LISINOPRIL

Introduction

Lisinopril is a long acting **angiotensin converting enzyme inhibitor (ACE Inhibitor).**

It does not undergo metabolism and is excreted unchanged entirely in the urine.

It essentially has the same indications, contraindication and adverse effects profile of all the ACE inhibitors.

Outside of the ED the ACE inhibitors, as a class, have clinical utility in:

1. Hypertension:
2. Heart failure:
3. Post myocardial infarction
4. Reduction of cardiac disease risk **irrespective** of blood pressure level before treatment.
5. Some renal disease

Its principle adverse effects include:

1. Hypotension
2. Angioedema
3. Hyperkalemia

See also separate documents on:

- **ACEI Overdose (in Toxicology folder).**
- **Angioedema (in Allergies folder).**

History

Lisinopril was the third ACE inhibitor (after captopril and enalapril) to be introduced into clinical practice in the early 1990s.

Chemistry

Lisinopril is a lysine analogue of enalaprilat (the active metabolite of the prodrug, enalapril).

Lisinopril itself is *not* a prodrug.

Classification

ACE Inhibitors (ACEI) include:

1. Captopril
2. Enalapril
3. Fosinopril
4. **Lisinopril**
5. Perindopril
    - Perindopril (arginine)
    - Perindopril (erbumine)
6. Quinapril
7. Ramipril
8. Trandolapril

Angiotensin II receptor blocking (ARB - also known as "sartan") agents include:

1. Candesartan
2. Eprosartan
3. Irbesartan
4. Losartan
5. Telmisartan
6. Valsartan

Supposed advantages for specific ACE inhibitors are claimed based on pharmacokinetic, metabolic or tissue ACE-binding characteristics, however, these do not translate into significant clinical differences. [2]

Most (except **captopril**) maintain an antihypertensive effect for up to 24 hours and so can be given once daily. [2]

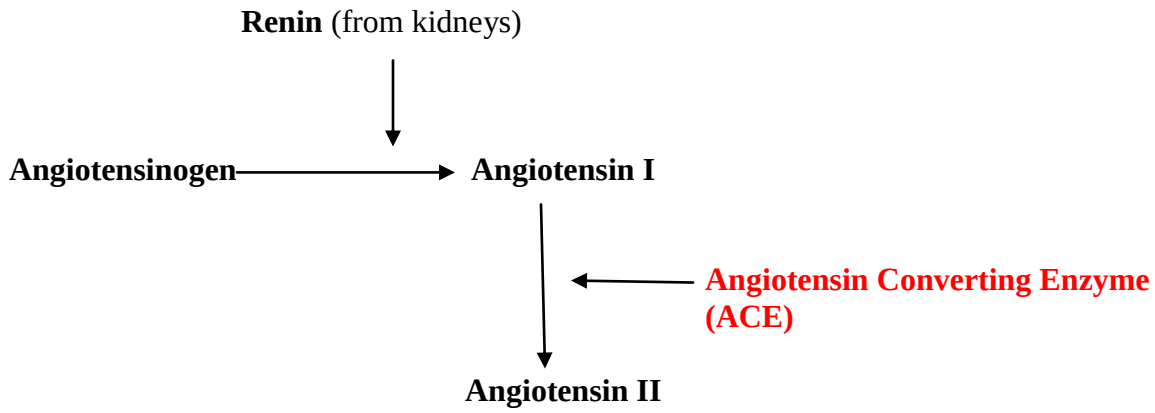
Preparation

Tablets:

Lisinopril dihydrate as:

- 5 mg, 10 mg, 20 mg.

Physiology



The renin-angiotensin-aldosterone system (see also Appendix 2 below)

Renin, is an enzyme synthesized by the kidneys, into the circulation in response to hypotension.

Renin acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide.

Angiotensin I is then converted enzymatically by **angiotensin converting enzyme (ACE)** to the octapeptide **angiotensin II.** The conversion of angiotensin I to angiotensin II takes place in the pulmonary circulation (rather than the plasma).

