ENALAPRIL TREATMENT OF PROTEINURIA IN NORMOTENSIVE CHILDREN

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ENALAPRIL V LIEČBE PROTEINÚRIE U NORMOTENZNÝCH DETÍ

Abstract

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A retrospective study was performed in 48 normotensive proteinuric children to evaluate the effect of enalapril (n=17), a combination of enalapril and prednisone (n=11) and prednisone alone (n=20) on urinary protein excretion and systemic blood pressure. Enalapril treatment was associated with significant and persistent diminution of proteinuria from 1.32±0.23 to 0.53±0.11 and 0.44±0.07 g/day on the 4th and 8th week of treatment, respectively. Combined therapy with enalapril and prednisone resulted in a comparable significant reduction of proteinuria from a pre-treatment value of 2.06±0.42 to 0.63±0.22 and 0.52±0.17 g/daay on the 4th and 8th week of treatment, respectively. In contrast to this, in the group treated with prednisone alone, proteinuria decreased significantly only from the 6th week of therapy (p<0.02). Consequently, these children had significantly higher urinary protein losses at the 4th week of treatment as compared to patients on enalapril treatment (given either alone or combined with prednisone) (p<0.01 and p<0.05, respectively). Importantly, the enalapril-induced reduction of proteinuria was unrelated to variations in arterial blood pressure and no significant changes in this parameter were observed. The results indicate that enalapril can be used safety and effectively for symptomatic treatment of proteinuria in normotensive children with preserved renal function. ACE inhibitor provides additive antiproteinuric effect to corticosteroids by accelerating the rate of diminution of proteinuria. Its combination with prednisone may be of particular importance in those cases, where the degree of hypoproteinemia is a concern. ***(Tab. 2, Fig. 1, Ref. 29.)***
***Key words: Enalapri*l treatment, prednisone, proteinuria, normotensive children, blood pressure.**

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Abstrakt

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Enalapril v liečbe proteinúrie u normotenzných detí
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Na hodnotenie účinku enalaprilu (n=17), kombinácie enalaprilu a prednizónu (n=11) a samého prednizónu (n=20) na vylučovanie proteínov močom a hodnotu systolického krvného tlaku bolo uskutočnené retrospektívne sledovanie u 48 normotenzných detí s proteinúriou. Liečba enalaprilom viedla k signifikantnej a pretrvávajúcej redukcii proteinúrie z 1,32±0,32 na 0,53±0,11 a 0,44±0,07 g/deň v 4. a 8. týždni liečby. Kombinovaná liečba s enalaprilom a prednizónom viedla k porovnateľne signifikantnej redukcii proteinúrie z predliečebnej hodnoty 2,06±0,42 na 0,63±0,22 a 0,52±0,17 g/deň v 4. a 8. týždni liečby. Na rozdiel od týchto výsledkov v skupine liečenej prednizónom proteinúria klesla signifikantne až od 6. týždňa liečby (p<0,02). Tieto deti mali aj signifikantne vyššie straty proteínov močom 4. týždeň liečby v porovnaní s pacientmi liečenými enalaprilom (buď samostatne alebo v kombinácii s prednizónom) (p<0,01 a p<0,05, resp.). Dôležité bolo pozorovanie, že enalaprilom indukovaná redukcia proteinúrie nebola spojená s variáciami arteriálneho krvného tlaku a nepozorovali sa žiadne signifikantné zmeny tohto parametra. Tieto výsledky naznačujú, že enalapril sa môže bezpečne a účinne použiť v symptomatickej liečbe proteinúrie u normotenzných detí so zachovanou funkciou obličiek. ACE-inhibítor poskytuje prídavný antiproteinurický účinok ku kortikosteroidom akceleráciou rýchlosti redukcie proteinúrie. Jeho kombinácia s prednizónom môže mať význam najmä v prípadoch závažnejšej hypoproteinémie. *(Tab. 2, obr. 1, lit. 29.)*
Kľúčové slová: liečba Enalaprilom, prednizón, proteinúria, normotenzné deti, krvný tlak.

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Introduction

Treatment of proteinuria and nephrotic syndrome is, if by any means possible, directed to improve the underlying disorder. In many cases, however, no such curative approach is possible, and therapy will be restricted to symptomatic approach. This symptomatic treatment aims at lowering urinary protein loss, not only to prevent the plasma albumin (and other proteins) to fall and plasma cholesterol to rise, but also prevent a progressive loss of renal function. The types of treatment advocated for this purpose are the non-steroidal anti-inflammatory drugs, dipyridamole, low protein diets and, more recently, the angiotensin-converting enzyme (ACE) inhibitors (4, 5, 16, 22, 23).

