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THE EFFECTS OF ENALAPRIL ON EXPERIMENTAL GENTAMICIN NEPHROTOXICITY

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We examined the effects of Enalapril on glomerular and tubular renal changes induced by Gentamicin. The control group of Wistar rats was treated by physiological solvent. The second group was treated with Gentamicin in the dose of 100 mg/kg b.m. The third group was treated with Gentamicin in the same dose and with Enalapril in the dose of 1 mg/kg b.m. The levels of sodium, potassium, urea and creatinine from the blood samples were analyzed. The kidneys were taken out and processed in a standard histological way, by haematoxilin eosin and periodic acid shift coloring for light microscopy. Our results showed that simultaneous treatment with Gentamicin and Enalapril intensified and extensified the nephron morphological changes which corresponded to biochemical changes. The decrease of sodium serum concentration ($p<0,01$) and potassium serum concentration ($p<0,05$) as well as the increase of urea ($p<0,001$) and creatinine ($p<0,001$) in animals treated with Gentamicin compared to the control group were detected. The combination of Enalapril and Gentamicin resulted in more pronounced kidney damage than caused by Gentamicin alone, so that the levels of urea concentration in serum ($p<0,001$) and creatinine concentration ($p<0,05$) were higher in this experimental group. Sodium loss was more stressed by Enalapril treatment ($p<0,05$), while potassium concentration in serum was higher compared to the group treated with Gentamicin ($p<0,01$). Potassium significantly correlates with urea and creatinine values in rats treated with Gentamicine ($C=0.418$, $C=0.536$; $p<0.05$) and Gentamicin and Enalapril ($C=0.359$, $p<0.05$; $C=0.596$; $p<0.01$). Sodium also showed significant correlation with creatinine in rats treated with Gentamicin and Enalapril ($C=0.459$, $p<0.05$). Our findings support hypothesis that Enalapril causes exacerbation of Gentamicin nephrotoxicity. *Acta Medica Medianae 2014;53(2):16-21.*

Key words: *Enalapril, Gentamicin nephrotoxicity, epithel desquamation, proximal tubules, rat*

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Introduction

Gentamicin is one of the most commonly used aminoglycoside antibiotics for the treatment of infections caused by Gram-negative aerobes. Despite its beneficial effects, serious complications like nephrotoxicity are dose-limiting factors in the use of aminoglycosides (1). Recent studies have postulated that renal inflammation is involved in the damage (2). There is also evidence that necrosis of renal tubular epithelial cells (3), mitochondrial dysfunction and activation of renal matrix metalloproteinases (4) are also involved in gentamicin-induced nephrotoxicity. Gentamicin causes damage acting through free radicals (5). Gentamicin expresses pro-oxidative effect by moving ferro and free oxygen radicals from mitochondria epithel cells (5), while Jesus (6) clarifies that calcium reaches the point of citotoxicity in cells by alteration of genes expression for sodium-calcium transport protein.

Gentamicin increases urinary excretion of sodium and potassium and this hypokalemia is mostly due to the chronic administration of the drug (7). High urea and creatinine concentration in blood due to Gentamicin nephrotoxicity is a relatively late consequence caused by depression of glomerular filtration after extensive necrosis of proximal tubules (8). Rise in serum creatinine is dependent on the degree of tubular necrosis (9). Glomerular filtration decreased in less than a week under treatment, but proximal tubule pathological changes can be noticed in biopsy material earlier (10).

Some authors (11) explain Gentamicin nephrotoxicity effects by glomerular changes. Gentamicin decreases glomerular filtration decrea-

sing the density and diameter of fenestre at the capillary loop. In addition, Angiotensin II is reported as an important factor in Gentamicin kidney damage. It is emphasized that Angiotensin II has prooxidative, vasoconstrictive effects and causes hypoperfusion, and it is the reason that the angiotensin-converting enzyme (ACE) blocking has protectively important role for the kidney (12), although Gentamicin damage may be emphasized by ACE inhibitors (13,14). ACE-inhibition reduces efferent vascular tone and thus filtration rate. This may modify the renal and blood pressure responses to kallikrein and prostaglandin pathways as well as with the sympathetic nervous system (15).

Using experimental model of kidney insufficiency, we investigated the Enalapril effects in Gentamicin nephrotoxicity as well as the kind of changes in some nephron parts.

