Cardiovascular Drugs: Calcium channel blockers

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Calcium channel blockers

- Calcium channel blockers (CCBs) were initially introduced for use in the United States in 1981, and extended-release formulations were available 10 years later.

- Indications for use of these drugs are angina, hypertension, arrhythmias, subarachnoid hemorrhage and migraine prophylaxis.

Structure of CCB's

1- Phenylalkylamines: Verapamil

2- Benzothiazepines: Diltiazem

3- Dihydropyridines: nifedipine, felodipine, nimodipine, nicardipine, amlodipine, lercanidipine

4- Diarylaminopropylethers: Bepridil

5- Tertraline Derivatives: Mibefradil

Pharmacology of CCB's

Antagonisms of L-Type channels results primarily in effects on the heart and peripheral vascular smooth muscle.

- Negative chronotropy (decreased heart rate)
- Negative inotropy (decreased cardiac contractility).
- Decrease cardiac out put and Hypotension.

Pharmacokinetics of CCB's

	Absorption (%)	Vd (L/KG)	Protein binding (%)	Half life (h)
Verapamil	>90	4.7	90	4-7
Diltiazem	>90	5.3	80-90	4
Nifedipine	>90	0.8-1.4	90	5
Amlodipin	100	21.4	>95	35

Calcium channel blockers

Block calcium channels (L-type) in heart and blood vessels

- prolong depolarisation
  ↑QRS width
- block SA and AV node conduction
  - heart block
  - asystole
- vasodilators
- cerebral protection

Calcium channel blockers

- Hypotension
  peripheral vasodilatation and myocardial depression

- Bradycardia
  AV and SA node block

Pathophysiology

- CCB's have three main sites of action
  - Myocardial muscle
  - Cardiac conduction system
  - Vascular smooth muscle

- L-type, voltage sensitive, slow Ca++ channels located in cardiac, smooth and skeletal muscle.

Pathophysiology

In myocardial cells, Ca++ entry via L-type channels triggers release of stored intracellular Ca++ affecting excitation contraction coupling

- In cardiac pacemaker cells, Ca++ entry via L-type channels allows for intracardiac conduction via SA and AV nodes

- In vasculature, Ca++ influx maintains tone

Clinical manfestations of CCB's Toxicity

- Hypotention
- Cardiac dysrhythmics: Bradycardia
- Gastroanerities
- Adult Respiratory Distress Syndrome
- Depressed level of consciousness, …
- Hyperglycemia
- Lactic acidosis

Treatment of CCB's Toxicity

- Establish ABCs, obtain intravenous (IV) access, provide Oxygenation.
- Administration of activated charcoal: repeated doses may be used, especially with ingestions of sustained-released agents.
- Whole bowel irritation with polyethylene glycol solution
- Sodium bicarbonate
- Atropin

Treatment of CCB's Toxicity

- Ca salt: Cacl2 10 % (Verapamil and Diltiazem)
- Glucagon (5-10 mg, 2-10 mg/h): Acts via cAMP to increase cardiac contractility and also may decrease heart block.
- Inamrinone (inhibitor of phosphodiesterase III)
- Insulin-Dextrose: 0.1-1 Units/kg/h IV, with mean doses of 0.5 Units/kg/h.
- Hemodialysis and hemoperfusion are not effective.