Angiotensin II has the following actions:

- It is a potent arteriolar **vasoconstrictor**

- It stimulates **aldosterone** secretion from the adrenal cortex, thereby contributing to **sodium** (and so fluid) retention and potassium loss.

Mechanism of Action

The ACE inhibitors:

1. Inhibit the action of ACE:

    - They are highly specific competitive inhibitors of angiotensin I converting enzyme, (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II.

2. Inhibit the breakdown of bradykinin, (see Appendix 1)

Pharmacodynamics

Clinical effects include:

1. Reduction of blood pressure

    - Antihypertensive activity is seen in 1-2 hours after oral administration with peak reduction of blood pressure achieved by about 6 hours.

    - Antihypertensive effects last around 24 hours.

    - Optimal blood pressure reduction may require up to 2 - 4 weeks of therapy.

    - Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure

2. There is a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate

Pharmacokinetics

Absorption:

- Lisinopril is given orally.

  Following oral administration, peak serum concentrations of lisinopril occur within about 7 hours.

Distribution:

- Lisinopril does not have significant protein binding.

Metabolism and excretion:

- **It does not undergo metabolism and is excreted unchanged entirely in the urine.**

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is **< 30 mL/min.** [3]

Indications

Indications for the ACE Inhibitors as a group include:

1. Hypertension:

    - Used as standard treatment, often in combination with other agents.

2. Heart failure:

    - Angiotensin converting enzyme inhibitors (ACEI) are particularly useful in patients with systolic (and probably diastolic) dysfunction. [1]

    - They are frequently used in combination with a diuretic in patients with symptomatic heart failure.

3. Post Myocardial infarct:

    - In patients with left ventricular dysfunction.

      Captopril is indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction, manifested as an ejection fraction less than or equal to 40%, and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients. [3]

4. Reduction of cardiac disease risk:

    - ACEI decrease cardiovascular disease (CVD) risk in patients with established CVD or high absolute CVD risk due to multiple risk factors (particularly hypertension and diabetes), **irrespective** of blood pressure level before treatment.

5. Some renal disease:

    - Diabetic nephropathy (type 1 diabetes)

    - Prevention of progressive renal failure in patients with persistent proteinuria (> 1 gram daily).

Contra-indications/precautions

Contraindications and precautions of the ACE Inhibitors as a group include:

1. History of hypersensitivity to an ACE inhibitor

2. History of angioedema:

   - This can be hereditary, idiopathic or ACE inhibitor-induced. ACE inhibitors increase risk of further episodes.

3. Hypotension

4. Hyperkalemia, (which can also be a side effect)

5. Volume or sodium depletion:

   - This activates the renin - angiotensin - aldosterone system.

     Initiation of an ACE inhibitor this may result in excessive hypotension. Correct before treatment and/or monitor carefully.

6. Caution with other drugs that can raise potassium levels:

   - Potassium supplements and potassium sparing diuretics (use only with **caution** and **close monitoring**).

7. Primary hyperaldosteronism:

   - An ACE inhibitor may have reduced effectiveness of be ineffective; seek specialist advice.

8. Patients with renal artery stenosis:

   - The risk of renal failure is increased, (especially if bilateral).

9. Renal impairment:

   Use with caution and monitor closely:

   As a guide: [2]

   Renal impairment increases risk of hyperkalaemia and may affect the excretion of some ACE inhibitors; use lower initial doses and monitor potassium concentration.

   Renal impairment may worsen, especially in people with hypovolaemia, or if used with NSAIDs (including selective COX 2 inhibitors).

   Serum creatinine may increase after starting treatment or increasing the dose (usually stabilizes within the first 2 months):

- If increase is < 30% or glomerular filtration rate (GFR) reduction is < 25%, there is no need to adjust dose

- If increase is > 30% (or GFR reduction is >25%), investigate other causes and if necessary, reduce dose or stop ACE inhibitor and consider specialist referral.