Material and methods

Experimental investigation was conducted on Wistar rats of both sexes, body mass (b.m.) about 300 g, six months old, divided into three groups, eight rats each. The first group - control group (C) was treated by physiological solvent. The second group (G) was treated by Gentamicin in the dosage of 100 mg/kg b.m. The third group (GE) was treated by Gentamicin in the same dose as G group (100 mg/kg b.m.) and with Enalapril in dose of 1 mg/kg b.m.

The substances were injected intraperitoneally, once a day in duration of eight days. The animals were sacrificed on the ninth day from the beginning of the experiment. The levels of sodium, potassium, urea and creatinine from the blood samples, taken from aorta, were analyzed. The kidneys were taken out and processed in a standard histological way, by haematoxilin eosin (HE) and periodic acid shift (PAS) coloring for light microscopy.

The mean and standard deviation were used for descriptive statistic. Pearson's bivariate correlation was used for continual numerical data correlation analysis. Student's t test was used for comparing means after evaluating normality of samples by Levens test. Data were analyzed using SPSS v16.0 analytics software.

Results

Biochemical Parameters

The sodium concentration in serum was lower in both G and GE groups compared to the C group ($p<0,01$). In addition, the greatest loss of sodium by excretion via urine was reported in GE animals and it resulted in statistically significant difference between G and GE groups ($p<0,05$) (Table 1). Potassium concentration in serum in G group was less than in C group ($p<0,05$), whereas Enalapril caused increasing in potassium in GE group ($p<0,05$). Statistically important difference in potassium level was found between GE group and G group ($p<0,01$) (Table 1). The urea value in serum was higher in G group ($p<0,001$) and GE group ($p<0,001$) than in the control group. A higher level of urea in GE group compared to G group ($p<0,001$) (Table 1) was found. The creatinine level was also statistically higher in G group ($p<0,001$) compared to the control group. The creatinine level was higher under Gentamicin and Enalapril treatment than Gentamicin alone, and that difference was statistically significant ($p<0,05$) (Table 1).

Potassium significantly correlates with urea in rats treated with Gentamicine and Gentamicin & Enalapril ($C=0.418$, $C=0.536$; $p<0.05$). This association is also shown between potassium and creatinine values ($C=0.359$, $p<0.05$; $C=0.596$; $p<0.01$) in rats treated with Gentamicin and Gentamicin & Enalapril. Sodium also showed significant correlation with creatinine in rats treated with Gentamicin & Enalapril ($C=0.459$, $p<0.05$). These correlations were not seen in healthy animals (Table 2).

Table 1. The values of sodium, potassium, urea and creatinine and statistical significance of differences between the groups

Groups	Control	Gentamicin	Gentamicin &Enalapril
sodium	148,87 ± 2,712	143,2 ± 3,067 *	142,25±4,683 †
potassium	4,912±1,115	4,29±0,388	6,03±1,243 ‡
urea	6,65±0,72	41,42±9,64 ||	50,2±11,07 §, ¶
creatinine	67,6±10,89	390,8±141,28 *	658,2±197,11 †

The values are expressed as mean ± SD in mmol/l.
Statistically significant difference between:
* gentamicin and control for the level of $p<0.01$;
† gentamicin & enalapril and control for the level of $p<0.01$;
‡ gentamicin and gentamicin & enalapril - for the level of $p < 0.01$;
§ - gentamicin and gentamicin & enalapril - for the level of $p < 0.001$;
|| -gentamicin and control for the level of $p<0.001$;
¶ - gentamicin and gentamicin & enalapril - for the level of $p < 0.01$.
Part of the results was taken from previously published papers (16,17) to better present the correlation in this paper.

Table 2. Association between serum electrolytes and nitrogen equivalents according to groups

	Control	Gentamicin	Gentamicin &Enalapril
with urea			
sodium	0.05	0.231	0.314
potassium	0.211	0.418*	0.536*
with creatinine			
sodium	0.153	0.338	0.459*
potassium	0.257	0.359*	0.596**

Statistically significant difference of Pearson's correlation:
* for the level of $p<0.05$; ** for the level of $p<0.01$;

