Enalapril influence on blood pressure and echocardiographic parameters in children with acute postinfectious glomerulonephritis

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Key words: *glomerulonephritis, blood pressure, echocardiography, angiotensin-converting enzyme inhibitors.*

Summary. *The aim of the study was to evaluate the effects of early treatment with the angiotensin-converting enzyme inhibitor, enalapril, on the blood pressure and left ventricular diameters and function in children suffering from acute postinfectious glomerulonephritis.*

Patients and methods. A total of 51 children with acute postinfectious glomerulonephritis were involved in the study. Out of them, 26 patients were treated with enalapril for 6 weeks, 25 patients served as their controls. Their blood pressure was measured every other day in the early course of the disease, after 6–8 weeks, and after 6 months. 2D, M-mode, pulsed-wave Doppler echocardiography were performed on 18 enalapril treated patients and 14 controls on admission to the hospital and after 6–8 weeks.

Results. An earlier decline in blood pressure was found in the enalapril treated patients, with no difference between the groups at 6 months after onset of acute postinfectious glomerulonephritis. Comparison of the echocardiographic findings at the onset of acute postinfectious glomerulonephritis and after 6–8 weeks of enalapril treatment showed a significant decrease of left ventricular end-diastolic diameter (4.42±0.71 cm before treatment vs. 4.19±0.69 after treatment, $p<0.001$), left ventricular end-systolic diameter (2.81±0.59 cm vs. 2.64±0.48 cm, respectively, $p=0.04$), left ventricular mass (102.56±51.86 g vs. 86.77±43.54 g, $p<0.001$), and mitral peak flow velocity of late filling (0.54±0.11 m/s vs. 0.49±0.09 m/s, $p=0.02$). Other parameters, although statistically nonsignificant, showed better improvement in the enalapril treated patients than in those untreated. In the enalapril untreated group, echocardiographic parameters did not change significantly.

Conclusion. A better antihypertensive effect was found in the enalapril treated patients, as well as better improvement of echocardiographic parameters, early in the disease. Whether these effects of enalapril have some influence on the outcome of acute postinfectious glomerulonephritis requires further study.

Introduction

Acute postinfectious glomerulonephritis (APGN) is a frequent form of glomerulonephritis in developing countries. In most cases, the outcome of APGN is favorable: more than 90% of patients have no later effects (1). However, D. S. Baldwin *et al.* (2) and R. Sesso *et al.* (3) assert that from 30% to 60% of adults and one-third of children suffer from irreversible changes, such as proteinuria, high blood pressure, and impaired renal function. Complications in the acute phase of the disease include hypertensive encephalopathy, and acute renal and heart failure. Hypertension, edema, electrolyte imbalance, anemia, and complement activation products may influence cardiac function and structure (4). Heart involvement, as well as proteinuria and high blood pressure, are factors that influence the outcome of renal diseases (5, 6).

Because the long-term prognosis of the disease is controversial, it is important to identify medication that will best influence a positive outcome for the patient. There are only few studies on the management of APGN (7). Angiotensin-converting enzyme (ACE) inhibitors are well known for their renoprotective action in adults and children (8, 9), as well as for the management of cardiovascular diseases, from hypertension to heart failure (10, 11). As cardiac involvement is found in APGN patients (12), we can postulate that enalapril might be a useful drug in the treatment

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of these patients due to its positive effect on the heart and kidneys. We evaluated the influence of enalapril on the blood pressure (BP) and echocardiographic left ventricular (LV) parameters, systolic and diastolic function in children with APGN.

