ACE Inhibitors & Angiotensin II Antagonists

October 1997 [ii]

Highlights

- ACE Inhibitors (ACEIs) are considered second line agents to thiazide diuretics and β-blockers in patients with uncomplicated hypertension. They may be preferred in patients with coexisting CHF or diabetes.
- ACEIs have similar efficacy and side effect profiles.
- Low initial dosages should be chosen in patients at high risk for hypotension.
- Lisinopril has the advantage of low cost, od dosing, ↓ mortality data in CHF, & a favorable peak/trough ratio.
- Losartan (Cozaar®) may be an alternative in patients with hypertension who do not tolerate ACEIs.

The past decade has seen a dramatic increase in cardiovascular agents and available dosage forms. This edition of *The Rx Files* will evaluate and compare the angiotensin converting enzyme inhibitors (ACEIs) and the angiotensin II (AII) receptor antagonists.

Pharmacokinetics

All ACEIs are active when taken orally. With the exception of captopril (Capoten®) and lisinopril (Prinivil®/Zestril®), the majority are prodrugs that are converted in the liver to their active metabolites. Captopril has a rapid onset of <1 hr but a short duration that necessitates BID-TID dosing. Lisinopril and the prodrugs have a slower onset (1-2hr) but generally a 24h duration of action so most can be given once daily; some patients may require BID dosing if the desired effect diminishes significantly towards the end of the dosing interval. ACEIs are excreted in whole or in part by the kidney and all but fosinopril (Monopril®) require dose reduction in renal impairment.

Hypertension

At equipotent doses, the ACEIs are similar in efficacy and safety. When used alone, ACEIs will control BP in approximately 50% of patients[1]; black patients and those with low renin concentrations may not respond as well. Combination therapy with a thiazide diuretic or calcium channel blocker will control BP in an additional 30% of patients.[1] In uncomplicated patients, thiazides and β-blockers are still considered first line antihypertensives because long term trials have shown reductions in mortality. Until more is known about ACEI effect on morbidity and mortality, they remain *second line* therapy, except in patients where thiazides or β-blockers are contraindicated or not tolerated.[2,34] ACEIs may be preferred as first line antihypertensives in patients with diabetes or CHF.[2]

Agents that can be given once daily may improve patient compliance. To be suitable for once daily dosing, the FDA suggests an antihypertensive's trough effect should be ≥50 % of the peak effect.[3] Compared to other ACEIs, enalapril (Vasotec®) and lisinopril may offer better 24h BP control with once daily dosing due to minimal fluctuation between peak and trough effect[3].

Congestive Heart Failure

ACEIs are effective in the treatment of patients with heart failure (HF) and have been shown to significantly reduce morbidity and mortality.[4,5,6,7,8,9] ACEI therapy reduces both symptoms and hospitalizations due to HF.[10,11] Long term benefits appear greater in patients with low ejection fractions. Captopril, enalapril, lisinopril and ramipril (Altace) have shown decreased mortality in studies, although the effect is thought to be a class effect.[12]

The optimal dosing of ACEIs in HF is unknown. Lower dosages are effective in improving symptoms and exercise performance. However, major clinical trials showing reductions in mortality have used somewhat larger target doses (See ACEI Comparison Chart: dosage range*). Slow titration up to the target dose is recommended to reduce side effects. Initial dosages (po) used in studies included enalapril 5mg bid, captopril 12.5mg tid, lisinopril 5mg od, and ramipril 2.5mg bid.[4,6,9,10,13,14,15] Patients at high risk for hypotension were started at half the usual initial dose and titrated as tolerated.

