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Full Length Research Paper

Effect of cimetidine on gentamicin-losartan induced - nephrotoxicity in rats

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Drug-induced nephrotoxicity is an important cause of renal failure. Aminoglycoside antibiotics, such as gentamicin can produce nephrotoxicity, due to in part to an imbalance of pro and anti-oxidants (oxidative stress). Cytochrome P 450 is one enzyme that involved in acute renal failure. Inhibition of this enzyme may decrease drug-induced nephrotoxicity. The aim of present study was evaluating the effect of cimetidine on gentamicin-losartan nephrotoxicity in rats. A control group (saline, group 1, n = 6) was compared with rats administrated gentamaicin by intrapritoneal injection, at dose rate of 80 mg/kg, once daily for 7 days (group 2, 3 and 4). The effect of losartan (group 3) and losartan and cimetidine in combination (group 4) were compared on gentamaicin-induced nephrotoxicity. Losartan alone (group 5) and losartan with cimetidine (group 6) were used for evaluation effect of these drugs in absence of gentamicin. Renal function was assessed using serum biochemical markers including creatinine, blood urea nitrogen (BUN), sodium and potassium. Serum creatinine concentration was increased significantly in group 2 compared with group 1. Serum creatinine concentrations were significantly elevated in groups 3 than in group 2 (p = 0.001). Serum creatinine concentration was significantly decreased in groups 4 than in group 3 (p = 0.001) . Serum creatinine concentration in group 5 and 6 was similar group 1. Serum BUN concentrations were significantly elevated in groups 3 than in group 2 (p = 0.001). The cimetidine prevented BUN elevation in group 4 with comparison to group 3 but serum BUN in this group was significantly more than groups 1 and 2. Serum sodium level was significantly decreased in group 3. Serum potassium level significantly increased in group 3 and 4. Losartan severely increased gentamicin-induced nephrotoxicity. Cimetidine appears to have protective effect on gentamicin-losartan-induced nephrotoxicity in rats.

Key words: Gentamicin, cimetidine, losartan, vitamin E, rats, nephrotoxicity.

INTRODUCTION

Gentamicin is an aminoglycoside antibiotic widely used for the treatment of bacterial infections. Therapeutic doses of gentamicin and other aminoglycoside antibiotics can produce nephrotoxicity in humans and animals and use of this class of antibiotics is known as one of the most common causes of acute renal failure (Cuzzocrea et al., 2002), possibly due to increased renal uptake of the antibiotic, mainly by the proximal tubules. The effect of gentamicin on biological membranes appears to be important in its toxicity. It has been proposed that the accumulation of aminoglycosides in proximal tubular epithelial cells leads to membrane structural disturbance and cell death by reactive oxygen species (ROS) involvement (Kadkhodaee et al., 2005) . ROS produce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage (Cuzzocrea et al., 2002).

Hydroxyl radical scavengers such as dimethylthiourea, superoxide dismutase (SOD) and dietary antioxidants

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Abbreviation: BUN, Blood urea nitrogen; **ROS,** reactive oxygen species.

(vitamin E, selenium, vitamin C, taurine and the carotenoids (beta-carotene, lutein and lycopene)) can decrease the gentamicin-induced reduction in the glomerular filtration rate and the severity of the tubular damage (Ali, 1996; Anganeyulu and Chopra, 2004; Ekor et al., 2006; Kavutcu et al., 1996). In addition, garlic has been shown to prevent the tubular and glomerular alterations induced by gentamicin (Pedraza-Chaverrı et al., 2003). This is possibly due to prevention of lipid peroxidation and the preservation of manganese SOD and glutathione peroxidase activities (Fauconneau et al., 1995; Yanagidaa et al., 2004).

The renin-angiotensin system plays an important role in the physiological regulation of the kidney function, including the control of renal microvascular and tubular function. Angiotensin-converting enzyme (ACE) inhibitors including enalapril and angiotensin receptor (AT1) antagonist such as losartan are widely used for the treatment of hypertension, but these drugs may induce reversible renal failure (Goodfriend et al., 1996; Matsukawa and Ichikawa, 1997). The AT1 receptor has been shown to play a role in the stimulation by angiotensin II of a number of renal vasodilator substances, including bradykinin and NO (Douglas, 1996).