Cardiovascular Drugs
ACE Inhibitors

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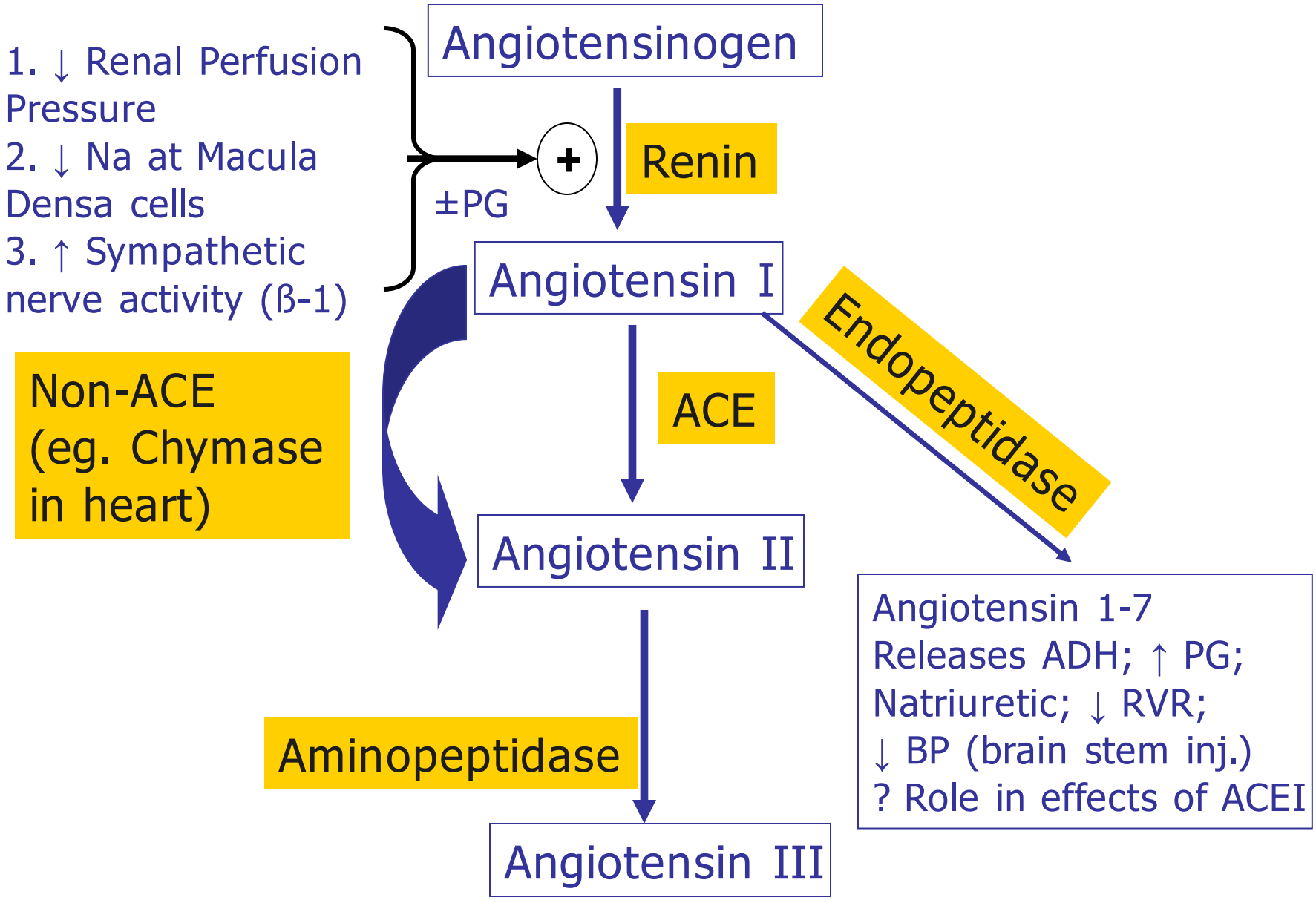
Angiotensin Converting Enzyme Inhibitors

- This class of drugs includes **alacepril**, **captopril**, **enalapril**, **fosinopril**, **lisinopril**, **ramipril**.