Morphological findings

Our results show the crucial changes in the kidney cortex. Moderate blood stasis in glomeruls and segmental necrosis of capillary loops were found in the G group. Mesangium was normally present, but Bowman's capsules were reduced in two thirds of cases. Dominant changes were present in the proximal tubules, especially in the subcapsular areas which seemed porous at places where lumen was extended and where the tubule cells disappeared. Mesangium is normally present. In 2/3 of the space capsule glomerulus is reduced or minimized, except in rare cases where it is easily expanded if it contains a small amount of pink mass. In certain tubule lumen and groups of tubules which are clustered, there is a pink homogeneous mass, especially in the Henle's loop lumen. Suprapapillary tubule cells are only "bare nuclei" without cytoplasm (Figure 2). The marked degenerative changes in glomeruli and significant desquamation of proximal tubules were registered in GE animals. Stasis was documented in the glomeruli; capsular spaces were mainly reduced, but segmental necrosis along with cell reduction in capillary loops could be seen. Tubulorexis and coagulation necrosis of cell cytoplasm with cariolitical nuclei were present in the cortex. Stasis changes were also present, mainly trombotical, with rare perivascular hemorrhage and lympho-plasmacytic infiltration (Figure 3). Glomeruli were congestive, their capsular spaces are often reduced, showing segmental necrosis of capillary loops with a reduction of cells and desquamation podocytes. The cortex showed coagulative necrosis of the cytoplasm of cells, which is seen as a partial lysis (Figure 4). Basal membranes of tubules in the cortex are in areas of necrosis with separate fibers, often interrupted; in the cytoplasm of the cell protruding PAS positive substance cannot be seen. There are pinkish-reddish colored hyaline ingredients in the lumen of medulla tubules (Figure 5).

Discussion

Among antibiotics, mostly applicated medicines in medical treatment, responsible for about 35 % of reported nephrotoxicity, amino-glycosides are documented in 75% of cases, which is more than Tetracycline, Cephalosporine, Sulphonamide, Ciprofloxacine, Riphampicine (18). Disturbance of glomerular filtration and higher renine-angitensine-aldosterone (RAA) system activity, according to the haemodynamic changes in the kidney, are the key effects of Gentamicin in some authors' opinion. Researchers suggest that different doses of gentamicin are nephrotoxic (19). Gentamicin has been shown to cause damage when administered at doses 5-10 times the normal therapeutic dose (20).

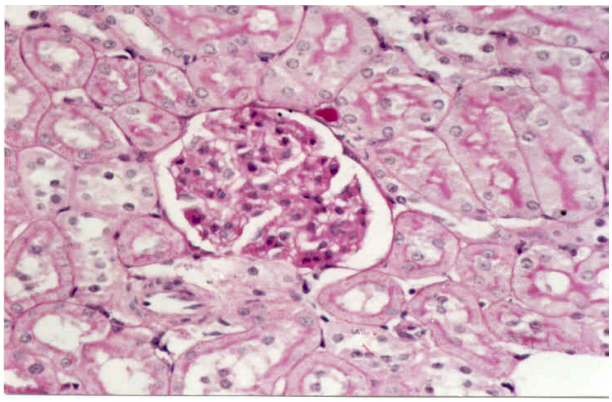

Figure 1. Kidney of the control group. Glomerulus with relatively broad subcapsular space, there are endothelial cells and podocytes; PAS positive mesangium, PAS positivity of the basal membrane, PAS positivity of their apical parts. PAS x 150

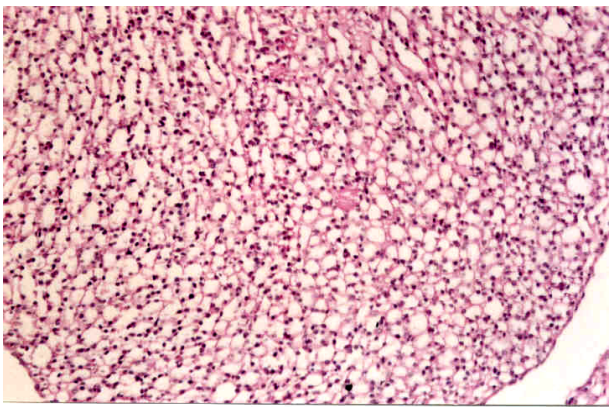

Figure 2. Kidney of an animal treated by Gentamicin. Suprapapillary segment of medulla with preserved, bare nuclei of tubular epithelial cells due to the absence of cytoplasm. HE x 120