The antiproteinuric efficacy of ACE inhibitors has been extensively investigated in hypertensive and normotensive adults with various types of nephropathies; in most studies, ACE inhibitors lowered proteinuria by about 50 % (5, 6, 17, 19). Moreover, in experimental models, ACE inhibition has been shown to alleviate or arrest glomerular sclerosis, at least partly, by reducing proteinuria (1, 2, 11, 18, 27, 29). This antiproteinuric and renoprotective efficacy of the ACE inhibitors is not shared by most other conventional antihypertensive medications and may be related not only to theirinfluence on systemic and renal hemodynamics, but also on permeability characteristics of the glomerular basement membrane (7, 9, 10).

To date, there is still limited experience on the use of ACE inhibitors in treatment of normotensive children with proteinuria and nephrotic syndrome (15, 19, 23, 28). Therefore, in this retrospective study, we decided to evaluate the effect of enalapril treatment on urinary protein excretion and systemic blood pressure in normotensive proteinuric children with or without nephrotic syndrome.

Patients and methods

During a 18 months period, 48 children were studied. Patients were included into the study according to the following criteria: (1) persistent proteinuria of more than 0.5 grams per day in at least three consecutive urine samples, with or without clinical and biochemical features of nephrotic syndrome; (2) serum creatinine of less than 1.0 μmol/L; (3) normal arterial blood pressure for appropriate age and weight; (4) no limitation in dietary protein and salt intake and (5) renal biopsy prior to the treatment with light-microscopic, immunofluorescent and electron-microscopic evaluation of the renal tissue samples.

According to the treatment schedules, patients were divided into three groups, which were comparable by age and sex of the subjects and also by the character of the underlying morphological lesions (Tables 1 and 2). The first group of patients (n=17) received enalapril for their proteinuria (ENAP group). A second

Tab. 1. Clinical data and morphological characteristics of the glomerular disease in three groups of children with proteinuria. Patients were treated for their proteinuria with enalapril (ENAP group), with enalapril in combination with prednisone (COMBI group) or received monotherapy with prednisone (PRED group).
Tab. 1. Klinické údaje a morfologické charakteristiky glomerulárnych ochorení v troch skupinách detí s proteinúriou. Pacienti boli liečení pre proteinúriu enalaprilom (ENAP skupina), enalaprilom v kombinácii s prednizónom (COMBI skupina) a samým prednizónom (PRED skupina).

	ENAP group	Combi group	PRED group
Number of children	17	11	20
Mean age (range) years	13.7 (8-17)	12.6 (7-16)	12.3 (6-16)
Sex (male/female)	10/7	6/5	12/8
Minimal change NS	10	4	11
Membraneous GN	3	3	4
Mesangioproliferative GN	2	3	3
Membranoproliferative GN	2	1	2

GN = glomerulonephritis, NS = nephrotic syndrome
GN = glomerulonefritída, NS = nefrotický syndróm

Tab. 2. Effect of various treatment regimens on mean arterial pressure, GFR, serum creaatinine and albumin concentrations and urinary protein excretion in three groups of proteinuric children.
Tab. 2. Účinky rôznych liečebných režimov na priemerný artériový tlak, GFR, sérové koncentrácie kreatinínu a albumínu na exkréciu proteínov močom v troch skupinách proteinurických detí.

Treatment	Enalapril	Enalapril	Enalapril+ Prednisone	Enalapril+ Prednisone	Prednisone	Prednisone
Patients n	17	17	11	11	20	20
Time interval	before treatment	after 8 weeks of treatment	before treatment	after 8 weeks of treatment	before treatment	after 8 weeks of treatment
Mean AP mmHg	78.17±2.05 (79.17)	77.17±2.51 (77.50)	75.33±4.06 (70.00)	67.33±3.55 (68.33)	83.50±2.56 (80.00)	84.90±2.52 (85.00)
GFR ml/s/1.73 m^2	1.99±0.09 (2.00)	1.90±0.12 (1.89)	1.84±0.14 (1.98)	2.19±0.10 (2.20)	1.61±0.10 (1.65)	1.89±0.08 (2.05)
Serum creatinine μmol/L	57.90±3.72 (55.50)	64.76±4.53 (57.50)	47.68±4.55 (46.00)	53.20±5.78 (45.00)	60.25±4.66 (55.00)	55.90±3.15 (49.00)
Serum albumin g/L	40.36±1.31 (42.30)	41.52±1.04 (41.25)	23.62±1.67 (25.70)	40.00±0.87 (40.40)	32.85±1.64 (34.50)	39.50±1.63 (40.50)
Proteinuria g/day	1.32±0.23 (1.19)	0.43±0.07 (0.40)	2.06±0.42 (2.10)	0.52±0.17 (0.42)	1.67±0.23 (1.50)	0.42±0.14 (0.18)