Patients and methods

Fifty-one children treated in the Vilnius University Children's Hospital for APGN were included into a randomized, open, controlled, III phase trial. The inclusion criteria were: acute tonsillopharyngitis or other infection of upper respiratory tract, or impetigo 1–4 weeks before kidney disease; at least one symptom of acute nephritic syndrome: edema, hypertension, macrohematuria, or azotemia; and urine changes characteristic to APGN: proteinuria, hematuria, or casts. The exclusion criteria were: patients under the age of three years; acute renal failure requiring dialysis; treatment with ACE inhibitors, calcium channel blockers, steroids, or other immunomodulators or immunosuppressants more than 3 days before the investigation; disease duration of more than three weeks; known allergy to ACE inhibitors; or the parents' refusal to participate in the trial. Twenty-six patients, selected in the randomized way, were treated with enalapril (Ednyt) for six weeks and 25 patients served as their controls, not receiving any ACE inhibitors. The enalapril treated group consisted of 19 boys and 7 girls with a mean age of 8.9±3.6 years (range 3–16), and the control group – of 18 boys and 7 girls with a mean age of 8.5±3.6 years (range 5–15). Patients did not differ by weight, height, and body surface area (in the enalapril group: 34±24.3 kg, 133.2±24.2 cm, 1.1±0.4 kg/m² and in the control group: 34±14.6 kg, 131.1±20.5 cm, 1.1± 0.3 kg/m², respectively). Written informed consent was obtained from the parents of all children involved in this study. The mean enalapril dose for children weighing up to 30 kg was 5 mg, and those above, 10 mg, given in two doses per day. For those patients who had reduced glomerular filtration rate (GFR) more than 50%, the dose was reduced twice. All these patients received all other needed drugs (ß-blockers, vasodilators, diuretics and central acting agents, if needed) for correction of hypertension and edema except for calcium channel blockers or other ACE inhibitors. The control group received the same medications except for enalapril.

Arterial blood pressure (BP) was evaluated on the day of admission to the hospital, on day 2, day 4, day 6, day 8, on the day of discharge from the hospital, after 6–8 weeks, and after 6 months.

Arterial blood pressure was assessed as mean arterial pressure (MAP) and calculated as follows: diastolic BP+(systolic BP–diastolic BP)/3. The MAP was later evaluated with a 5-point system according to the findings of S. A. de Man *et al*. (13): 1 point – MAP lower than 50th percentile, 2 points – equal 50th percentile, 3 points – MAP in the range of 50–95th percentile, 4 points – MAP equal 95th percentile, 5 points – MAP above 95th percentile. Edema was ranked by a 3-points scale: 0 points – no edema, 1 – edema in one part of the body (face, legs), 2 – edema in more parts of the body, 3 – ascites, edema of the entire body. Proteinuria level, serum creatinine and potassium levels were evaluated by standard laboratory techniques before and after the treatment.

Eighteen patients in the enalapril group and 14 patients in the control group underwent randomized M-mode, 2D, pulsed-wave and color-flow Doppler echocardiographic examination using an echocardiograph (AU3 Partner, Esaote Biomedica, with 2.5–3.5 Hz transducer) within the first two days after admission to the hospital, and at follow-up after 6–8 weeks.

Echocardiography was performed in the left lateral supine position by the same experienced echocardiographer (A. M.), who was blinded to the patient's status and treatment. From 2D directed M-mode echocardiography left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness in diastole (IVSd), and left ventricular posterior wall thickness in diastole (LVPWd) were measured in the parasternal long axis cut. M-mode measurements were made according to the recommendations of the American Society of Echocardiography (14) at or just below the tips of the mitral valve leaflets. The left ventricular mass (LVM) was calculated using the formula of R. B. Devereux *et al.* (15). Relative wall thickness (RWT) was measured at the end-diastole as: 2×LVPWd/ LVEDD.

Left ventricular systolic function was evaluated by means of left ventricular fractional shortening (FS) (%) (FS=((LVEDD–LVESD)/LVEDD)×100). Left ventricular diastolic function was estimated by measurement of the mitral peak flow velocity of early filling (E), and peak flow velocity of late filling (A) from pulsed-wave Doppler tracings across the mitral valve, with the sample volume placed between the tips of the leaflets from the apical four-chamber position. The E/A ratio was calculated from these measurements. Deceleration time (DT) was measured as the time required for the E velocity to recline from its

peak to the baseline value. The mean values of 3 to 5 sinus beats were used in the statistical calculations.