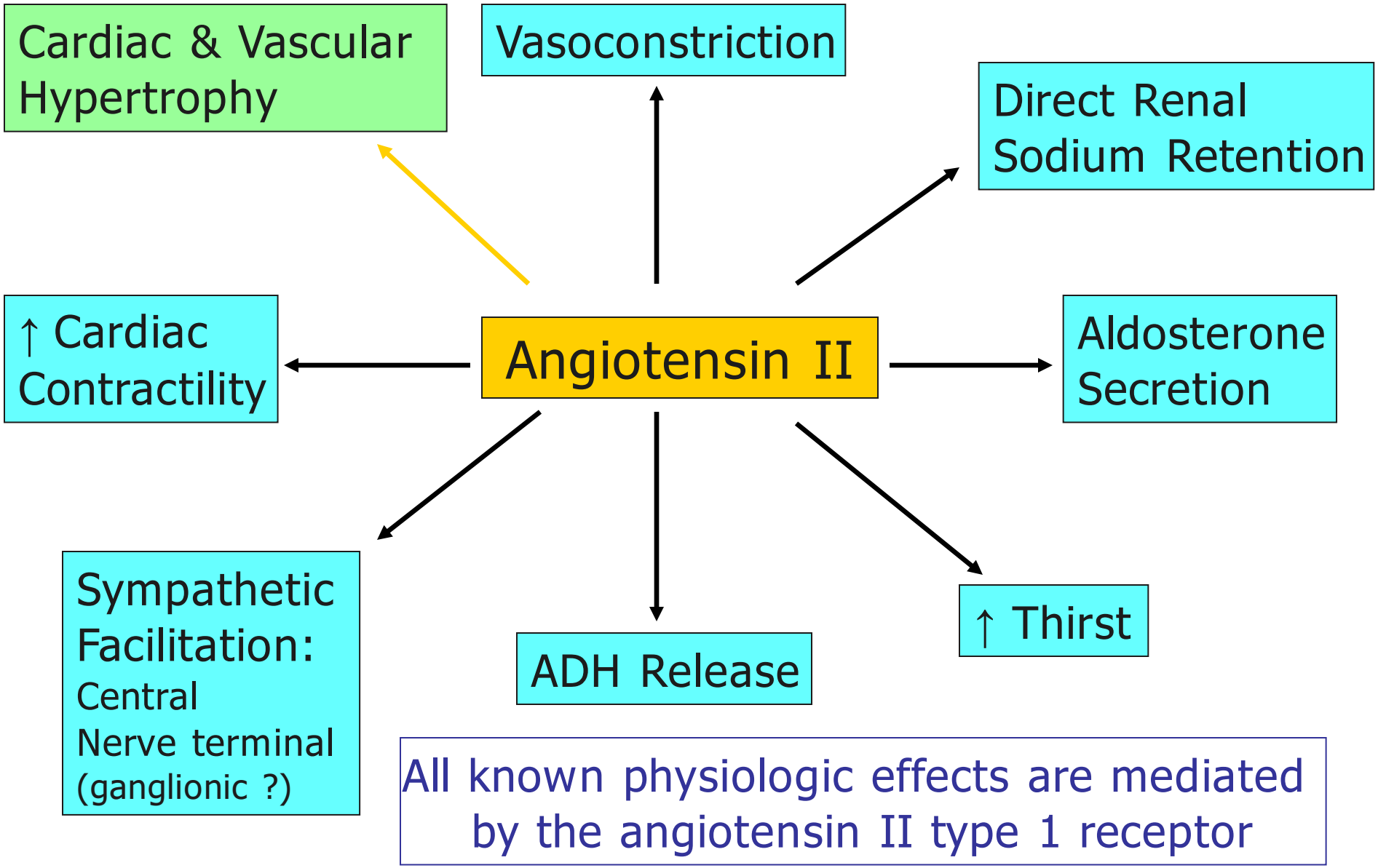
These drugs have a similar therapeutic indications, adverse effects and contraindications and differ mainly in the following:

1. Potency
2. Route of elimination
3. Duration of action
4. Being prodrugs or active drugs (**pentopril, ramipril,** and **enalapril** are prodrugs).

The Renin-Angiotensin System



ANGIOTENSIN II - SUPPORT OF THE BLOOD PRESSURE



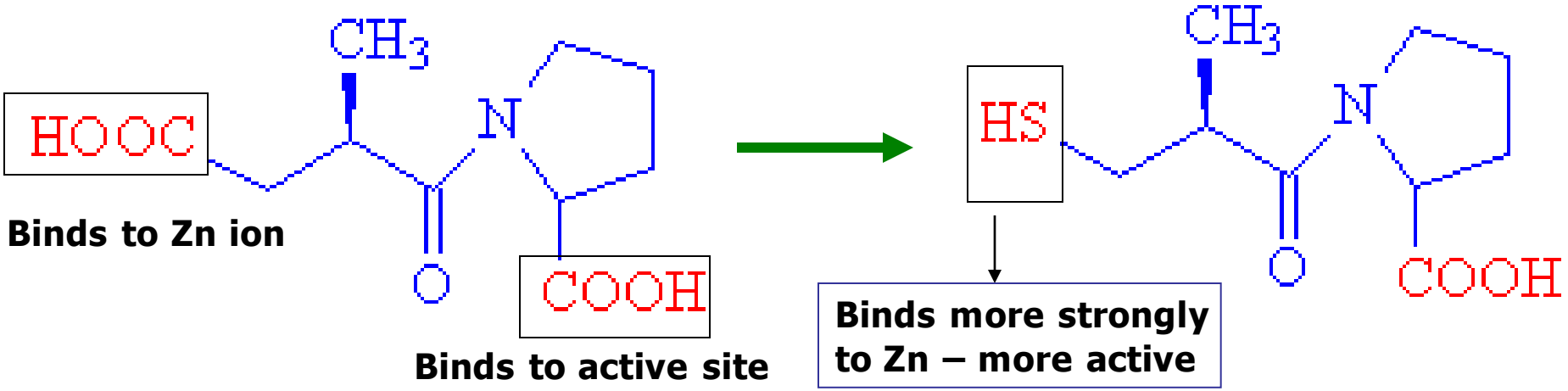
All known physiologic effects are mediated by the angiotensin II type 1 receptor

Adverse Effects

- Hypotension
- Renal Insufficiency (if bilateral renal artery stenosis)
- Hyperkalemia – special group of patients (Na restricted, on K-sparing diuretic, COX inhibitors)
- Cough (20 %)
- Angioedema

