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Renoprotective effects of ace - I in patients with chronic kidney diseases

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There is a growing number of evidences that corroborate the renoprotective effects of ACE-I in chronic kidney diseases. This class of medicaments is going to be indispensable in the treament and prevention of renal diseases. I would like to design my discussion in three parts:

1.Pathogenic aspects of chronic kidney diseases
2.Clinical trials
3.Therapeutic management of chronic kidney deseases with ACE-I.

According to glomerular hyperfiltration theory, all renal diseases that affect the renal parenchyma and also the surgical partial ablation, have as a serious consequence the loss of nephron mass. This nephron loss, is followed by the adaption of remained nephrons. This is reflected by an increase of blood flow in these nephrons, increase of glomerulary capillary pressure and finally, hyperfiltration. The hyperfiltration is the basis for further nephrosclerosis , the loss of nephrons number and the total reduction of renal function and the patient goes toward end-stage renal disease (1)

Later on it was postulated (Barker hypothesis), that even low birth weight is the cause of end -stage renal disease in adult life. Low birth weight is associated with low nephron number and this event is complcated later in the adult life by hypertension and progressive glomerulopathy. In this case, similar to the partial renal ablation, the progression of nephropathy ends in uremia.

It was shown that, in all these cases, some measures can be taken , to slow the progressive renal injury. These measures consists in dietetic protein restriction and the use of ACE-I and ARB (angiotensin II receptor blockers). These measures aim the improvement of elevated glomerular capillary pressure and the slowing of glomerular scarring with reduced nephron dropout. (2)

In the process of progressive nephropathy, Ang II plays a central and very important role. Ang II exerts this effect through glomerular hemodynamic changes as well as through the following non-hemodynamic effects(3):

1. Oxydant injury
2. Aldosterone injury
3. Proteinuria
4. NF-kβ

NF-kβ has the ability to upregulate various cytokines, chemokines, TGF-β, cell adession molecules etc.

The direct consequences of Ang II effects are:

- Mesangial cell proliferation
- Increased extracellular matrix proteins

- Stimulation of PAI-1
- Macrofage activation

All these events directly influences the focal and global glomerulosclerosis and tubulo- interstitial fibrosis.

Let us see now some of the most important clinical trials that demostrate the positive effect of ACE-I in the progressive renal injury.

The Collaborative Study Group (Lewis et al. New Eng J. Medicine. 1993) in his study included 407 patients They were diabetics with proteinuria > 500 mg/ dl. These patients were divided in two groups: The first group was treated with captopril (ACE-I). The second group received placebo. After the study period the conclusion was that in the captopril group the effect was a 50 % reduction of combined risk (ESRD or death).

Later on, in another important study (EUCLID trial, 1996), 530 patients with IDDM were treated for 24 months with Lisinopril 10-20 mg/d or placebo. At the end of the study there was a difference (5 mmHg) of the diastolic blood pressure in the lisiniopril group vs placebo treated patients. Beyond that, albumin excretion rate reduction was 18.8 % greater in the lisinopril group vs. placebo group. In patients with macroalbuminuria this parameter was 49.7 % greater in the group of patients treated with lisinopril. Retinopathy was seen at the end of the study in 24 % of the lisinopril group vs. 26 % in the placebo group.

At the same time, Maschio et al. published the AIPRI trial in the New Eng. J. Med. (Angiotensin converting enzyme inhibition in progressive renal disease). In this study, 583 patients with chronic renal disease were divided in two groups: 1.Benazepril group (treated for three years) 2. placebo group. At the end of the study it was shown that treatment with ACE-I resulted in 53 % reduction of doubling of serum creatinine or need of hemodialysis.

One year later, the REIN study (Ramipril efficacy in Nephropathy (Lancet 1997) sudied 352 patients with non diabetic renal diseases were treated with Ramipril (first group) or placebo (second group). It was observed that in patients with proteinuria .> 3 gr / d there was significantly lower rate of decline of GFR when treated with ACE-I.

A metaanalysis was published in 2001 in Ann Int Med (AIPRID study) . This included 11 randomised trials.1860 non diabetic patients were studied. The conclusion was that ACE-I are more effective than other antihypretensives in: a. slowing the progression of renal diseases b. reducing proteinuria. (4)

Recently the COOPERATE trial (Lancet 2003) studied 336 patients with non diabetic renal diseases. These patients were followed for 3 years. they were divided according to the therapy in three groups: a.) losartan b.) trandolapril c.) losartan + trandolapril . It was that combination treatment (group c.) was more effective in reducing progression of renal disease. Also the combination treatment was more effective in reducing urinary protein excretion.