10. Elderly:

    - May be more predisposed to first-dose hypotension, hyperkalaemia and renovascular disease than younger patients. Start treatment with lower doses; monitor renal function closely.

11. Pregnancy, (contraindicated): [1,4]

    - When pregnancy is suspected, treatment with ACE inhibitors should be discontinued immediately and changing to an alternative antihypertensive, such as methyldopa or labetalol, (see below).

Pregnancy

Lisinopril is a category D class drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Breast feeding:

There have been no reports following the use lisinopril during breastfeeding, and the effects on the breastfed infant are unknown. Consider an alternative medicine where possible.

Shorter acting angiotensin converting enzyme (ACE) inhibitors such as captopril or enalapril are preferred and considered safe to use during breastfeeding

Adverse Effects

Adverse effects of the ACE Inhibitors as a group include:

1. Hypotension:

    - Including **postural hypotension.**

      This most commonly occurs in patients:

      ♥ Commencing treatment (**first dose** in particular).

- ♥ Who are taking other antihypertensive agents.
- ♥ Who have *severe* congestive heart failure

2. Cough: [2]

- A persistent, nonproductive cough is common, possibly due to a bradykinin effect.

  It is not dose-dependent

  It is unlikely to respond to treatment.

  It can occur within days to months of starting treatment.

  The cough may be mild and tolerable, however, some patients need to stop treatment (usually then improves within 1- 4 weeks of stopping).

  Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

3. Angioedema:

- This is usually mild to moderate, but can occasionally be life-threatening.

  It is thought to be due to bradykinin build up.

  Icatibant can be used to treat it.

4. Hyperkalemia:

- Because the ACE inhibitors decrease the formation of angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5 mEq/L may occur.

  Frank hyperkalaemia may occur in patients who have impaired renal function and/ or are taking other agents that can elevate the serum potassium levels and /or are diabetics.

5. Dermatological hypersensitivity reactions.

Dosing [2]

In general terms:

1. Hypertension:

    - *Adult*, initially 5 - 10 mg once daily; if necessary, increase at intervals of 2 - 4 weeks up to 20 mg once daily. Maximum 40 mg daily.

    - *Child > 6 years*, 0.07 mg/kg (maximum 5 mg) once daily; if necessary, increase up to 40 mg once daily. Give first dose under medical supervision.

2. Heart failure:

    - *Adult*, initially 2.5 mg once daily, increased at 4-week intervals up to 20 - 40 mg once daily according to clinical response.

3. Post MI:

    - *Adult*, initially 5 mg within 24 hours of the onset of symptoms (2.5 mg in patients with systolic BP < 120 mm Hg), followed by 5 mg after 24 hours; then 10 mg once daily for 6 weeks; continue treatment in patients developing heart failure.

4. Renal impairment, elderly or taking a diuretic:

    - *Adult*, initially 2.5 - 5 mg once daily.

Monitoring:

Check renal function and electrolytes before starting an ACE inhibitor and review after 1 - 2 weeks of treatment.

Note on concomitant treatment with sartans:

Treatment with an **ACE inhibitor *and* a sartan**: [2]