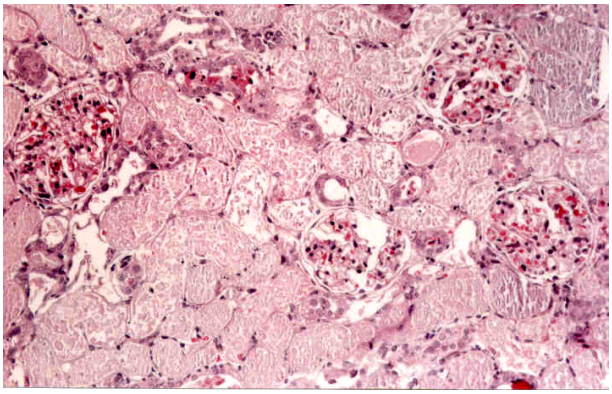

Figure 3. Kidney of animal treated with Gentamicin and Enalapril. Glomeruli are with significant stasis, mostly with total reduction of subcapsular space and with partial capillary necrosis; almost all tubules are damaged except for small spaces with preserved intertubular interstitial cells (HE x 120).

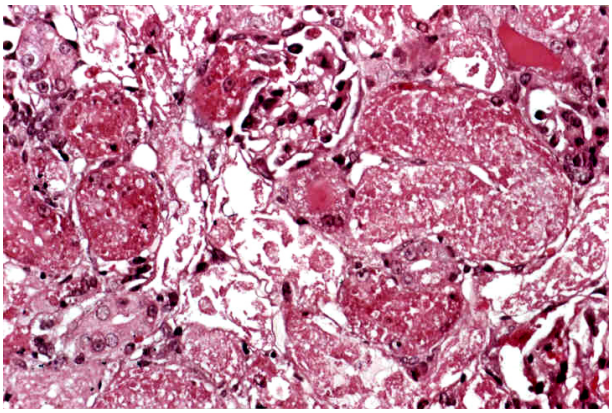

Figure 4. Kidney of an animal treated with Gentamicin and Enalapril. Focal necrosis of the walls of some glomerular capillary loops and coagulation necrosis of epithelial tubules that meets lumen; in individual tubules homogeneous pink material can be seen; tubular portion is relatively preserved. HE x 150

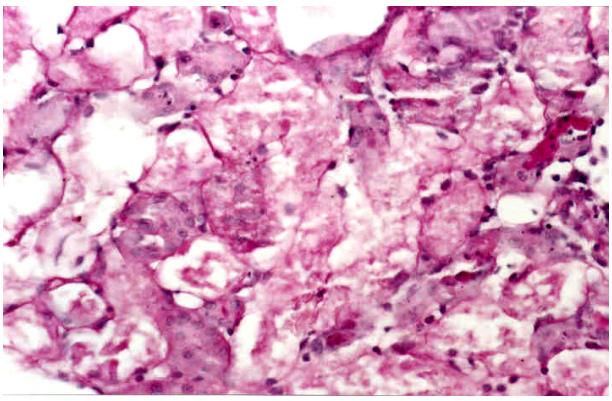

Figure 5. Kidney of animal treated by Gentamicin and Enalapril. Basal membranes of some tubules are PAS positive, whereas others are interrupted. PAS positive material is blurred in areas of devastated tubules. PAS x 150

It is well known that (RAA) system plays a major role in the development of chronic kidney disease (21).Chronic administration of angiotensin II in rats produces renal injury (22). It has been also found that Perindopril intensifies the renal damage by Gentamicin. Gentamicin treatment induced significant decrease in angitensin converting enzyme blood levels, while simultaneous treatment with Perindopril induced a greater fall in blood levels than after the administration of Perindopril alone (23).

Some researchers have reported that ACE inhibitors induced functional renal insufficiency, while others have declared that captopril partially inhibits the development of the functional and morphological damage (24). Other investigations have demonstrated a significant reduction in blood pressure, protein excretion and glomerular and tubulointerstitium fibrosis under the treatment of Trandolapril (25). Suppression of angiotensin formation with Kaptopril can reduce glomerular capillary pressure and thus filtration rate. Reduced aldosterone release also contributes to the natriuresis and results in positive potassium balance (26). Angiotensin-converting enzyme inhibitors have little effect on glomerular filtration rate, but they increase effective renal plasma flow at renal perfusion pressures within the normal autoregulatory range and renal vascular resistance is decreased (27).