The cimetidine is inhibitor of Cytochrome P 450 and this enzyme plays important role in nephrotoxicity by oxidative stress especially related to drug-induced renal failure. In other side, we have seen that the nephrotoxicity of rats was increased by co-administration of losartan and gentamicin. Thus in present study, effect of cimetidine was evaluated on gentamicin-losartan renal toxicity in rats.

MATERIALS AND METHODS

Animals

Adult male Wistar rats, 10 to 11 weeks old and weighing 200 - 250 g, were obtained from Jundishapour laboratory animal center (Ahvaz- Iran). Animals were allowed to acclimatize in our facility for at least 7 days before treatment. The animal room was maintained at 22°C and fluorescent lighting was controlled with an automatic timer (8:00 a.m. on/10:00 p.m. off). The animals were housed in polycarbonate cages containing additive-free corncob bedding and were allowed free access to Laboratory Rodent Diet Shooshtar Co.

Experimental protocol

The rats were allocated to five groups (n = 6 per group)

Group 1 (Controls): Saline in equal volume of gentamicin was injected to rats for inducing similar condition (injection and handling) to other groups.
Groups 2 - 4 (Gentamicin groups): Gentamicin sulfate was administrated intraperitoneally at dose rate of 80 mg/kg once daily for 7 days.
Group 3: Losartan was administered orally at dose rate of 80 mg/kg once daily for 7 days.
Group 4: Losartan similar group 3 and cimetidine was administered intraperitoneally at a dose rate of 100 mg/kg once daily for 7 days.
Group 5: Losartan (similar group 3) was administered orally once daily for 7 days.
Group 6: Losartan (similar group 3) and cimetidine (100 mg/kg) were administered once daily for 7 days.

Blood sampling and analytical methods

After 7 days, the rats were anesthetized by ketamine at dose 100 mg/kg to obtain their blood. The serum of rats was isolated. Urea nitrogen and creatinine were determined using commercial reagents (obtained from Parsazmoon Co., Iran). Sodium and potassium were measured with flame photometry apparatus (Cornig 410c, England).

Data analysis

The arithmetic mean of creatinine, BUN, sodium and potassium were compared between groups using one-way analysis of variance (ANOVA) and post hoc Fisher Least Significant Difference tests (SPSS, version 11). The level of significance was set at 0.05.

RESULTS

Serum creatinine concentration was increased significantly in group 2 compared with group 1 (Figure 1). Serum creatinine concentrations were significantly elevated in group 3 than in group 2 ($p = 0.001$). Serum creatinine concentration was significantly decreased in groups 4 than in group 3 ($p = 0.001$). Serum creatinine concentration in group 5 and 6 was similar group1. Serum BUN concentrations were significantly increased in group 3 than in group 2 ($p = 0.001$) (Figure 2). The cimetidine prevented BUN elevation in group 4 with comparison to group 3 but serum BUN in this group was significantly more than groups 1 and 2. Serum sodium level was significantly decreased in group 3 (Figure 3). Serum potassium level significantly increased in group 3 and 4 (Figure 4). Losartan severely increased gentamicin-induced nephrotoxicity. Cimetidine appears to have protective effect on gentamicin-losartan-induced nephrotoxicity in rats.

DISCUSSION

The present study showed that the administration of gentamicin to rats once daily for 7 days reduces glomerular function, as reflected by increased serum creatinine concentrations. Aminoglycoside- induced nephrotoxicity is characterized by a decrease in the glomerular filtration rate and direct tubular injury. The interaction between the cationic aminoglycoside and membrane anionic phospholipids is considered to be the first cytotoxic step. Some studies suggest that aminoglycoside antibiotics can stimulate the formation of ROS, which may be directly involved in gentamicin-induced acute renal failure and membrane lipid peroxidation. It has been found that O_2°, hydrogen peroxide (H_2O_2) and hydroxyl radicals

