Clinical Toxicology

ACE inhibitors toxicity

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ACE Inhibitors

- An angiotensin-converting-enzyme inhibitors (ACE inhibitor) are a pharmaceutical drug used primarily for the treatment of hypertension (elevated blood pressure) and congestive heart failure.
- This group of drugs cause relaxation of blood vessels, as well as a decreased blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart.
- They inhibit the angiotensin-converting enzyme, an important component of the renin-angiotensin-aldosterone system.

ACE Inhibitors

- ACE inhibitors were initially approved for the treatment of hypertension, and can be used alone or in combination with other antihypertensive medications. Later, they were found useful in other cardiovascular and kidney diseases including:
- Acute myocardial infarction (heart attack)
- Cardiac failure (left ventricular systolic dysfunction)
- Kidney complications of diabetes mellitus (diabetic nephropathy)

Toxic dose of ACE inhibitor drugs

- Only mild toxicity has resulted from most reported overdoses of up to 7.5 g of captopril.
- About 440 mg of enalapril (serum level 2.8 mg/L at 15 hours),
- 420 mg of lisinopril.

Case Reported

A 75-year-old man was found dead after ingesting approximately 1125 mg of captopril, and he had a postmortem serum level of 60.4 mg/L.

- A 33-year-old survived a captopril level of 5.98 mg/L.
- A 45-year-old woman recovered without sequelae after intentional ingestion of 160 mg of candesartan cilexetil along with several other drugs.
- A 2.5-year-old girl ingested 2 mg/kg of perindopril and experienced an asymptomatic transient drop in blood pressure to 65/45 mm Hg approximately 4 hours later.
- A 14-month-old boy ingested 15 mg/kg of irbesartan and reportedly became unsteady on his feet within 1 hour of ingestion and had mild hypotension, but he was acting normally 3 hours later and was discharged home.

Mechanism of toxicity

- **A.** ACE inhibitors reduce vasoconstriction and aldosterone activity by blocking the enzyme that converts angiotensin I to angiotensin II. AR blockers directly inhibit the action of angiotensin II leading to hypotension.
- **B.** Angioedema and cough associated with ACE inhibitors are thought to be mediated by bradykinin, which normally is broken down by angiotensin-converting enzyme. This mechanism induce dry cough and angioedema.
- Note: ARABs dose not induce dry cough and angioedema.
- C. Blocking the aldosterone hormone cause reduction in potassium secretion leading to hyperkalemia.

Clinical presentation

- **A. Hypotension,** usually responsive to fluid therapy, has been reported with acute overdose. Bradycardia may also occur.
- **B. Hyperkalemia** has been reported with therapeutic use, especially in patients with renal insufficiency and those taking nonsteroidal anti-inflammatory drugs.
- **C. Bradykinin-mediated effects** in patients taking therapeutic doses of ACE inhibitors include dry **cough** (generally mild but often persistent and annoying) and **acute angioedema,** usually involving the tongue, lips, and face, which may lead to life-threatening airway obstruction.

Diagnosis

- **History**
- **Laboratory analysis for serum potassium, Blood urea nitrogen and glucose and serum creatinine**.

