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Investigation of the effect of aminoglycosides on angiotensin converting enzyme (ACE)

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ABSTRACT

Objective: The researcher's attention nephrotoxicity from antibiotics (as aminoglycosides), non-steroidal anti-inflammatory drugs, and antifungals, angiotensin-converting enzyme (ACE) inhibitors. Several drugs have resulted in produce an adverse effect on kidneys. Angiotensin-converting enzyme (ACE) is a component of the renin-angiotensin system (RAS), which leads to the conversion of Angiotensin-I to Angiotensin-II in vascular tissues. The aim of this work was to investigate the effect on serum angiotensin converting enzyme of the amikacin.

Material-Method: In this study, two different groups were formed as control (10 rats / Wistar-albino female) and experimental group (30 rats / Wistar-albino female). The experimental group was administered 15 mg/kg amikacin intraperitoneally (ip) for 14 days, and the control group was administered saline solution at the same rate.

Result: When the groups are compared according to the statistical results, it is seen that there is a significant increase in ACE activity of the experimental group compared to the control group ($p<0.001$).

Conclusion: As a result, it was determined that amikacin administered increased serum ACE activity and it was concluded that it may be useful to investigate the possibilities to evaluate it as a risk factor and indicator in the development of hypertension.

Keywords: *Amikacin, Angiotensin-Converting Enzyme, Antibiotics*

INTRODUCTION

The renin-angiotensin system (RAS) plays an important role in the pathogenesis of cardiovascular and renal diseases. The RAS system, maintains blood volume and regulates water, salt metabolism, vascular tone, kidney and heart function through the classical angiotensin-converting enzyme (ACE) angiotensin I-II receptor, types 1-2 pathway (Ma et al., 2014). The ACE is a monomeric and membrane-bound enzyme that activated with zinc and chloride. It is found in significant proportions of lungs, brain, testis, kidney tissues, in addition to physiological fluids such as plasma, semen, macrophages, vessels, endothelial cells (Burnier, 2001).

It has been determined that ACE is mostly found in the endothelium of large and small arteries and arterioles (Falkenhahn et al., 1995; Moncada et al., 1998). ACE plays a key role in cardiovascular and renal disease. The results of endothelial function impaired by response to risk factors such as hypertension, diabetes mellitus, smoking and hypercholesterolemia, is associated with the pathological activation of local ACE. At the same

time, this pathological activation has serious effects on the heart, blood vessels and kidneys (Dzau et al., 2001). ACE inhibitors are one of the main drug groups used in the treatment of hypertension (Mancia et al., 2009).

Although angiotensin receptor blockers (ARB) were initially considered as an alternative drug group to ACE inhibitors, they are now considered to be a completely different group. It has been observed in studies performed on isolated artery grafts that Angiotensin II receptor blockers suppress Angiotensin II response (Liu et al., 2000).

Aminoglycoside group antibiotics like amikacin are bactericidal antibiotics that are effective by inhibiting protein synthesis of Gram (-) bacteria. (Aygün, 2002; Yanagida et al., 2004). Aminoglycosides are potential of nephrotoxicity. Nephrotoxicity effects of aminoglycosides are either aggravating the previous kidney disease or creating new lesions in the kidney (Dilmener, 1986). Almost, 8% to 26% of the patient's aminoglycoside-inducing for several days improve slightly kidney impairment (Alimoradian et al., 2017). In study of Karahan et al. (2005), saw that aminoglycoside causes nephrotoxicity damage (Karahan et al., 2005).

The safe range of aminoglycosides is very narrow, and the most notable limitation of aminoglycosides is toxicity. The most common side effects are nephrotoxicity, ototoxicity, neuromuscular blockade. Nephrotoxicity can develop in all aminoglycosides and can be detected in 5-10% of aminoglycoside use (Mıstık, 2000; Aygün, 2002).

The aim of this work was to investigate the effect on serum angiotensin converting enzyme of the amikacin.

