THE EVALUATION THERAPEUTIC EFFECTS OF RAMIPRIL IN PEDIATRIC NEPHROTIC SYNDROME

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Abstract: *angiotensin-converting enzyme (ACE) inhibitors delay progression of nephrotic syndrome (NS) and have antiproteinuric effects beyond their effects on blood pressure. While the antihypertensive and renoprotective potency of angiotensin-converting enzyme (ACE) inhibitors is well-established in adults with hypertension and/or nephrotic syndrome, little experience exists in pediatric nephrotic syndrome. The aim of the present study was to investigate the effect of ramipril on proteinuria and blood pressure (BP) in children with steroid- resistant nephrotic syndrome (SRNS).*

Keywords: *ramipril, steroid-resistant nephrotic syndrome, hypertension, proteinuria, blood pressure monitoring.*

ОЦЕНКА ТЕРАПЕВТИЧЕСКИХ ЭФФЕКТОВ РАМИПРИЛА ПРИ НЕФРОТИЧЕСКОМ СИНДРОМЕ У ДЕТЕЙ

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Аннотация: *ингибиторы ангиотензинпревращающего фермента (АПФ) задерживают прогрессирование нефротического синдрома (НС) и оказывают антипротеинурический эффект помимо их влияния на артериальное давление. Хотя антигипертензивная и ренопротективная активность ингибиторов ангиотензинпревращающего фермента (АПФ) хорошо известна у взрослых с гипертонией и / или нефротическим синдромом, при нефротическом синдроме в педиатрии такой опыт мало изучен. Целью настоящего исследования было изучение влияния рамиприла на протеинурию и артериальное давление (АД) у детей с стероид-резистентным нефротическим синдромом (СРНС).*

Ключевые слова: *рамиприл, стероид-резистентный нефротический синдром, гипертония, протеинурия, мониторинг артериального давления.*

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Actuality: Most antihypertensive agents currently used in children are administered off label. Historically, explicit approval for pediatric use has usually not been applied for by the manufacturers because clinical studies in children are more demanding than trials in adult patients with respect to various ethical, biometrical, and practical issues [1]. Hypertension is not only a consequence of the nephropathy but, together with proteinuria, is also an important risk factor for progression of the primary renal disease. Angiotensin-converting enzyme (ACE) inhibitors are recommended drugs of choice in patients with renoparenchymal hypertension [2]. Many studies in adults have demonstrated that ACE inhibitors have not only antihypertensive but also antiproteinuric and renoprotective effects in patients with diabetic as well as nondiabetic nephropathies. In children, ACE inhibitors have been used since late 1980s, but these agents have usually been used for reduction of proteinuria in children with nephrotic syndrome. In recent years, routine blood pressure monitoring (RBPM) has also been shown to have various advantages over the casual blood pressure (BP) measurement in children [3]. In the pediatric clinical trials reported so far, only ACE inhibitors of the older generation (captopril, enalapril) have been studied. Ramipril is an ACE inhibitor of a newer generation that has been successfully used in adults. There are few studies on ramipril in children, which examined the effect of this agent on BP and albuminuria in 13 children with chronic kidney diseases. The aim of our

prospective study was to evaluate the efficacy and safety of ramipril in children with SRNS and hypertension, proteinuria, or both [4].

Materials and methods. The study was conducted in Republican Research Centre for Emergency Medicine during 1 year period. For trial was involved twenty cases of steroid-resistant nephrotic syndrome in children. Patients of nephrotic syndrome not showing decreasing in nephrotic range proteinuria (persistently more than 3.0 g/day) despite 12 weeks administration of oral prednisolone in the dose 2 mg/kg body weight on alternate days were considered to have steroid-resistant nephrotic syndrome irrespective of histologic type. The patients were advised to take a protein diet ranging between 0.7-1.0 gm/kg body weight /day depending upon renal function. Moreover, all patients were on sodium restricted diet. Normotension was defined as systolic and diastolic blood pressure less than 120 mmHg and 90 mmHg respectively without antihypertensive therapy. The patients

were examined every month. Daily urinary protein excretion, renal functional impairment (assessed by mean serum creatinine concentrations), mean arterial pressure, serum potassium and serum cholesterol and side effects of the drugs were carefully recorded in each patient during follow up.