ACEI therapy following MI has been shown to reduce progression to symptomatic heart failure and improve survival, especially when initiated within 24 hours.[13,14,15]

One conflicting study which used enalaprilat IV showed a trend towards harm, possibly due to overly aggressive administration and secondary hypotension.[16,33] Caution should be taken to avoid excessive hypotension. Current literature supports the use of ACEIs for 4-6 weeks post-MI in all patients who are clinically stable and do not have major contraindications to ACEIs (Table 2).[16] Patients with left ventricular dysfunction (ejection fraction of <35-40%) would benefit from longer term treatment.[16]

Diabetic Nephropathy

ACEIs are beneficial in preventing renal complications secondary to diabetes.[17] They reduce proteinuria and slow the progression of nephropathy in IDDM.[17,18] Some studies also show benefit in NIDDM. Beneficial effects are seen both in hypertensive and normotensive patients suggesting that some of their effects are independent of their antihypertensive effects. ACEIs also delay the development of nephropathy in diabetics with micro-albuminuria.[19,20,21] These appear to be a class effects.

Pregnancy/Pediatric Considerations

ACEIs are contraindicated in pregnancy and should be avoided. ACEIs are not officially approved for the pediatric age group. There is limited clinical experience with captopril in children but its use should be under the recommendation and supervision of a specialist.

Adverse Effects

ACEIs are generally well tolerated. Side effects are summarized in Table 3. **Hyperkalemia** is often associated with diminished renal function and/or concurrent use of potassium(K^+) sparing diuretics, K^+ supplements, or salt substitutes. Serum K^+ should be monitored in these patients and drugs that increase serum K^+ reduced or discontinued as necessary. **Acute renal failure** may occur especially in patients with bilateral renal stenosis or severe nephrosclerosis. **Angioedema** has been reported but is a rare, although potentially fatal reaction.[22] All ACEIs should be avoided if this occurs.

Hypotensive reactions may occur after the first dose of an ACEI. In some cases hypotension **can be severe**. Time course and duration depend on the drug's kinetics and metabolism; both onset and resolution are more rapid with captopril than the longer acting ACEIs. Risk factors include CHF, volume depletion due to Na^+ restriction, diuretic use, nephrotic syndrome, hemodialysis and hepatic disease. Stopping diuretics 24h prior to the first ACEI dose (given at hs) is recommended. Initial doses should be low and titrated upwards as tolerated.[22]

Dry, non-productive **cough** is now recognized as a frequent, bothersome side effect of ACEIs and is the most common reason for discontinuation. Incidence is conservatively estimated at 10%.[23] The mechanism responsible is likely related to ACE inhibition of bradykinin catabolism. Symptoms appear within days to weeks after starting ACEI therapy; resolution usually occurs within days of stopping the offending agent but may take up to 4 weeks.[24]

Severity of symptoms can sometimes be minimized with a reduction in dose. Successful changes to alternate ACEIs may be due in part to differences in dosages, rather than in the drugs themselves.[24] If patients find the cough intolerable, discontinuing the drug is often the only suc-cessful option. Switching to losartan may be effective.

Angiotensin II Antagonists

Recent research focusing on more selective modulation of the renin-angiotensin system (RAS) has resulted in the development of **losartan** (Cozaar®), the first of the angiotensin II (AII) receptor antagonists. Losartan specifically inhibits angiotensin II at the tissue level. Unlike ACEIs, losartan has no effect on the kallikrein-kinin system so safety and tolerability are likely to be improved if bradykinin related side effects such as cough can be avoided.[25] In comparative clinical trials, losartan demonstrated similar efficacy in hypertension to ACEIs. Losartan has also shown a decrease in mortality in CHF and further studies are currently in progress.[25, 26, 33]

Currently losartan is only approved for treatment of hypertension, and until more is known about its overall effect on morbidity and mortality, it is considered a second line agent. Like the ACEIs, it is reserved for patients in whom thiazides or β-blockers are ineffective, contraindicated, or poorly tolerated.[27] An initial dose of 25mg daily can be used in elderly or volume depleted patients while 50mg daily will control BP in most individuals. Increasing the dose does not appear to significantly improve efficacy although some patients may require up to 100mg per day. Maximum BP lowering may take up to 6 weeks, therefore one should allow adequate time before increasing the dose.[25,27]