MATERIALS and METHODS

Animal Material

The experiments were conducted according to ethical guidelines and under the supervision of Yuzuncu Yil University Local Ethics Committee of Animal Experiments.

A total of 40 female Wistar-Albino rats weighing 200-250 g formed the study material. The rats were kept in cages at 22±2°C temperature with 12 hours dark-light period and continuous fresh food and water. The rats were fed standard pellet diet and distilled water ad libitum.

Study groups: The rats selected randomly were divided into two groups as the experimental (n=30) and the control (n=10) groups.

Control Group: The rats in this group were intraperitoneally administered 0.9% saline solution for 14 days.

Experimental Group: The rats in this group were administered 15 mg/kg amikacin from the aminoglycoside group (Sigma, St. Louis, MO, USA) every day for 14 days intraperitoneally.

Method

At the end of the experiment, blood samples were taken from the control and experimental group rats, under ether anesthesia, from the left ventricle of their hearts and put down in tubes with gel. Tubes were centrifuged. Serum samples obtained were transferred to eppendorf tubes and frozen at -18°C until the date of the experiment.

Assay of ACE enzyme activity

Measurement of ACE activity performed by using a commercial kit (Colorimetric ACE Angiotensin-Converting Enzyme, Assay-Enzymatic Bühlman Laboratories AG). The angiotensin-converting-enzyme catalyzes the conversion of angiotensin I to angiotensin II. This reaction stopped by the addition of hydrochloric acid (HCl) and complexes with cyanuric chloride after the release of hippuric acid. The absorption of this complex measured at 382 nm. One unit of ACE activity defined as the amount of enzyme required to release 1 µmol of hippuric acid per minute and liter in 37°C serum. Control/sample and control blank/sample blank readings calculated on the spectrophotometer (Boeco S–22 UV/Vis (Germany)).

Statistical analysis

The data from groups were analyzed with the Duncan test was applied for multiple comparisons. Differences were considered significant when the p-value was less than 0.05 (SPSS 22.0).

RESULTS

There is a significant increase in ACE activity between the amikacin-administered rat group and the control group (Table 1).

DISCUSSION

ACE is primarily found in the endothelial cell membrane of the lung, and it is mostly seen as small amounts in the kidney cells and plasma. The ACE in plasma is secreted by endothelial and renal cells.

Table 1. ACE activity of the control and experimental group.

	n	Control Group (Mean ± SD)	n	Experimental Group (Mean ± SD)	p
ACE activity (U/L)	10	82.19±8.87	30	92.82±9.52*	<0.001

*As a result of statistical analysis, the p-value is less than 0.001 and a significant difference observed as statistically.

ACE, a part of RAS, plays a vital role in regulating blood pressure and converts from Angiotensin-I to Angiotensin-II, a potent vasoconstrictor (Balcı-Ekmekçi et al., 2002). In the past, it was thought that almost all of the angiotensin 2 production was pulmonary because the ACE concentration in the lungs was higher than in other organs. However, today it has been shown that angiotensin 2 can be synthesized locally in many organs such as kidney, endothelium, adrenal and brain. One of the most common examples of local RAS activation occurs in the proximal tubule in the kidney. ACE and angiotensin 2 receptors of these cells are shown in proximal tubular cells. Besides, the concentration of angiotensin 2 in this region is approximately 1000 times higher than in the systemic circulation. This locally active system enables a number of physiological functions to be carried out independently of renin secretion (Koçak et al., 2017).