Results. All patients completed the study period of six month. At the end of 6 months of treatment the mean 24 hours urinary protein excretion decreased from 3,5 ± 1,5 g/day to 1,7 ± 0,8 g/day in 15 children and declined from 3,5 ± 1,5 g/day to 2,0 ± 1,2 g/day in 5 children. The reduction in proteinuria was statistically significant from the 2nd month and stayed lower than the initial level throughout the study period. The crucial reduction of proteinuria was occured at the end of 6 months only in 5 patients. At the end of 6 months of treatment, 11 (55%) patients had full remission of proteinuria (< 0,3 g/day) and 9 (45%) patients had proteinuria, ranging between 0,3-0,8 g/day. Average arterial pressure declined from 128/90 mmHg to 115/80 mmHg in 13 (65%) patients during in 1 months of treatment period and remained in this degree till the end of 6 months period. In 6 (30%) patients, mean arterial pressure declined from 130/92 mmHg to 118/88 mmHg second month treatment period and stayed stayed in normal degree till the end of treatment period. In one patient (5%), the treatment respond to Ramipril in terms of decreasing arterial pressure has occurred from 4th month treatment period. The average serum albumin level increased from 2.55 ± 0.70 gm% to 3.32 ± 0.46gm%. There was not significant change in the mean S. Creatinine at the end of 6 months of therapy. The kidney function remained stable. There was a significant reduction in serum cholesterol level, no substantial changes in the serum sodium and potassium levels were noted during the study.

Conclusions: Numerous short-term studies have shown that ACE inhibitors are superior to other antihypertensive drugs (with the exception of carvedilol, verapamil, and diltiazem) in their ability to reduce proteinuria in patients with kidney diseases of nondiabetic etiology. In one of the largest randomized placebo

controlled studies have studied the efficacy and safety of ramipril in patients with kidney disease of non-diabetic origin [5-6]. Thus, in the REIN study (Ramipril Efficacy in Nephropathy), the effects of ramipril in 352 patients with chronic non-diabetic kidney disease and proteinuria more than 1 g / day were evaluated using a double-blind method. The effects of ramipril were studied in patients of two different categories - with proteinuria from 1.0 to 2.9 g / day and with proteinuria more than 3 g / day. The severity of proteinuria in patients with nephrotic syndrome correlates strongly with an increase in progression of nephropathy. Moreover, recent clinical trials support the concept that reduction of proteinuria correlates with a slowed progression of nephropathy with preservation of renal function in subjects with proteinuric non-diabetic nephropathies. Further, the greater the degree of proteinuria reduction, the greater the slowing of renal disease progression in subjects with non-diabetic nephropathies. Thus, heavy proteinuria is responsible for all the clinical manifestations and complications of nephrotic syndrome and severity of proteinuria is a strong independent risk factor for the progression of renal disease. Therefore, reducing proteinuria should be a therapeutic goal in itself in proteinuric patients with progressive renal failure. This study showed that reduction in proteinuria was statistically significant from 1st month onwards in ramipril and this reduction was sustained throughout the period of 6 months. Ramipril had a sustained antiproteinuric effect with proper control of BP and well-maintained serum albumin concentration (within normal limits). Renal function remained stable. The renoprotective effect of ramipril was all the more it is expressed, the more was the original proteinuria and the more daily proteinuria decreased under the influence of therapy. Renoprotective effect of long-term therapy with Ramipril was most significant in those patients in whom proteinuria was more severely reduced after a month of therapy [7-8]. Therefore, to a certain extent, it is possible to predict the effectiveness of long-term treatment of ACE inhibitors in chronic non-diabetic kidney diseases according to the degree of reduction of the initial proteinuria after a short course of treatment. According to REIN trials, patients with severe proteinuria in further observed for 3 years, during which they all received an ACE inhibitor ramipril. Kidney damage progressed to the stage of terminal CRF in 30% of patients initially randomized to receive placebo, but none of the patients originally randomized to receive ramipril. In the group of patients with proteinuria of less than 3 g / day, GFR decreased to the same extent in those receiving ramipril and placebo. Proteinuria increased by 15% in placebo and decreased by 13% in those receiving ramipril ($p = 0.003$). The increase in proteinuria and the progression of kidney disease to the terminal CRF stage in patients who received placebo were significantly more common than in patients who received ramipril (relative risk 2.72, $p = 0.01$; 2.40, $p = 0.005$, respectively). Thus, ACE inhibitor ramipril reduces proteinuria and slows the progression of non-diabetic kidney disease to the stage of terminal CRF, and its renoprotective effects are more pronounced in patients with significant proteinuria.

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