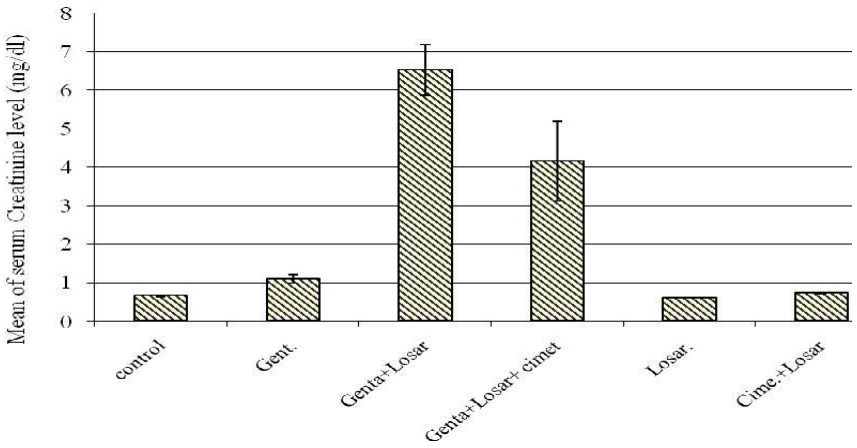

Figure 1. Mean (±SE) of serum creatinine level in rats. Co-administration losartan-gentamicin significantly increased serum creatinine level and this was lowered by cimetidine.

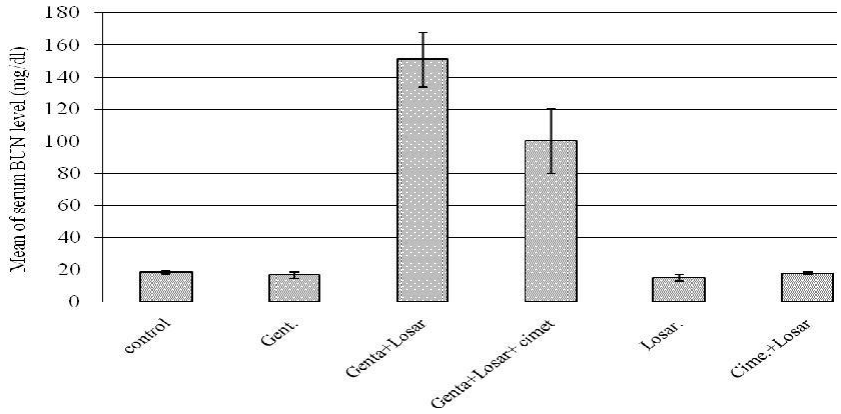

Figure 2. Mean (± SE) of serum BUN level in rats. Co- administration losartan-gentamicin significantly increased serum BUN level and this was lowered by cimetidine.

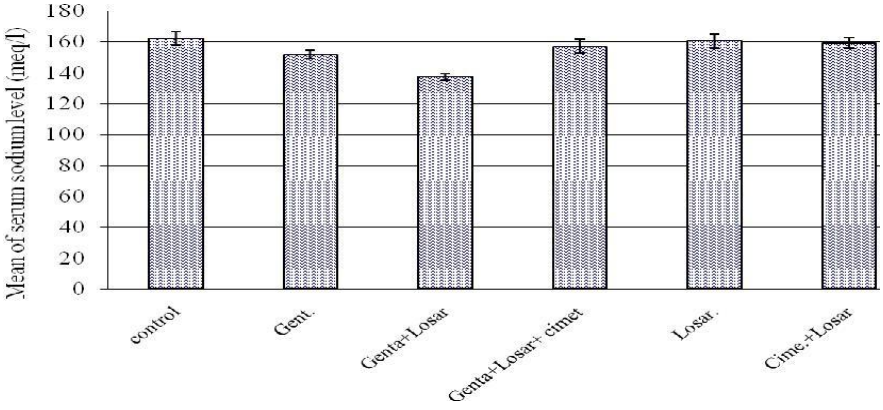

Figure 3. Mean (± SE) of serum sodium level in rats. Co-administration losartan-gentamicin significantly decreased serum sodium level but this was not corrected by cimetidine.