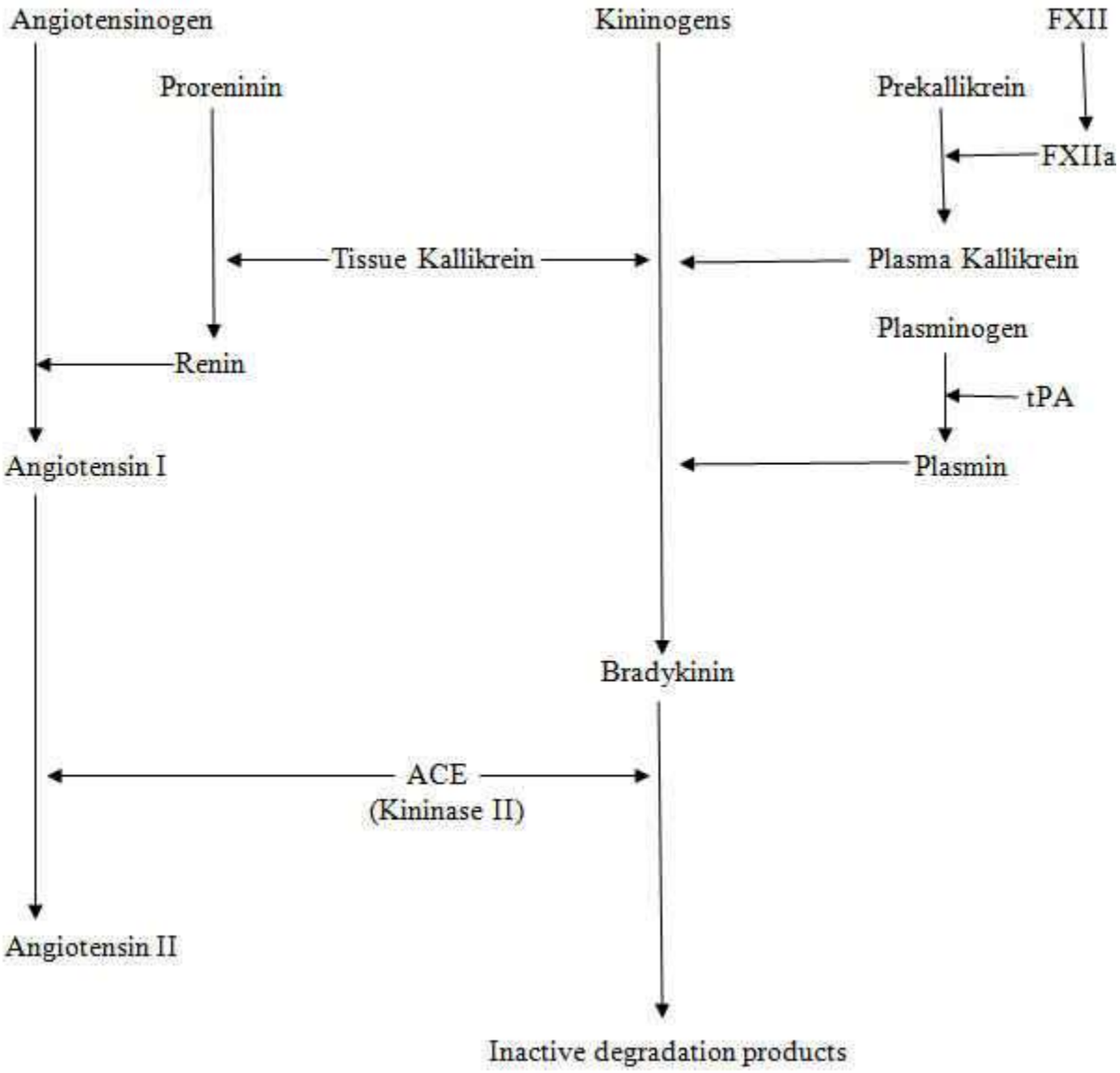
- In trials the combination worsened renal function and increased the risk of symptomatic hypotension and hyperkalaemia

- The combination did not provide additional benefit in patients at high risk of vascular disease nor improve survival in patients with left ventricular failure/dysfunction after MI

- Aldosterone antagonists are preferred to sartans in patients with heart failure who remain symptomatic despite optimal treatment with an ACE inhibitor and a beta-blocker.

- Despite conflicting trial results, it may be an option, e.g. for **selected** patients with chronic heart failure or non-responsive blood pressure, **seek specialist advice.**

