatibant in a patient with recurrent HAE attacks, four of which affected the larynx, in which icatibant was efficacious in relieving symptoms and reducing edema, as documented by laryngoscopy[17].

Four years later, Cicardi evaluated icatibant in 11 patients with laryngeal edema (part of the FAST-1 and FAST-2 studies), reporting improved symptoms in patient self-evaluation within 0.6–1 hour of subcutaneous administration of icatibant (FAST-1 and 2, in turn), but with seemingly no reference to laryngoscopy examination[14]. Recently Csuka *et al.* reported improved symptoms within 48 minutes and resolution of symptoms within 6.8 of icatibant administration in 6 patients with 12 HAE attacks, 3 of whom had upper airway involvement[18]. Boccon-Gibod *et al.*, in a study with 45 patients with laryngeal and abdominal attacks (46% exclusively laryngeal, 10% laryngeal and facial, 5% laryngeal and abdominal and 5% laryngeal, abdominal and mucocutaneous) reported that self-administration of icatibant was efficacious in resolving symptoms, and well tolerated[19].

In our study, the five patients with pharingolaryngeal attacks also reported symptom relief within hours of icatibant administration. We add further that the documented pharingolaryngeal improvement was not just through subjective evaluation of symptoms but also objective re-evaluation via indirect laryngoscopy performed within 6–24 hours of the first laryngoscopy, making it an indubitable asset in this documentation of efficacy.

Pharingolaryngeal attacks can become asphyxia, needing intubation, irrespective of the pharmacological treatment administered. In 2003, in a series of 123 patients with 596 laryngeal attacks, Bork reported 6 patients needed intubation for asphyxia, four needing tracheotomy[16]. Seven years later Cicardi described in the FAST-1 study a patient needing intubation for laryngeal attack, within 5 minutes of icatibant administration[14]. No patient in our series needed intubation.

All patients reported relief from symptoms after one sole dose of 30 mg subcutaneous icatibant, and this was only associated with local adverse reactions which were of low intensity and well tolerated.

In the literature, icatibant was frequently associated (49-100%)[12,13,16,18,20] with adverse local reactions, such

as pain, edema, burning and pruritus, and, in under 10% of cases, systemic reactions such as nausea, abdominal pain, fatigue, dizziness, headaches, exanthema and nasal congestion[13,20]. In our series, 88.9% of patients complained of pain and/or a burning sensation in the abdominal wall, which were overall of mild intensity and reasonably well tolerated. We found no adverse systemic effects.

Another interesting aspect of this study stemmed from the attempt to draw a comparison, albeit subjective and retrospective, with all the limitations therein, between the swiftness of action of C1 INH and icatibant. We found that 3 of the 4 patients who had experienced both drugs perceived icatibant worked faster. The other patient was incapable of describing which drug worked quicker.

The literature describes that after administration, icatibant takes 30 minutes to reach its maximum concentration in plasma (C_{max})[14] while C1 INH concentrate takes 48 minutes[21]. The first signs of symptom improvement are described within 20–30 minutes with both drugs, however[2,22]. Icatibant's half-life (t ½) is around 1–2 hours[19], while C1 INH concentrate has a t ½ of approx. 30–40 hours, depending on C1 INH consumption[2,21,23].

The cost of treatment depends on the patient's weight (in the case of C1 INH concentrate) and any need to repeat the dose (possible in both drugs but more seen with icatibant). For someone weighing 75 kg the total price of a subcutaneous administration of 30 mg of icatibant is EUR 1352 while intravenous administration of C1 INH concentrate is EUR 1678 (prices taken from the HSM IT system).

In our patients, the time between admission to hospital and icatibant administration varied greatly (15 minutes–10 hours), with mean 2.44 hours following hospital admission. Median time was 1 hour, however, which we feel to be reasonable. This time factor can be explained by the fact that patients come in with their disease identification cards and many ER team are made up of physicians from the Immunoallergology Department. That said, in two cases administration took 5–10 hours, which highlights the importance of maintaining an adequate degree of vigilance and the need for ER team to receive continuous training in this pathology.

The European Medicines Agency (EMA) recently authorized self-administration of icatibant for patients who have already successfully received this type of treatment in acute attacks, thus allowing the availability of a specific and immediate treatment for high-risk patients. It requires prior training and adequate training in the technique and decision to self-administer.

Like that seen in self-administration of C1 INH[17,24] it is expected that self-administration of icatibant can have a better result than hospital administration as less time is taken before administration of a suitable medication[22]. All patients with a laryngeal attack are instructed to go to ER, even after self-administration of icatibant, however[25]. The current phase IIIb study EASSI (Evaluation of the Safety of Self-Administration with Icatibant), is assessing the safety, local tolerance, convenience and efficacy of icatibant self-administration in acute attacks in 56 HAE patients. It shows self-administration is efficacious in the resolution of symptoms and is preferred by the majority of patients (94.6%)[26]. Another study, with 45 patients with laryngeal or abdominal attacks, reported that self-administration of icatibant was efficacious in the resolution of symptoms and well tolerated, allowing patient autonomy[19].

To sum up, this study showed that subcutaneous administration of icatibant, even in single doses and in patients with severe HAE attacks, has a good efficacy and safety profile in the treatment of pharingolaryngeal, abdominal or mucocutaneous attacks of the face/tongue, and is associated with only mild and reasonably well-tolerated local adverse effects. In addition, this work

allowed us to identify patients who, in having responded well to icatibant even in severe attacks, are possible candidates for future self-administration programmes, after suitable training.

CONCLUSIONS

We describe the use of icatibant in 9 patients with severe HAE attacks admitted to HSM's Immunoallergology Department: 4 pharingolaryngeal, 1 pharingolaryngeal and abdominal, 2 exclusively abdominal and 2 mucocutaneous of the face/tongue. All patients needed only subcutaneous administration of 30 mg of icatibant, reporting symptom relief within 120 minutes. Laryngoscopy, performed by ENT in 7 patients, showed edema of the upper airway in three patients, with subsequent documentation of its resolution when laryngoscopy was performed 6–24 hours later.

We conclude that the use of icatibant in the treatment of these severe HAE attacks is efficacious and safe, and is only associated with mild and reasonably well-tolerated local adverse effects.

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