Angiotensin Converting Enzyme Inhibitor (ACE inhibitor) Toxicity

In addition to their antihypertensive properties, angiotensin-converting enzyme (ACE) inhibitors have been widely accepted for their capacity to slow progressive renal, cardiac, and/or vascular disease. Outcome studies with a variety of ACE inhibitors have resulted in usage indications in conditions, such as congestive heart failure, post-myocardial infarction, and diabetic nephropathy. Most recently, a treatment indication has been granted to the ACE inhibitor ramipril for reducing cardiovascular events in the high-risk cardiac patient without evident left ventricular dysfunction.

Classification:

ACE Inhibitors can be divided into three groups based on their molecular structure:

- Sulfhydryl-containing agents:
  - Captopril, the first ACE inhibitor
- Dicarboxylate-containing agents:
  - Enalapril
  - Ramipril
  - Quinapril
  - Perindopril
  - Lisinopril
  - Benazepril
- Phosphonate-containing agents:
  - Fosinopril

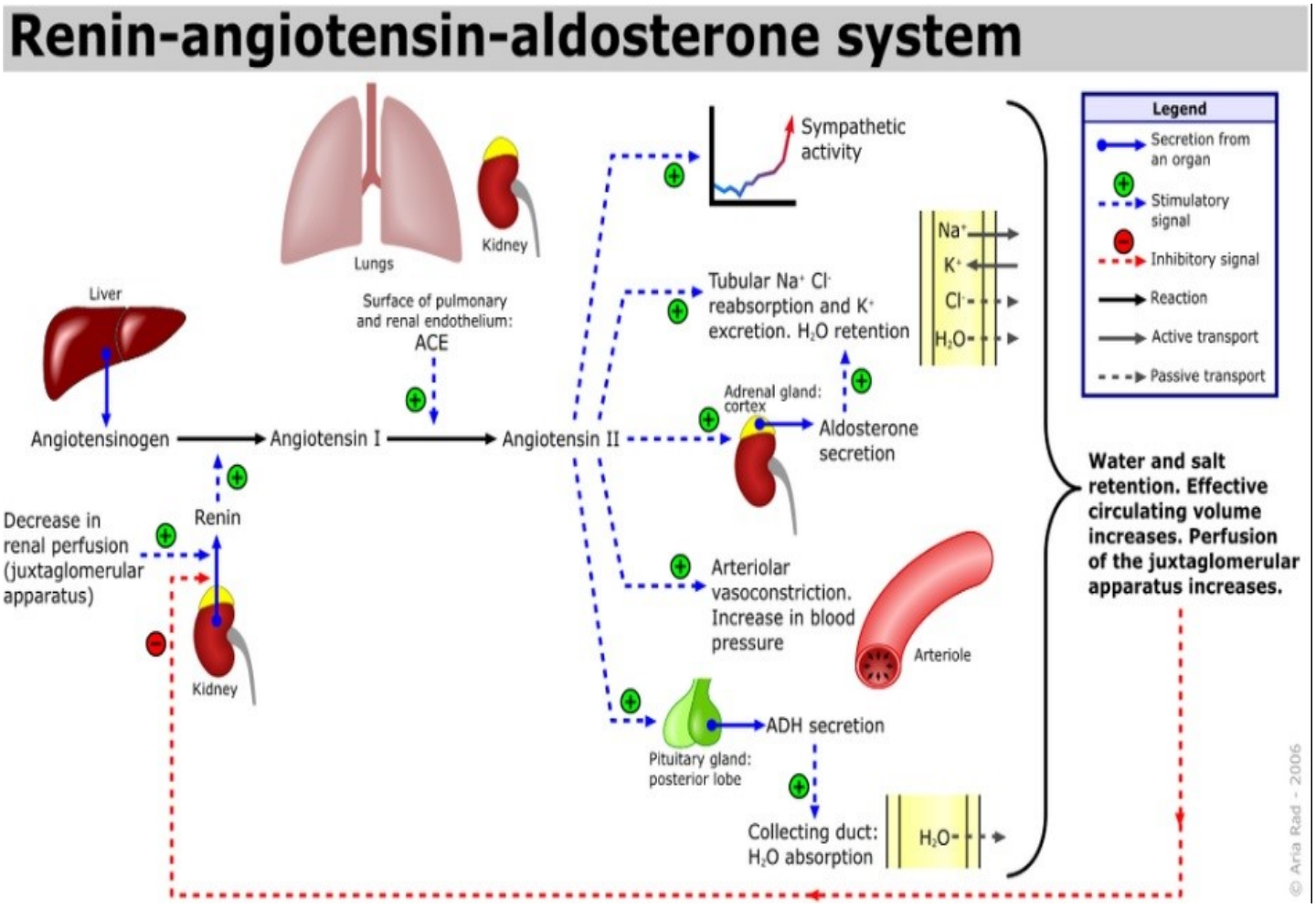
Pharmacokinetics

All of the ACE inhibitors are orally bioavailable as a drug or prodrug. All but captopril and lisinopril undergo hepatic conversion to active metabolites, so these agents may be preferred in patients with severe hepatic

impairment. Fosinopril is the only ACE inhibitor that is not eliminated primarily by the kidneys and does not require dose adjustment in patients with renal impairment. Enalapril is the only drug in this class available intravenously. These drugs are generally well absorbed orally and have highly variable half-lives, volumes of distribution, and protein binding.