Taking into consideration earlier findings, we examined the effects of Enalapril under conditions of already damaged renal function by Gentamicin. The presence of biochemical and pathological changes of kidney as a consequence of the damage caused by Gentamicin and Enalapril applied simultaneously were noticed. Our results showed the increasing of urea and creatinine serum concentrations under the effects of Enalapril and Gentamicin compared to the effects of Gentamicin alone. The changes in serum are in accordance with the morphological kidney changes which can be noticed after Enalapril and Gentamicin simultaneous effects. Degeneratively changed glomeruls and especially proximal tubules led to decreasing of the kidney capability in excretion of these substances. Higher renal loss of sodium, which is reabsorbed in the proximal tubules under physiological conditions, appears in the GE animals. This can be explained by the presence of dysfunction and morphological nephron changes, especially in proximal tubules. Increase in serum creatinine with the rise in blood urea nitrogen and a significant fall in creatinine clearance has been previously reported with gentamicin (28). The research has shown that when there is a nephrotoxic damage with retention of potassium and creatinine, then the values of urea and sodium are relatively stable providing that diuresis is maintained and there is good hydration (22,29). This is in keeping with our results. The degeneration and desquamation of epithel cells of proximal tubules caused by Gentamicin and Enalapril simultaneously applied did not bring about decrease of potassium concentration in serum in our experiment; there was a statistically significant increase in the potassium value in

blood, which could not be explained as renal function improvement. These effects are typical of ACE inhibitors.

With its vasodilatation effects, Enalapril can possibly increase the accumulation of Gentamicin in the glomerular and proximal tubules an decrease the renal blood pressure, which further compromises renal hemodynamics. Finally, we can conclude that Enalapril emphasizes changes in the kidney nephron caused by Gentamicin.

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UTICAJ ENELAPRILA NA EKSPERIMENTALNU GENTAMICINSKU NEFROTOKSIČNOST

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Ispitivali smo efekte Enalaprila na glomerularne i tubularne promene bubrega pacova izazvane Gentamicinom. Kontrolna grupa pacova Wistar soja tretirana je fiziološkim rastvorom. Druga grupa je tretirana Gentamicinom u dozi od 100 mg/kg t.m. Treća grupa je tretirana Gentamicinom u istoj dozi i Enalaprilom u dozi 1 mg/kg t.m. U krvi su određivani nivoi natrijuma, kalijuma, uree i kreatinina. Bubrezi su obrađeni za histološku analizu svetlosnom mikroskopijom haematoxilin eosin i periodic acid shift bojenjem. Naši rezultati su pokazali da simultani tretman Gentamicinom i Enalaprilom intenzivira morfološke promene nefrona koje korespondiraju sa biohemijskim promenama. Smanjenje serumske koncentracije natrijuma ($p<0,01$) i kalijuma ($p<0,05$), kao i povećanje uree ($p<0,001$) i keatinina ($p<0,001$) detektovano je kod životinja tretiranih Gentamicinom u poređenju sa kontrolnom grupom. Kombinacija Enalaprila i Gentamicina dovela je do izraženijih oštećenja bubrega nego pojedinačno delovanje Gentamicina, tako da su nivoi serumske koncentracije uree ($p<0,001$) i kreatinina ($p<0,05$) bili veći. Gubitak natrijuma bio je izraženiji dejstvom Enalaprila ($p<0,05$), dok je koncentracija kalijuma u serumu bila viša u poređenju sa grupom tretiranom Gentamicinom ($p<0,01$). Vrednosti kalijuma značajno koreliraju sa vrednostima uree i kreatinina kod pacova tretiranih Gentamicinom ($C=0.418$, $C=0.536$; $p<0.05$) i onih tretiranih Gentamicinom i Enalaprilom ($C=0.359$, $p<0.05$; $C=0.596$; $p<0.01$). Vrednosti natrijuma takođe pokazuju značajnu korelaciju sa kreatininom kod pacova tretiranih Gentamicinom i Enalaprilom ($C=0.459$, $p<0.05$). Naši nalazi podržavaju hipotezu da Enalapril uzrokuje pogoršanje gentamicinske nefrotoksičnosti. *Acta Medica Medianae 2014;53(2):16-21.*

Ključne reči: *Enalapril, gentamicinska nefrotoksičnost, deskvamacija epitela, proksimalni tubuli, pacov*