Statistical methods. Data are presented as mean± SD. The Student's t-test was used to assess the difference between group means. The paired t-test was used for comparison of the echocardiographic findings at onset of disease and after 6–8 weeks. A p-value of <0.05 was considered statistically significant.

Results

Patients' groups did not differ by edema level and its regression: in the enalapril treated group, edema averaged 1.38 points and lasted up to 4.15 days, and in the untreated group it was 1.68 points and lasted an average of 4.96 days. In the enalapril group, patients received diuretics for 4.81 days and in the control group, accordingly 4.08 days, with no statistically significant difference. The enalapril patients received on average 2.6 antihypertensive drugs and the control group 2.1, with no statistically significant difference. Proteinuria levels at the onset of the disease were 2.4± 3.58 g/l in the enalapril group and 1.74±1.81 g/l in the control group (p=0.42), after 6–8 weeks 0.02±0.04 g/l and 0.04±0.09 g/l (p=0.6); and after 6 months 0.03±0.06 g/l and 0.04±0.09 g/l, respectively (p=0.7). The glomerular filtration rate in the acute period of the disease was 77.6±29.2 ml/min/1.73m² in the enalapril group, and 83.1±21.9 ml/min/1.73m² in the control group (p=0.55). Creatinine concentration in the acute phase of the disease was 95.4±38.94 μmol/l in the enalapril group, and 78.65±33.41 μmol/l in the control group (p=0.12). After 6–8 weeks, creatinine concentration was 57.09±15.67 μmol/l in the enalapril group, and 59.11±17.93 μmol/l in the control group (p=0.7). Potassium levels in the acute phase were 5.08±0.68 mmol/l in the enalapril group, and 4.92± 0.65 mmol/l in the control group (p=0.47). After 6–8 weeks it was 4.35±0.27 mmol/l in the enalapril group, and 4.32±0.35 mmol/l in the control group (p=0.74).

Blood pressure. On admission and during first six days, BP did not differ between the enalapril and control groups (Figure). BP was statistically different on the eighth day and on the day of discharge: it was lower in enalapril treated group (2.56 *vs.* 3.50 on day 8; 2.31 *vs.* 3.17 on discharge, p=0.03). Comparing BP between the groups after 6–8 weeks, the difference