Mechanism of action:

ACE inhibitors reduce the activity of the renin-angiotensin-aldosterone system (RAAS) as the primary etiologic (causal) event in the development of hypertension,



Clinical use of ACE Inhibitor:

ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy. Beneficial effects on renal function may result from decreasing intraglomerular pressures, due to efferent arteriolar vasodilation. ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction. Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction. ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease. All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.

Therapeutic and Maximal dose of ACE inhibitor:

Drug	Dose	Start dosing	Usual dose	Maximal dose
Benazepril	10 mg	10	10-20	80 mg
Captopril	50 mg	12.5-25 mg	25-50 mg	450 mg
Enapril	5 mg	5 mg	10-40 mg	40 mg
Fosinopril	10 mg	10 mg	10-40 mg	80 mg
Moexipril	7.5 mg	7.5 mg	7.5-30 mg	30 mg
Perindopril	4 mg	4 mg	4-8 mg	16 mg
Quinapril	10 mg	10 mg	20-80 mg	80 mg
Ramipril	2.5 mg	2.5 mg	2.5-20 mg	20 mg
Trandolpril	2 mg	1 mg	2-4 mg	8 mg

Adverse and Toxic effect of ACE inhibitor:

- Hypotension, 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.
- Dry cough – this is the most frequent symptom (5–30% of cases) during chronic dosing. The cause is unknown, but it may be due to kinin accumulation stimulating cough.
- Functional renal failure – this occurs predictably in patients with hemodynamically significant bilateral renal artery stenosis, and in patients with renal artery stenosis in the vessel supplying a single functional kidney, acute reduction in renal function in this setting is that glomerular filtration dependent on angiotensin-II-mediated efferent arteriolar vasoconstriction, and when angiotensin II synthesis is inhibited, glomerular capillary pressure falls and glomerular filtration ceases. This should be borne in mind particularly in ageing patients with atheromatous disease.
- Hyperkalaemia is potentially hazardous in patients with renal impairment and great caution must be exercised in this setting. This is even more important when such patients are also prescribed potassium supplements and/or potassium-sparing diuretics.
- Fetal injury – ACEI cause renal agenesis/failure in the fetus, resulting in oligohydramnios. ACEI are therefore contraindicated in pregnancy.
- Sulphhydryl group-related effects – high-dose **captopril** causes heavy proteinuria, neutropenia, rash and taste disturbance, attributable to its sulfhydryl group.

- ACE inhibitors cause angioedema most commonly present with swelling of the lips, tongue, or face, although another presentation is episodic abdominal pain due to intestinal angioedema.

Range of toxicity:

Adults: Patients have ingested the following with only mild hypotension reported: 7.5 g captopril, 300 mg enalapril, and 420 mg lisinopril. Fatalities have occurred after ingestions of 1125 mg captopril and 180 mg perindopril.

Children: Less than 6 years old remained asymptomatic after ingestion of up to 8 mg/kg captopril or up to 2 mg/kg enalapril or lisinopril without gastrointestinal decontamination. In one study, children remained asymptomatic after ingestions of up to 100 mg captopril or 30 mg enalapril.

Diagnosis of Toxicity:

Depend on the following:

1) Case history
2) Clinical signs
3) Blood pressure
4) BUN (6–20 mg/dL)
5) serum creatinine
6) ECG
7) Electorlytes (Na, K and Cl)

Treatment:

1. **Stabilization:** Initially, evaluate and correct immediate life-threatening complications (eg, airway, breathing, and circulation). The most common symptom of ACE-inhibitor overdose is hypotension.
2. **Emesis:** Ipecac which can be administered within 30 to 90 minutes of ingestion.

Dose of ipecac syrup:

- Adult: Dose: 15 to 30 milliliters
- Adolescent: Dose: 15 to 30 milliliters
- Child 1 to 12 years: Dose: 15 milliliters
- Child 6 to 12 months: Dose: 5 to 10 milliliters. Position: child in left lateral decubitus position to reduce risk of aspiration.

3. **Activated charcoal:** Consider prehospital administration of activated charcoal as an aqueous slurry in patients with apotentially toxic ingestion who are awake and able to protect their airway. Activated charcoal is most effective when administered within one hour of ingestion.
4. **Hypotensive episode:** Infuse 10 to 20 milliliters/kilogram of isotonic fluid and keep the patient supine. If hypotension persists, administer dopamine or norepinephrine.
5. **Angiotensin Amide:** Angiotensin infusion at doses ranging from 8.5 to 18 mcg/minute has been successful in reversing hypotension in patients who did not respond to volume and pressor infusions.
6. **NALOXONE:** Administration of naloxone has been reported to antagonize the hypotensive effect of captopril.
7. **Hemodialysis**

NOTE:

Asymptomatic patients should be observed for at least four hours post ingestion with frequent monitoring of vital signs. Symptomatic or hypotensive patients should be admitted for at least 24 hours post ingestion or until symptoms have completely resolved.