Values are given as mean±SE (median).
Hodnoty sú udávané ako priemer±medián

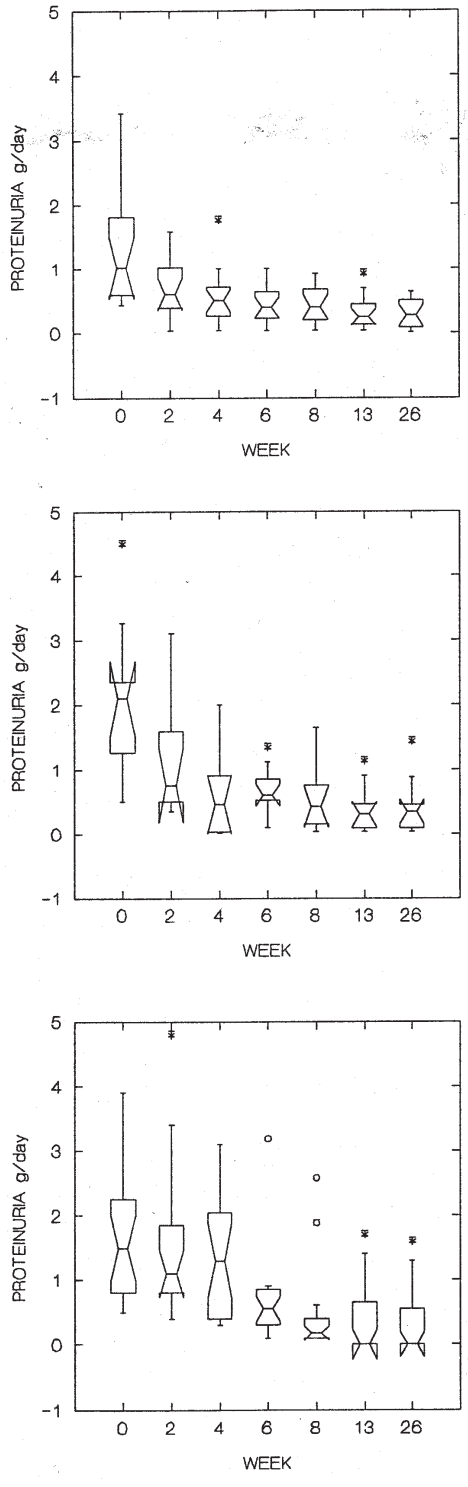

Fig. 1. Sequential changes of urinary protein excretion in normotensive children with various glomerular diseases treated with enalapril (upper panel), enalapril and prednisone (middle panel) or prednisone alone (lower panel).
Obr. 1. Postupné zmeny exkrécie proteínov močom u normotenzných detí s rôznymi glomerulárnymi chorobami liečenými enalaprilom (horný panel), enalaprilom a prednizónom (stredný panel) a samým prednizónom (dolný panel).

group of 11 patients received enalapril in combination with prednisone (COMBI group). Data of this group were compared with results from a third group of proteinuric children (n=20) who were treated with prednisone (PRED group). Monotherapy with enalapril was generally indicated in children with mild or moderate proteinuria, while combined enalapril—prednisone treatment or monotherapy with corticosteroids was prefered in more severe forms of proteinuria usually with clinical and laboratory features of nephrotic syndrome. Enalapril was administered, in both the ENAP and the COMBI groups, at a dose of 2.5 to 5 mg/day; prednisone was given, either alone or in combination with enalapril, at a dose of 1 to 2 mg/kg until the cessation of proteinuria, but at least for 6 months.

