Angiotensin Converting Enzyme inhibitors (ACEi) and Angioedema

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Overview

- Case study
- Classification of angioedema
- Pathophysiology of angioedema
- ACEi-induced angioedema
- Is this a drug allergy?
- Management and what’s new?
Case 1

75/Female/Caucasian

On fosinopril for many years

Nasoendoscopy: swollen piriform fossa & epiglottic folds

Intubated

Normal complements

Negative sIgE to prawn
Case 2

49/Male/ Aboriginal

Took first dose of perindopril for hypertension and 24 hours later......

He developed gross lower lip and facial swelling
## Classification of angioedema

<table>
<thead>
<tr>
<th>Category</th>
<th>Bradykinin mediated</th>
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<tr>
<td></td>
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# Classification of angioedema

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<td></td>
<td>HAE2</td>
<td>IgE-mediated urticaria</td>
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Renin-angiotensin-aldosterone System

Angiotensin converting enzyme (ACE)

Angiotensin I → Angiotensin II

In the lungs

Angiotensin II: active vasoconstrictor

↑ blood pressure

Primary peptidase involved bradykinin degradation

Dipeptidylcarboxypeptidase
Dipeptidyl peptidase
Kininase II
Kinin-kallikrein System

Factor XII → Prekallikrein → Kallikrein

Plasminogen → Plasmin → Inactive peptides

HMW Kininogen → Bradykinin

ACE
Bradykinin $\rightarrow$ Inactive peptides

**ACE**

Short $t_{1/2}$ 17 sec

Metabolised primarily by ACE (kininase II)
- neutral endopeptidase (NEP)
- aminopeptidase P (APP)
secondarily by dipeptidyl peptidase IV (DPPIV)
- kininase I

*Des-Arg9-BK* is an active metabolite of bradykinin formed primarily due to the kininase I enzyme (also degraded by DPPIV)

*decreased activity of DPPIV correlated to a prolonged half life of substance P, only in the presence of ACE inhibition – a requirement for multiple enzymes defects to inhibit degradation*
Bradykinin → Inactive peptides

ACE

ACE inhibitor
Bradykinin degradation prolonged

ACE inhibitor

Vasodilation

↑ vascular permeability
(postcapillary venules)

Plasma extravasation into submucosal tissue

This is the result from defective degradation of at least three vasoactive peptides:
- Bradykinin (*level increase – may be 10 fold*)
- des-Arg9-BK (a metabolite of bradykinin)
- substance P (can increase vascular permeability)
ACE inhibitors (ACEi) and Angioedema

• Commonly prescribed for hypertension, cardiac failure, myocardial infarct and diabetic nephropathy

• About 35 to 40 million people worldwide are taking ACEi

• Angioedema reported to occur in 0.1-2.5% of patients taking ACEi


• Potentially life-threatening when it involves the airway

• Fatalities reported

• Increased use of ACEi; substantial proportion of angioedema cases presenting to the Emergency Department

• May occur with any ACEi

• Diagnosis may be missed unless drug history is taken

• Perindopril accounted for the majority of cases in our experience → reflection of prescribing patterns
  (perindopril – 54% of all ACEi prescriptions in Australia in 2012-2013)
Triggers and nature

• Seldom identified

• May occur as early as within 24 hours of the first dose, or as long as 20 years


• Incidence highest during the 1st month of treatment, but majority of cases occur after 1 month of treatment; about 1/3 of cases after 6 months

• Higher incidence in African-Americans (4-5 times) compared to white Americans


• Susceptibility may be genetically determined


- Smoking
- Female sex
- Age >65
- Seasonal allergies
- Concomitant use of mTOR inhibitors (sirolimus, everolimus) in renal transplant recipients

**effects of immunosuppressants on decreasing the activity of circulating levels of dipeptidyl peptidase IV (DPPIV)**
• A predilection for the lips, tongue, face and upper airway
  **Bradykinin receptors are expressed in the tongue, laryngeal areas and parotid gland**

• Lip and anterior tongue being the most common sites of involvement in a series


• May rarely involve the bowel wall

So, is this a drug allergy?
Fok JS et al

Mario, 71, presented with an episode of gross swelling of the lower face. He had a similar milder swelling of the lip a month ago. Three months ago he commenced perindopril for hypertension.
So, is this a drug allergy?

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<th>Health profession</th>
<th>Type of reaction N (%)</th>
<th>Severity of reaction N (%)</th>
<th>Level of contraindication N (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Allergy</td>
<td>Intolerance</td>
<td>Mild</td>
</tr>
<tr>
<td>Medical (n=160)</td>
<td>109 (68.1)</td>
<td>48 (30.0)</td>
<td>14 (8.8)</td>
</tr>
<tr>
<td>Nurse (n=50)</td>
<td>38 (76.0)</td>
<td>11 (22.0)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Pharmacist (n=96)</td>
<td>73 (76.0)</td>
<td>23 (23.9)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Medical student (n=88)</td>
<td>74 (84.1)</td>
<td>14 (15.9)</td>
<td>9 (10.2)</td>
</tr>
<tr>
<td>Overall (n=394)</td>
<td>294 (74.6)</td>
<td>96 (24.4)</td>
<td>28 (7.1)</td>
</tr>
</tbody>
</table>

Majority = Allergy!!
Management

Recognition of problem

- Lack of reliable history in a patient presenting acutely
- Lack of knowledge of the association of ACEi with angioedema
- Misattribution to an allergic cause
- Poor understanding of the time course of angioedema in those taking ACEi
ACEi cessation

- Stop the culprit medication
- Not to be replaced with other ACEi (*class effect*)
- If clinically indicated, an angiotensin receptor blocker (ARB) may be tried in the future
- For unclear reason, angioedema has been reported in association with the use of ARB but the rate is substantially lower
Pharmacological therapy

- Antihistamines
- Corticosteroids
- Adrenaline  
  Usually ineffective
  More for allergic, histamine-mediated angioedema

- Intubation (if airway compromise)

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<th>Type 1 angioedema</th>
<th>Lip &amp; anterior tongue involvement</th>
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<tr>
<td>Type 2 angioedema</td>
<td>Floor of mouth, palatal or oropharyngeal oedema</td>
</tr>
<tr>
<td>Type 3 angioedema</td>
<td>Laryngeal or hypopharyngeal oedema</td>
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• Bradykinin B2 receptor antagonist

• Approved for HAE acute attacks

• Most likely effective if given in the first few hours of attacks

• Usually only one dose required (subcutaneously; 30mg)

• Well tolerated; pain at injection site

• Efficacy recognised and documented in literature
An RCT involving 27 adults with ACEi angioedema


An observational study involving 13 adults with ACEi angioedema


- We treated 13 consecutive emergency department patients, who had not improved with adrenaline and/or corticosteroids, with icatibant 30mg subcutaneously for ACEi-associated upper respiratory tract angioedema according to an agreed protocol
An observational study involving 8 adults with ACEi angioedema

Summary

ACEi-induced angioedema
• is bradykinin mediated

• reflects intolerance instead of allergy

Icatibant appears to be effective in relieving symptoms