A review of icatibant use; the bad, the good and the ACE.

Helen Dixon[1], Nikhita Serrao[2], Mai Phan[2], Erini Mathiopoulos[1]

[1] Pharmacy Department St Vincent's Hospital Melbourne

[2] RMIT University

ST VINCENT'S HOSPITAL MELBOURNE

A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Background

Hereditary angioedema is a rare condition which is characterised by attacks of swelling that can occur anywhere in the body including face, larynx, gut or limbs. It can be painful, particularly with gastrointestinal attacks, and if the larynx is affected asphyxiation and death can occur.

The condition is caused by the dysfunction or absence of the C1-esterase-inhibitor which is thought to lead to increased vascular permeability due to unregulated bradykinin activation.

Three types of hereditary angioedema have been classified:

Type I results from a mutation in the gene that encodes the C1-esterase-inhibitor which results in a reduction in its synthesis.

Type II also results from a mutation in the gene that encodes the C1-esterase-inhibitor. In type II it results in the formation of a dysfunctional protein.

Type III was first described in the year 2000. It is clinically indistinguishable from the others, however the gene that encodes the C1-esterase-inhibitor is normal.

Antihistamines and corticosteroids have no role in the management of hereditary angioedema. The role of adrenaline in the treatment of hereditary angioedema is not well established.

Icatibant, is a synthetic decapeptide. It has a similar structure to bradykinin and acts as a competitive B2-receptor antagonist. Inhibiting bradykinin during an acute attack reduces the ongoing inflammatory processes.

Icatibant was registered by the therapeutic goods administration (TGA) in September 2010 for symptomatic treatment of acute attacks of hereditary angioedema in adults with C1-esterase-inhibitor deficiency. It was listed on the PBS in 2012 and listed on St Vincent's Hospital formulary in 2014.

Aim

To review the use of icatibant at St Vincent's Hospital Melbourne.

Method

A retrospective review used pharmacy dispensing and medical records to identify patients who received icatibant between 2015 and 2018. These records were analysed to identify the patient demographics, presenting complaints and the treatments given.

Results

Seven patients received icatibant in the study period (four female and three male).

The youngest patient was 18 and the oldest 89.

Six patients presented via ambulance to the emergency department and two required admission to the intensive care unit.

Presenting complaints ranged from a swollen eye to respiratory arrest.

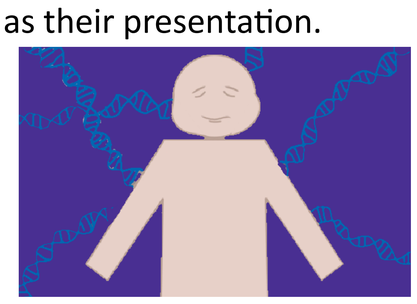
Patient	Presenting Complaint
A	Swollen tongue
B	Respiratory Arrest
C	Swollen lips and throat
D	Swollen tongue
E	Swollen tongue, lips and mouth
F	Swollen right eye and left forearm
G	Swollen tongue and lips

Two patients (B and C) had a history of hereditary angioedema previously treated with icatibant.

Patient B has type III hereditary angioedema and a history of anaphylaxis. The admission was thought to be triggered by a food allergy and asthma exacerbation. Icatibant was administered as the patient failed to respond to adrenaline.

Patient B required admission to the intensive care unit and was discharged home the following day.

Patient C has type III hereditary angioedema and a history of anaphylaxis. They responded to the treatment and were discharged home on the same day as their presentation.



Three patients (A, E and F) received icatibant without a valid indication.

Patient A had tongue swelling associated with uremia and end-stage renal disease. This patient was palliated and died two weeks later.

Patients E and F had suspected severe allergic reactions.

Patient E had an idiopathic urticaria, likely to be histamine mediated. This patient had an unsubstantiated history of ACE-inhibitor use.

Patient F presented with an allergic reaction with no justification for icatibant use.

Patients E and F were discharged on the same day as their presentation.

Results (continued)

Patients D and G were taking perindopril. Patient D had been taking perindopril for 8 days, while patient G had been taking it for over 10 years.

ACE-inhibitor induced angioedema was the suspected cause of their presentations.

They both had no known allergies and were both initially treated with adrenaline and corticosteroids.

ACE-inhibitor induced angioedema is not a TGA approved indication for icatibant. The available evidence is conflicting and does not support its use. The most recent evidence, a large clinical trial published in 2017 (after patient D was treated), included 121 subjects from 31 centres in 4 countries. Adults on ACE-inhibitors who presented within 12 hours of the onset of angioedema were randomised 1:1 to icatibant 30mg or placebo administered subcutaneously. The study showed no difference between the icatibant and placebo groups in the time for subjects to meet discharge criteria or the time to onset of symptom relief.

The ACE-inhibitor was ceased in both patients D and G.

Patient D was discharged on day 3 and Patient G was discharged on the same day as their presentation.

Icatibant was administered after other medications in all cases.

All patients except for patient F received adrenaline.

All patients except for patient E were treated with a corticosteroid.

Minimal time between administration of other medications and icatibant made it difficult to interpret the exact contribution of icatibant to symptom resolution.

Conclusion

Icatibant was used appropriately to treat hereditary angioedema in only two out of seven cases.

Icatibant was used in two patients with ACE-inhibitor induced angioedema an indication that is not supported by the latest evidence.

We found inappropriate use of icatibant to treat severe allergic reactions highlighting the need for education on icatibant's mechanism of action and optimal treatment of allergic reactions.

Reference

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Contact

Helen Dixon, Deputy Chief Pharmacist
St Vincent's Hospital Melbourne
helen.dixon@svha.org.au