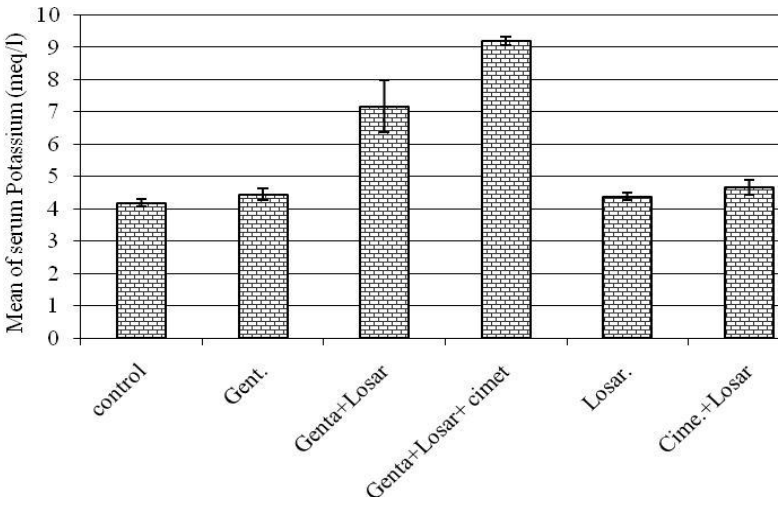

Figure 4. Mean (± SE) of serum potassium level in rats. Co-administration losartan-gentamicin significantly increased serum potassium level and this was more elevated by cimetidine.

increase with gentamicin-treatment and H_2O_2 and O_2° induce mesangial cells contraction, alter the filtration surface area and modify the ultrafiltration coefficient, factors that decrease the glomerular filtration rate. Therefore, some antioxidants had protective effect on gentamicin-induced nephrotoxicity (Ademuyiwa et al., 1990; Ali, 2003).

Soliman and et al. (2007), Al-Majed et al. (2002) used gentamicin at dose 80 mg/kg for experimental nephrotoxicity in rats and they resulted similar our study. Patil et al. (2010) applied gentamicin at dose 100 mg/kg for nephrotoxicity in rats and their results were similar our study.

Daily disulfide which is a garlic-derived compound with antioxidant properties has been evaluated for its possible renoprotective effects in gentamicin-induced nephrotoxicity in rats (Pedraza-Chaverrı et al., 2003) . It was noted that the antioxidant activity of vitamin E and probucol had potentially protective effects against gentamicin-induced nephrotoxicity and observed that co-administration of these agents had produced a more pronounced improvement in urine gamma-glutamyl transferase, N-acetyl- D-glucosaminidase, serum creatinine and urea concentrations (Pedraza- Chaverrı et al., 2003; Kumar et al., 2000; Abdel-Naim et al., 1999). Cuzzocrea et al. (2002) investigated the potential role of the superoxide anion in gentamicin-induced renal toxicity by using M40403, low molecular weight synthetic manganese containing a SOD mimetic that selectively removes superoxide. They observed a significant increase in kidney myeloperoxidase activity and lipid peroxidation in gentamicin-treated rats. Mazzon et al. (2001) demonstrated that N-normalized serum MDA concentrations in gentamicin- induced nephropathy in rats. Kadkhodaee et al. (2005) evaluated the effects of co-supplementation of vitamins E and C on gentamicin-induced nephrotoxicity in rats and demonstrated that vitamin C prevented increases in urine lactate dehydrogenase, alkaline phosphatase and N-acetyl– D-glucosaminidase but did not prevent decrease in renal glutathione concentration and filtration failure. Melatonin prevents the tubular necrosis induced by gentamicin in rats, presumably because it is a potent antioxidant and restores antioxidant enzyme activity in the rat kidney (Ozbek et al., 2000).

Losartan was shown to have paradoxical effects on renal function (Goodfriend et al., 1996; Matsukawa and Ichikawa, 1997). On the one hand, it caused renal vasodilatation, prevented decreasing glomerular filtration rate in hypertension, reduced proteinuria and improved morbidity and mortality in diabetic nephropathy, while on the other hand, in states of low fixed renal blood flow such as those arising in bilateral artery stenosis, severe congestive heart failure and severe sodium and volume depletion, it could worsen renal function and even precipitate acute renal failure (Goodfriend et al., 1996; Matsukawa and Ichikawa, 1997). Azzadin et al. (2002) observed the losartan increased gentamicin –induced nephrotoxicity in rats. The result of this study confirmed our results.

In conclusion, we demonstrated losartan severely increased gentamicin–induced renal failure and cimetidine has protective effect on gentamicin–losartan-induced kidney disfunction in rats.

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