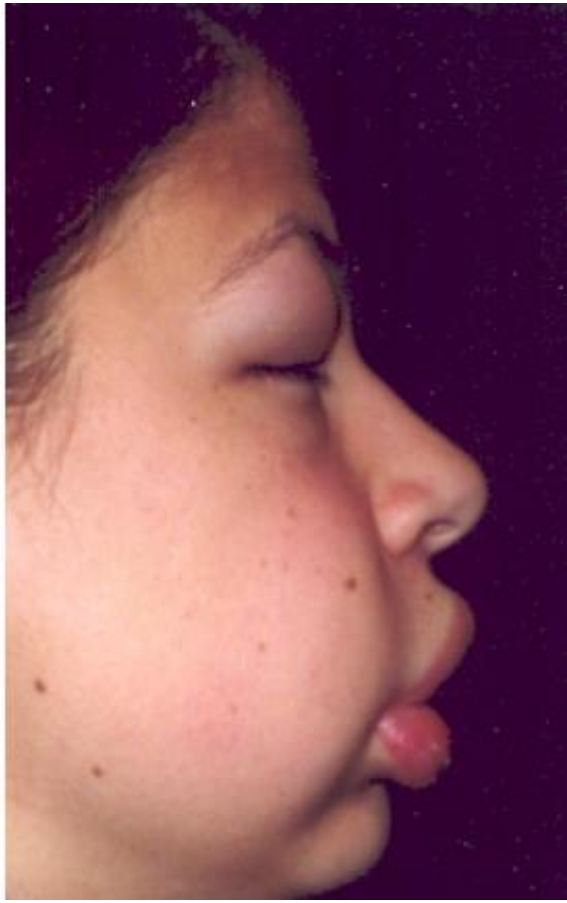
ACE Inhibitors

- **ACE adverse effects**

- Common adverse drug reactions include: hypotension, cough, hyperkalemia, headache, dizziness, fatigue, nausea, and renal impairment. ACE inhibitors might increase inflammation-related pain, perhaps mediated by the buildup of bradykinin that accompanies ACE inhibition.
- The main adverse effects of ACE inhibition can be understood from their pharmacological action. The other reported adverse effects are hepatotoxicity and effect on the fetus.
- Renal impairment is a significant potential adverse effect of all ACE inhibitors, that directly follows from their mechanism of action. Patients starting on an ACE inhibitor usually have a modest reduction in glomerular filtration rate (GFR) that stabilizes after several days.

ACE Inhibitors

- **ACEI-Induced Angioedema**
- Now most common exogenous cause of angioedema seen in emergency rooms
- Angioedema is an inflammatory reaction in which there is increased capillary blood flow and permeability, resulting in an increase in interstitial fluid.
- Angioedema most commonly involves the periorbital, perioral, or oropharyngeal tissues.
- If this process is confined to the superficial dermis, urticaria develops; if the deeper layers of the dermis or subcutaneous tissue are involved, angioedema results.



ACE Inhibitors

- This swelling may progress rapidly over minutes and result in complete airway obstruction and death.
- The pathogenesis of acquired angioedema involves multiple vasoactive substances, including histamine, prostaglandin D2 , leukotrienes, and bradykinin.
- Because ACE also inactivates bradykinin and substance P, ACE inhibition results in elevations in bradykinin concentrations that appear to be the primary cause of both ACEI-induced angioedema and cough.
- There is no evidence that the ACEI-induced angioedema phenomenon is IgE mediated.

ACE Inhibitors

- Face and lips most commonly involved but laryngeal edema reported
- Can cause dramatic swelling of tongue, pharynx, or larynx may require intubation or tracheostomy acutely
- Risk factors include obesity, prior endotracheal intubation and face and neck surgery
- ACE inhibitors will trigger attacks in those with hereditary angioedema (HAE), so avoid in these patients.

ACE Inhibitors

- Angioedema develops in 0.1% to 0.5% of those receiving the drug
- Onset from 1st week of use to 2-3 years of use
- Symptoms resolve within 24-48 hours of cessation of drug
- Most commonly seen with captopril and enalopril, but described with all ACE inhibitors
- Genetic factors may be important
- Subjects with a history of angioedema from other causes are more susceptible to ACE-induced angioedema

ACE Inhibitors

Management

- **Emergency and supportive measures.** Monitor blood pressure and heart rate for 6 hours after ingestion. If symptomatic or significant hypotension develops, observe for at least 24 hours.
- **1.** If hypotension occurs, treat it with supine positioning and IV fluids (Normal saline). **in the most severe cases, hypotension may require pressor therapy (eg. Nor adrenaline).**
- **2.** Treat angioedema with usual measures (eg, Diphenhydramine, corticosteroids) and discontinue the ACE inhibitor. Switching to an AR blocker may not be appropriate as angioedema has also been reported with these agents.

ACE receptor antagonists

- **3. Treat hyperkalemia** if it occurs by administration of (Calcium chloride, Sodium bicarbonate, Glucose plus insulin, inhalation of Beta2 agonist (salbutamol) and hemodialysis which rapidly lower the potassium level.
- **4. Decontamination** Administer activated charcoal orally if conditions are appropriate.
- 5. **Enhanced elimination**. Hemodialysis may effectively remove these drugs but is not likely to be indicated clinically.
- **Note:** ACE receptor antagonists are generally considered to be safe and there are few cases of poising has been reported.

Case study

A 6-year-old white male presents to the emergency department with his parents after accidently ingesting one nadolol tablet. One hour following the ingestion, the child became dizzy and vomited. Because the child appeared to be very sleepy, the parents brought him in for evaluation.

- PMH: None.
- Physical Examination:
- T: 37 °C HR: 100 bpm RR: 22 breaths per minute BP: 100/60 mm Hg
- General: Sleepy, but easily aroused.
- Normocephalic, pupils equal and reactive to light.
- Pulmonary: Clear to auscultation.
- CV: Regular rate and rhythm.
- Neurologic: Unremarkable.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