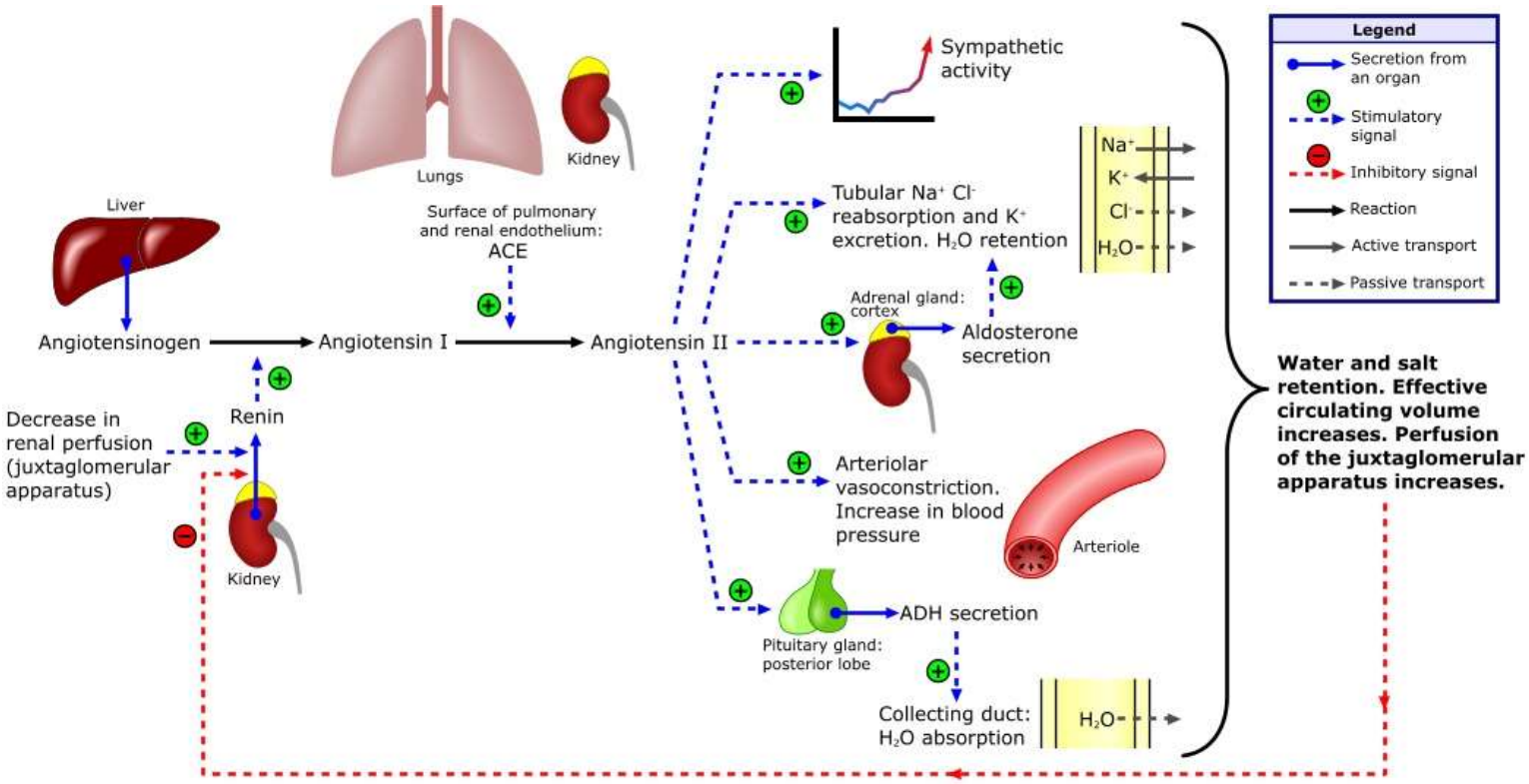
Appendix 1



Biochemical pathways, demonstrating some of the relationships between tissue plasminogen, bradykinin and ACE, in the pathogenesis of angioedema.

Appendix 2

The Renin - Angiotensin - Aldosterone System:



References

1. eTG - July 2015

2. Lisinopril in Australian Medicines Handbook Website, Accessed November 2015.

3. Lisinopril in MIMs Website, 1 January 2015

4. Lisinopril in RWH Pregnancy & Breastfeeding Guidelines; 27 February 2015.

Dr J. Hayes.
December 2015.