A great debate still exists on which of the following medicaments is more beneficial:ACE-I or Diuretics? As a rule, the physician has to apply the strategy of acchieving BP goal using drugs hat are antiproteinuric and attenuate Ang II and aldosterone effects. The ALLHAT study (Appel et al, JAMA 2002) which aimed the evaluation of anti hypertensive and lipid lowering treatment to prevent heart attack concluded that chlortalidone reduced some cardiovascular risks better than ACE-I, DH-CCB or doxazocin. Then one has to ask: are diuretics the first line treatment of HBP? According to the ALLHAT study, this can be the truth but the clinician has to keep in mind that diuretics stimulate renin- angiotensin system. Beyond that, diuretics reduce only congestive heart failure in salt sensitive states and they reduce stroke only in African-Americans. So it is reasonable to consider that unless edema forming states or HF is present, ACE-I or ARB are preferred as initial therapy. This was corroborated also in MDRD study where 60 % of patients received no diuretics at all and they achieved the blood pressure goal. This was true also in 40 % of patients in AASK study (5).

Another question that has to be solved is: Which is better, ACE-I or ARB ? Generally ACE-I and ARB can be the initial choice (6). Both of them are antiproteinuric and reno-protective. But it yet has to be verified whether ARB are cardioprotective to the level of ACE-I. In an attempt to resolve this question the HOPE trial (New Eng J. Med. 2000) studied the effects of ACE-I. There was shown that ramipril significantly reduced the composite end point of death, stroke , miocardial inarction and each component of the composite end point. In fact the LIFE trial (Lancet 2002) showed that losartan reduced significantly the composite end-point of death, stroke, miocardial infarction but of the individual components, only stroke was significantly reduced.

The advantage of ACE-I vs.ARB can be explained even theoretically as follows:

- ACE-I increase bradikinin levels which is antifibrotic and vasodilatory
- ACE-I decrease PAI-1 (so degrade matrix protein)
- ACE-I suppress better aldosterone which is profibrotic
- Lisinopril, captopril, enalapril are available as generics while ARB are not generic

In the clinical situations, the pharmacological management of kidney diseases with ACE-I has the avantage of reducing proteinuria by 1/3. Also the greater the proteinuria, greater is the benefit of ACE-I in slowing CKD progression. Beyond that, ACE-I are generally well tolerated in renal insufficiency (serum creatinine > 3 mg/dl) but caution is advised.

As all the drugs , ACE-I are not without adverse effects, but they can not serve as an argument to negate the superority of these drugs. Some of the adverse effects of ACE-I are:

- Reversible acute renal failure. This is true mainly in stenosis of renal artery where the treatment

with ACE-I has to be considered carefully.

- Hyper-potassiemia.
- Anemia can be accentuated due to the loss of erythropoetin sensitivity from ACE-I use.
- Anaphylactoid reaction can occur in hemodialysis where filters with polyacrlonitrile are used.

What can be recommended as the the pharmacological regimen of ACE-I?

First, one has to begin with low doses of ACE-I. (lisinopril 2.5 mg) even if blood pressure is at goal. If the patient is intolerant to ACE-I, then ARB has to be applied.

Second, if blood pressure is not at goal after 2-4 weeks, titrate ACE-I upwards (lisinopril up to 10-40 mg) (7). After 2-4 weeks, if blood pressure yet is not at goal a diuretic therapy must be added. If blood pressure is not at goal even after 2-4 weeks of diuretic therapy establishment, then ARB can be added (2.8.)

Some suggested regimen in order of preference are:

1. ACE-I + ARB + Diuretics + β blocker
2. ACE-I + ARB + Diuretics + NDH-CCB
3. ACE-I + ARB + Diuretics + Clonidine
4. ACE-I + ARB + Diuretics + α blocker

As a conclusion what can be recommended as the best strategy for renoprotection in chronic renal patients? May be the magic formula proposed by Brenner (Kidney Internatonal 2003) is preferable: ASTACE (aspirin + lovastatin + lisinopril).

Actually on can be concluded that, the clinician has many alternatives available in the long way of renoprotection of patients with renal desases.

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