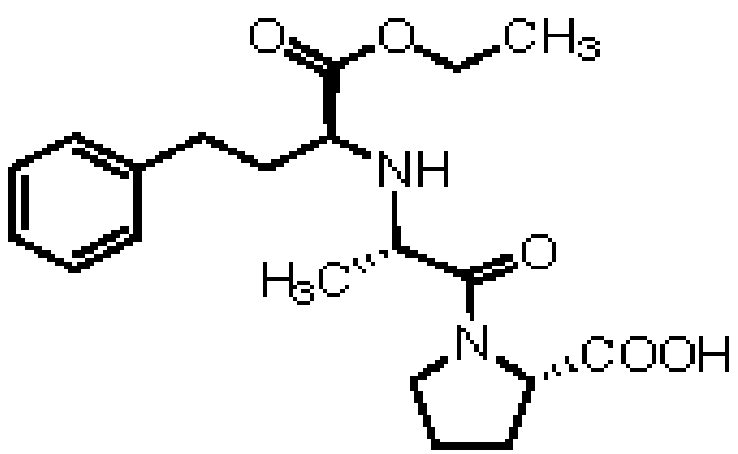
} Kinin-related (?)

- With captopril especially: neutropenia, nephrotic syndrome, skin rash, taste disturbances (SH group- related).

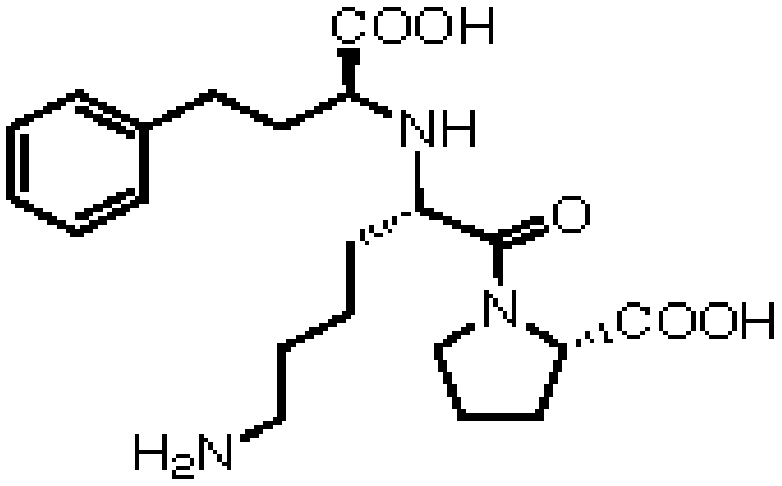


Succinyl derivative of proline

Captopril



Enalapril



Lisinopril

Pharmacology of ACE Inhibitors

- ACE inhibitors work by blocking ACE, located primarily in the pulmonary vascular endothelium and prevents the conversion of angiotensin I to angiotensin II
- Angiotensin II directly acts on blood vessels to cause vasoconstriction.
- Angiotensin II also stimulates aldosterone secretion, causing salt and water retention.
- Angiotensin II participates in the breakdown of bradykinin to inactive compounds. ACE inhibitor use results in accumulation of bradykinin, which may also reduce blood pressure.

Pharmacology of ACE Inhibitors

- The hemodynamic response to ACE inhibitors is mediated by substances that bind to opiate receptors. Angiotensin II is thought to be inhibited by endogenous beta endorphin.
- In vitro studies have demonstrated that captopril can inhibit encephalinase, the enzyme that degrades endorphins. so, the opiate antagonist naloxone is thought to interfere with beta-endorphin inhibition of angiotensin II

Pharmacology of ACE Inhibitors

- ACE inhibitors can cause renal damage by (1) reducing glomerular filtration pressure, (2) decreasing renal blood flow due to systemic hypotension, and (3) producing glomerulonephritis.

Overdose of ACE Inhibitors

Overdose has been reported with **captopril**, **enalapril**, and **lisinopril**. A review of the English literature reports 12 of overdose cases. Another study reviewed cases reported to five regional poison control centers in the United States over a 6-month period. Nineteen cases of overdose with **captopril**, 19 overdoses with **enalapril**, and 12 overdoses with **lisinopril** were reported.

Treatment of ACE Inhibitors Overdose

- Maintain airway and ventilation, serum electrolyte monitor especially sodium and potassium.
- Activated charcoal or hemodialysis.
- Hypotension can be treated by NaCl and Vasopressors.

Treatment of ACE Inhibitors Overdose

- Hypotension can occur with the first therapeutic dose of an ACE inhibitor, and this effect can be blocked by naloxone administration.

- Dysrhythmias can be treated by Lidocaine and Procainamide.