The effect of the various treatment regimens was evaluated during a 6-months follow-up period by serial measurements of arterial blood pressure, serum creatinine and albumin concentrations, 24 hours urinary protein excretion and creatinine clearance. Urinary protein excretion was determined in two-week intervals by biuret method in aliquots of 24-h urine collection. Systolic and diastolic blood pressure was measured weekly after at least 10min of supine rest with a standard mercury sphyngomanometer. Mean arterial pressure was calculated as diastolic blood pressure plus one third of pulse pressure. Serum albumin and creatinine as well as urinary creatinine were determined weekly using a standard autoanalyser.

Results were expressed as mean±SE as well as median values. Sequential changes of proteinuria in patients on individual treatment regimens were evaluated by ANOVA for repeated measures followed by post hoc test for multiple comparisons. The differences between the individual groups for a given time interval were tested by independent t-test and linear regression analysis was applied to detect correlations between the parameters of interest. Statistical significance was assumed at a P values of less than 0.05.

Results

The clinical and biochemical characteristics of the three groups at baseline and after 8 weeks of treatment are summarized in Table 2. Sequential changes of proteinuria in various treatment regimens during 6-months follow-up period are depicted on Graph 1.

Initial proteinuria prior to the treatment tended to be higher in both the COMBI or PRED groups (2.06±0.42 and 1.67±0.23 g/day, respectively) as compared to the ENAP group (1.32±0.23 g/day), however this difference did not reach statistical significance. Accordingly, initial plasma albumin levels were higher in the ENAP group (40.36±1.31 g/L) than either in the COMBI or the PRED groups (23.62±1.67 and 32.85±1,64 g/L, respectively) (Table 2). The lower rate of urinary protein loss and the higher plasma albumin values in the ENAP group reflect differences in entry criteria.

In the ENAP and COMBI groups, a significant decrease in proteinuria occured in the 4th week of therapy and urinary protein losses remained within similar levels during the whole treatment period (Table 2); the mean protein loss was 0.53±0.11 and 0.44±0.07 grams per day in the ENAP group and 0.63±0.22 and 0.52±0.17 grams per dayin the COMBI group at the 4th and 8th week of treatment, respectively. In contrast to this, the reduction

of urinary protein excretion was slower in the PRED group, where proteinuria decreased significantly and persistently only from the 6th week of therapy ($p<0.02$). As a result, at the 4th week of treatment, these patients continued to excrete significantly more proteins into their urine than subjects either from the ENAP or the COMBI groups ($p<0.05$ and $p<0.01$, respectively). The mean levels of urinary protein loss in the PRED group were 1.35±0.19 and 0.42±0.15 grams per day in the 4th and 8th week of treatment, respectively. There were no apparent differences in the antiproteinuric efficacy in subgroups of patients with different morphological features of the glomerular disease.

Reduction of proteinuria was associated with a significant increase in serum albumin levels in both the COMBI and PRED groups ($p<0.01$). Importantly, there were no significant changes in any of the groups in mean arterial pressure, serum creatinine, or glomerular filtration rate during the entire study (Table 2). In particular, no patient had to reduce the dose of enalapril due to the occurrence of hypotension or any other side effects of the drug. We did not find any significant correlation between changes in MAP and in protein loss ($r=0.08$, p=NS) or between variations in serum creatinine and in proteinuria ($r=0.19$, p=NS).

Discussion

Urinary protein loss is a laboratory finding that accompanies many renal diseases. Curative treatment of the underlying disorder is often not possible and, in these cases, therapy will be restricted to symptomatic approach. Attention has therefore drawn to therapeutic interventions that reduce urinary protein excretion and may give symptomatic relief to severe proteinuria and nephrotic syndrome with their accompanying risk factors for morbidity and mortality (3, 4, 13, 20, 24). Moreover, diminution of the rate of urinary protein excretion may be a contributing factor in slowing the progression of renal disease. Indeed, in experimental models, ACE inhibition has been shown to alleviate or arrest glomerular sclerosis, at least partly, by reducing proteinuria (1, 29).