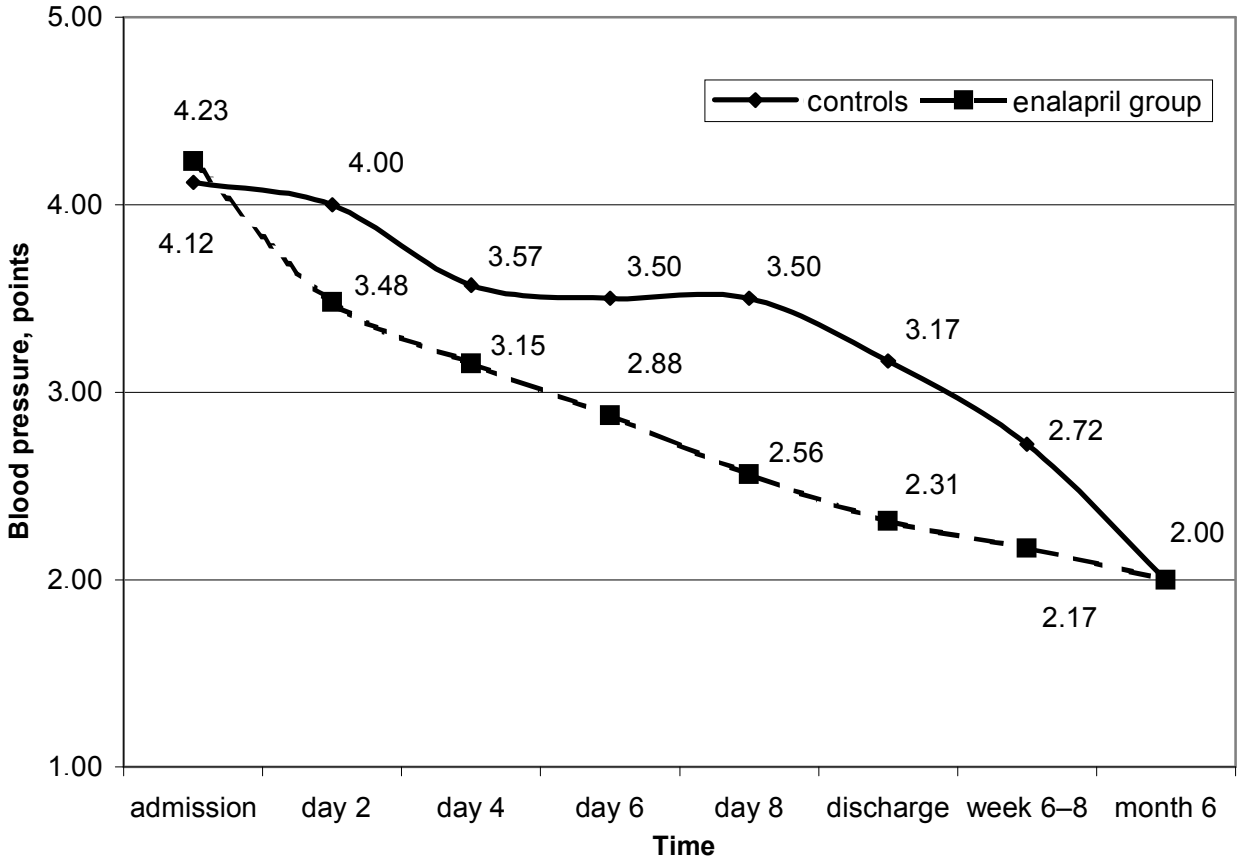

***Fig.* Changes in blood pressure in the enalapril treated and untreated patients' groups**

Table 1. **Echocardiographic parameters of the enalapril treated and untreated patients in the acute phase of acute postinfectious glomerulonephritis (mean±standard deviation)**

Parameter	Enalapril treated group (n=18)	Untreated group (n=14)	p-value
IVSd (cm)	0.68±0.14	0.65±0.11	0.48
LVPWd (cm)	0.76±0.14	0.7±0.11	0.19
LVEDD (cm)	4.42±0.71	4.29±0.46	0.56
LVESD (cm)	2.81±0.59	2.77±0.41	0.8
LVM (g)	102.56±51.86	87.06±31.3	0.3
RWT	0.35±0.05	0.33±0.05	0.29
FS (%)	36.67±5.40	35.64±4.81	0.58
E (m/s)	0.91±0.15	0.89±0.15	0.67
A (m/s)	0.54±0.11	0.49±0.08	0.13
E/A ratio	1.72±0.29	1.84±0.23	0.21
DT (s)	0.225±0.094	0.251±0.09	0.42

IVSd – interventricular septal thickness in diastole; LVPWd – left ventricular posterior wall thickness in diastole; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVM – left ventricular mass; RWT – relative wall thickness; FS – fractional shortening; E – mitral peak flow velocity of early filling; A – peak flow velocity of late filling; DT – deceleration time.

was not significant. After 6 months BP was normal in both groups with no differences.

Echocardiography. No statistically significant differences were found between the echocardiographic parameters of the enalapril and control groups at the onset of the disease (Table 1).

Comparison of the echocardiographic findings at the onset of APGN and after 6–8 weeks of treatment revealed evident differences in enalapril treated and untreated patients (Table 2). Echocardiographic parameters improved in both groups. However, only in the enalapril treated group there were statistically significant changes. A statistically significant decrease in LV end-diastolic diameter, LV end-systolic diameter, LV mass, mitral peak flow velocity of late filling was found in the enalapril treated patients. There were no significant changes in LV systolic function. Other parameters, although statistically unreliable, showed greater improvement in the enalapril treated patients.