The most common side effects (incidence >1%) seen with losartan include headache, dizziness, and fatigue. In clinical trials only dizziness occurred more frequently than with placebo.[28] In comparative trials, losartan had similar efficacy to other antihypertensives but caused less fatigue than β-blockers, less edema than calcium channel blockers, and less cough than ACEIs.[29] Compared with ACEIs, first dose hypotension is not as problematic with losartan probably due to more gradual generation of its active metabolite and lack of effect on bradykinin.[28] Hyperkalemia can occur but is less likely due to losartan's reduced effect on aldosterone.[30] Losartan does cause an increase in circulating angiotensin II but it is unknown if this causes any long term side effects.[28]

References available on request

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Supplementary Tables

Table 1

Major Drug Interactions
Lithium
levels can increase 3-4X after 2-4 days of ACEI initiation
reduce lithium dose and monitor lithium levels
Potassium Supplements, Potassium Sparing Diuretics
potassium retention, potential severe hyperkalemia
Diuretics
Increased risk of first-dose hypotension if hypovolemic
NSAIDs
sodium and water retention, decreased effect of ACEI, and increased risk of nephrotoxicity

Table 2

Contraindications
Absolute
pregnancy
history of angioedema or hypersensitivity to ACEIs
bilateral renal artery stenosis (RAS) or RAS of a solitary kidney
history of intolerance to ACEIs due to hypotension
severe hyperkalemia
Relative
• hypotension (SBP < 90mm)
• renal dysfunction
• hyperkalemia
• cough

Table 3

Adverse Effects
• symptomatic hypotension
• dizziness, fatigue, headache
• dry, non-productive cough (>10%)
• angioedema - rare but serious side effect (~0.1%)
• hyperkalemia (with drug interactions/renal insufficiency)
• taste disturbance - more common with captopril (2%)
• rash - more common with captopril (4-7%)
• acute renal failure in patients with *renal artery stenosis* or *severe nephrosclerosis*
• bone marrow suppression: neutropenia, thrombocytopenia, aplastic anemia, pancytopenia; extremely rare, but patients with *renal failure* or *collagen vascular disease* are at increased risk.
• nephrotic syndrome - rare but has been seen with high dose captopril >150mg/day

Table 4

ACEI Induced Cough[24]	
Treatment Options *	**Comments**
Discontinue ACEI and use alternate agent(s)	Easiest in hypertension because many treatment options; more difficult in CHF or nephropathy. Some success with switch to **losartan** (Cozaar®).
Reduce dosage	Not always possible or effective. May decrease severity but not occurrence.
Use **alternate ACEI**	Minimal success due to high cross-reactivity. Some reports suggest fosinopril best alternative.[31]
Sodium cromoglycate (Intal®)	Has shown some efficacy, and reasonably well tolerated. May induce bronchospasm.
Baclofen, NSAIDs, theophylline, nifedipine, & bupivacaine have also been tried but are **not generally recommended**.	

***** based on case reports and small trials

Table 5

Comparative Cost For 30 Days Treatment With Commonly Used Antihypertensives	
hydrochlorothiazide 12.5-25mg po daily	$ 8.00
atenolol 50mg po daily	$ 20.00
acebutolol 200mg po bid	$ 25.00
lisinopril 10mg po daily	$ 36.00
enalapril 10mg po daily	$ 42.00
enalapril 5mg po bid	$ 64.00
felodipine 10mg po daily	$ 43.00
diltiazem CD 180mg po daily	$ 50.00

We wish to acknowledge those who have assisted in the development and review of this newsletter: Dr. Z. Tymchak (FM), Dr. M. Jutras (FM), Dr. J. Akhtar (Cardiol.), Dr. R. Herman (Pharmacol.), Barb Evans, BSP, MSc, and the CDUP Advisory Committee.

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