Of the various antiproteinuric treatments, most evidence to date is available on the antiproteinuric and renoprotective efficacy of ACE inhibitors in hypertensive and normotensive adults with diabetic nephropathy and primary glomerular diseases (2, 3, 5, 6, 8, 14, 26). Our present study provides evidence that enalapril can be used safety to treat proteinuria also in normotensive children with preserved renal function. It has the ability to effectively decrease non-nephrotic proteinuria as well as proteinuria in the nephrotic range. We found, that enalapril lowered protienuria around 70 % during the first 8 weeks of therapy. This value is somewhat higher than the average reduction seen in adult patients (3) and might be, at least partly, due to different patient selection and/or sampling time in our study. We cannot exclude a more benign course of pediatric diseases with tendency to spontaneous improvement, however this seems to be a less likely explanation, as the degree of diminution of proteinuria in our patients was independent of the underlying glomerular pathology.

Importantly, the enalapril-induced reduction of proteinuria was unrelated to variations in mean arterial blood pressure and no significant changes of this parameter were observed during the study. This is in accordance with earlier reports in normotensive adults and children with diabetic nephropathy or primary glomerular diseases (5, 12, 14, 15). Monotherapy with enalapril was associated with significant and persistent reduction of urinary protein losses from the 4th week of treatment, indicating that the maximal antiproteinuric efficacy of ACE inhibition should be assessed only several weeks after start of treatment both in clinical practice and in future studies. Such a delayed onset of the maximal therapeutic effect suggests, that it may be related to mechanisms other than acute modification of systemic and renal hemodynamics (7, 8, 9). Although this aspect could not be directly tested in this clinical study, available data suggest, that several mechanisms may be involved, including improved intrarenal hemodynamics (reduced postglomerular arteriolar resistance), hormonal effect (reduced angiotensin II production and, hence, decreased glomerular hyperpermeability), changes in the permeability properties of the glomerular capillary wall (this might also result from a direct effect) and probably anti-inflammatory, anti-proliferative and antiplatelet activities of ACE inhibitors (3, 10, 13, 16, 21).

Since ACE inhibitors presumably lower proteinuria by different mechanisms than corticosteroids, combination of the two drugs seems to be beneficial in patients with severe proteinuria and nephrotic syndrome when pathogenetic treatment of the underlaying disorder is also indicated. It must be acknowledged however, that the present study was mainly retrospective and the individual treatment modalities were not randomly allocated. Nevertheless, the groups of interest treated either with combination of enalapril and prednisone or with prednisone alone were comparable in respect to age and sex of the subjects, type of the underlying renal disease and baseline serum creatinine and albumin levels, so it allows us to draw certain conclusions. Our results indicate, that ACE inhibition may provide additional antiproteinuric efficacy to corticosteroids by accelerating the rate of diminution of proteinuria during the first weeks of treatment without significantly influencing its overall velocity. In our patients, combination of enalapril and prednisone speeded up the diminution of proteinuria during the first weeks of treatment, so a statistically significant decrease of urinary protein excretion occurred earlier than in the group of patients treated with prednisone alone (Fig. 1). Therefore, it can be suggested to combine enalapril and prednisone, mainly in cases of severe proteinuria and nephrotic syndrome, where the degree of hypoproteinemia is a concern.

It should be mentioned, that Sauter and Bakris (26) described an initial increase in proteinuria during a three-week course of enalapril in subjects with idiopathic membraneous glomerulopathy, who also received prednisone in high doses. However, after withdrawal of enalapril, proteinuria returned to the pre-treatment value and, when these patients were re-challenged with enalapril, proteinuria decreased. It might be that the initial rise in proteinuria in their study was related to the concomitant treatment with glucocorticoids, however this phenomenon did not occur in any of our normotensive pediatric patients on combined treatment. Importantly, we found no evidence of a new nephrotic syndrome developing in any of the patients during enalapril treatment, given either alone or in combination with corticosteroids. Also, there were no apparent differences in the overall antiproteinuric efficacy of the treatment in subgroups of patients with different morphological features of the glomerular disease.

In conclusion, our data indicate, that enalapril has a potential to safety and effectively reduce urinary protein losses in normo-

tensive children with various glomerular diseases. Reduction of proteinuria occurs without alterations in the systemic blood pressure and is probably due to local effects of enalapril within the kidney. Enalapril in combination with corticosteroids speeds up the diminution or cessation of proteinuria; this may be preferable in cases where the level of hypoproteinemia is a concern. Whether enalapril-induced reduction in proteinuria will favorably influence the long-term outcome of renal function could not be evaluated from this study. Further studies are needed also to establish the categories of primary glomerular disease in children in which long-term treatment with converting enzyme inhibitors is best indicated.

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