Discussion

Enalapril is an efficient drug in treatment of children with heart failure due to congestive cardiomyopathy and arterial hypertension (AH) (16, 17). Our study showed that in the enalapril group, the patients' BP was better controlled during the acute phase of the disease than it was in the control group. However, later the differences were no longer statistically evident.

Although there were no statistically reliable differences in the echocardiographic parameters between the enalapril treated group and the control group at the onset of the disease, in patients who received enalapril, echocardiographic parameters improved more than in the untreated ones. In patients treated with enalapril, LVEDD, LVESD and LVM decreased statistically reliably. There are data, supported by evaluation of enalapril treatment in 24 patients from 0.3 to 16 years of age with mitral and aortic regurgitation (18), indicating that ACE inhibitors are effective not only in reducing LV overload, but left ventricular hypertrophy as well. Evaluation of adolescents' echocardiographic parameters after 6 months of enalapril treatment for primary AH revealed evident thinning of IVS and improvement of the LV systolic function parameters (19). We did not find any difference in systolic function between the enalapril treated and untreated patients. However, only in the enalapril group the mitral peak flow velocity of late filling diminished statistically significantly, suggesting a possible positive effect of enalapril on the LV diastolic function.

Hypertension is an important factor in progressive kidney disease. The mechanism causing hypertension in parenchymal renal disease reflects a continuum ran-

Table 2. **Echocardiographic parameters of the enalapril treated and untreated patients in the acute phase of acute postinfectious glomerulonephritis and after 6–8 weeks (mean±standard deviation)**

Parameter	Enalapril treated group (n=18), acute period	Enalapril treated group (n=18), after 6–8 weeks	p-value (paired)	Untreated group (n=14), acute period	Untreated group (n=14), after 6–8 weeks	p-value (paired)
IVSd (cm)	0.68±0.14	0.64±0.13	0.14	0.65±0.11	0.60±0.13	0.1
LVPWd (cm)	0.76±0.14	0.72±0.14	0.13	0.7±0.11	0.7±0.08	0.87
LVEDD (cm)	4.42±0.71	4.19±0.69	<0.001*	4.29±0.46	4.16±0.45	0.46
LVESD (cm)	2.81±0.59	2.64±0.48	0.04*	2.77±0.41	2.67±0.32	0.25
LVM (g)	102.56±51.86	86.77±43.54	<0.001*	87.06±31.3	78.6±25.22	0.06
RWT	0.35±0.05	0.35±0.06	1.0	0.33±0.05	0.34±0.05	0.36
FS (%)	36.67±5.40	36.78±2.62	0.94	35.64±4.81	35.93±4.03	0.84
E (m/s)	0.91±0.15	0.88±0.14	0.14	0.89±0.15	0.90±0.12	0.76
A (m/s)	0.54±0.11	0.49±0.09	0.02*	0.49±0.08	0.51±0.09	0.34
E/A ratio	1.72±0.29	1.82±0.31	0.16	1.84±0.23	1.79±0.26	0.59
DT (s)	0.225±0.094	0.237±0.096	0.13	0.251±0.09	0.255±0.13	0.88

IVSd – interventricular septal thickness in diastole; LVPWd – left ventricular posterior wall thickness in diastole; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVM – left ventricular mass; RWT – relative wall thickness; FS – fractional shortening; E – mitral peak flow velocity of early filling; A – peak flow velocity of late filling; DT – deceleration time.

* – statistically significant difference.

ging from pure volume-mediated hypertension to pure vasoconstriction-mediated hypertension, and combinations are common. In acute glomerular disorders, the prevailing cause is an acute drop in GFR leading to salt and water retention (20). In a detailed study of patients with acute glomerulonephritis, plasma renin concentrations were disproportionally high for the state of fluid balance, with a consequential increase in total peripheral resistance, and the hypertension was attributed to this inappropriate stimulation of the renin-angiotensin system (21). In accordance with this view, treatment with another ACE inhibitor, captopril, was reported to be effective in controlling hypertension due to acute glomerulonephritis (7). As in our study enalapril treated patients and controls did not differ in their levels of edema; differences between BP on the first week of the disease and better improvement of echocardiographic parameters in the enalapril treated patients might be attributed to the effect of enalapril on the factor of vasoconstriction during APGN.

The problem of blood pressure control in patients with APGN is very important. There was no significant hypertension in our patients (all blood pressures measured after day two were classified as four points or less, i.e. blood pressure was not greater than 95th percentile after day two, suggesting that hypertension was mild or transient). The positive antihypertensive effect of enalapril in the first week of treatment in mildly hypertensive APGN patients might be even more pronounced in patients with severe hypertension. The effects of enalapril noted in our study might influence the outcome of APGN, but for this statement to be supported, the groups must be larger and followed up for a longer period of time.

In conclusion, the drug was safe to use, as there was no rise in serum creatinine or potassium levels observed. The enalapril treated patients showed better antihypertensive effects early in the disease, as well as better improvement of echocardiographic parameters. Whether the effects of enalapril have some influence on the outcome of acute postinfectious glomerulonephritis requires further study.

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Enalaprilio įtaka vaikų, sergančių ūminiu poinfekciniu glomerulonefritu, arteriniam kraujospūdžiui ir echokardiografiniams parametrams

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Raktažodžiai: glomerulonefritas, kraujospūdis, echokardiografija, angiotenziną konvertuojančio fermento inhibitoriai.

Santrauka. *Darbo tikslas.* Ištirti gydymo angiotenziną konvertuojančio fermento inhibitoriumi enalapriliu įtaką vaikų, sergančių ūminiu poinfekciniu glomerulonefritu, arteriniam kraujospūdžiui ir kairiojo skilvelio echokardiografiniams parametrams bei funkcijai.

Tirtųjų kontingentas ir tyrimo metodai. Ištirtas 51 vaikas, sergantis ūminiu poinfekciniu glomerulonefritu. 26 ligonių, gydytų šešias savaites enalapriliu, duomenys buvo lyginami su 25 enalapriliu negydytų ligonių duomenimis. Arterinis kraujospūdis buvo matuojamas kas antrą parą ligos pradžioje, po 6–8 savaičių ir po 6 mėnesių. 2D, M ir doplerinė echokardiografija atlikta 18 enalapriliu gydytų ligonių ir 14 kontrolinių ligonių ligos pradžioje bei po 6–8 savaičių.

Rezultatai. Ligos pradžioje arterinis kraujospūdis greičiau normalizavosi enalapriliu gydytų ligonių grupėje. Palyginus echokardiografinius duomenis ūminio poinfekcinio glomerulonefrito pradžioje ir po 6–8 savaičių gydymo enalapriliu, reikšmingai sumažėjo kairiojo skilvelio diastolinis diametras (4,42±0,71 cm iki gydymo, 4,19±0,69 po gydymo, $p<0,001$), kairiojo skilvelio sistolinis diametras (atitinkamai – 2,81±0,59 cm ir 2,64±0,48 cm, $p=0,04$), kairiojo skilvelio masė (102,56±51,86 g ir 86,77±43,54 g, $p<0,001$) ir maksimalus vėlyvojo kairiojo skilvelio prisipildymo kraujotakos greitis A (0,54±0,11 m/s ir 0,49±0,09 m/s, $p=0,02$). Kiti echokardiografiniai parametrai (nors statistiškai nereikšmingai) labiau pagerėjo enalapriliu gydytų ligonių grupėje. Enalapriliu negydytų ligonių grupėje echokardiografiniai parametrai reikšmingai nepakito.

Išvada. Tyrimų duomenimis, enalapriliu gydytų ligonių grupėje greičiau normalizavosi arterinis kraujospūdis ir pagerėjo echokardiografiniai parametrai. Reikalingi tyrimai, įrodantys, ar šis enalaprilio poveikis gali turėti įtakos ūminio poinfekcinio glomerulonefrito baigčiai.

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