Nephrotoxicity due to aminoglycosides are characterized by direct tubular damage and increased glomerular filtrate rate (GFR) (Fauconneau et al., 1995; Mıstık, 2000). Ototoxicity, nephrotoxicity, and neurotoxicity are the three main side effects of aminoglycosides. Nephrotoxicity is characterized by the accumulation of aminoglycosides in the renal cortex and proximal tubules. Acute tubular necrosis, which is one of acute renal failure (ARF), causes vasoconstriction in afferent arterioles. Due to this response, renal blood flow decreases, and renin secretion increases in the juxtaglomerular apparatus, conversion from angiotensin-I to angiotensin-II. In addition to, studies suggest that there is a relationship between renal disease and activation of the intrarenal renin-angiotensin-aldosterone system (Siragy and Carey, 2010). Ziai et al. (2002) stated that serum ACE activity can be considered as an indicator in patients with bone fractures given 80 mg of gentamicin for 3 days. The significant increase in ACE activity of the experimental group treated with aminoglycosides seems to be consistent with the literature.

Diabetes is one of the most important causes of nephrotoxicity. The studies investigating ACE activity in diabetes-dependent nephrotoxicity have been conducted. Ozmutlu et al. (2012), determined that they found statistically significant increase in ACE activity between diabetes and control groups. They stated that nephropathy, a result of diabetical complications, might cause increase in the ACE activations. Ma et al. (2014), investigated relationship between renal injury in diabetic rats and the antagonism ACE/ACE-II. They were found significant pathological changes in the kidney of Streptozotosin (STZ)-treatmented rats. ACE/ACE-II mRNA levels were significantly higher STZ-treated groups than control groups. In the study presented, the same result was obtained in the nephrotoxicity induced by amikacin.

There are some studies investigating the change in ACE activity due to aminoglycoside and the reasons for this. It is claimed that the endothelial ACE in mice with diabetic nephropathy is a crucial player in the development of tubular ACE and is a central regulator of the glomerular filtration rate (GFR) (Eriguchi et al., 2018). Singhal and Prajapati (2011) reported that treatment with aminoglycoside (such as amikasin) causes an important free radical production, which causes oxidative stress and a significant damage to kidney and hepatic tissue.

It has been determined that free radicals and their derivatives cause tissue damage due to amikacin, which is an antibiotic drug of aminoglycosides category and significantly, reduce antioxidant enzyme activities (SOD, Catalase and Glutathione reductase) along with increased free radical mediated damage (as evidenced by enhanced MDA levels) as well as some extracellular antioxidants (Creatinine, Uric acid and Total bilirubin) in treated mice (Singhal and Prajapati, 2011; Caner and Değer, 2018).

In rats with renal toxicity caused by gentamicin, ACE activity was measured in serum, lung and kidney. The damage to the proximal kidney tubule was evident by the histological analysis and increase in the urinary excretion of N-acetyl-β-d-glucosaminidase (NAG). Kidney ACE activity decreased while lung and serum ACE activity didn't change until day 7 (administration 1, 3, 5, and 7 consecutive days). Ziai et al. (2003), evidenced that occur renal toxicity by presence of proteinuria, polyuria, and declined creatinine clearance at rats with gentamicin-induced. ACE activity was measured in serum, lung and kidney.

ACE activity decreased in kidney, and didn't change in serum, lung. In this study, ACE activity increased in serum. The reason for this increase may be related to the amount of antibiotics administered.

Physiologically, ACE is a crucial enzyme in the renin-angiotensin system, converting angiotensin I into the potent vasopressor angiotensin II and also inactivating the vasodilator bradykinin. Increased serum ACE activity (SACE) has been reported in pathologies involving stimulation of the monocytic cell line, primarily granulomatous diseases. Angiotensin II stimulates the production of various profibrotic and proinflammatory cytokines in tissues independent of their hemodynamic effects. (Bénéteau-Burnat and Baudin, 1991; Ecder, 2009). In parallel with this study, we saw that the serum ACE activity increased in our study as well.

CONCLUSION

ACE activity is increased in rats aminoglycoside administered and the increased ACE activity has many side effects as mentioned in the sources given above. As a result, it was concluded that the monitoring of the renin-angiotensin-aldosterone system may be important in preventing the progression of renal failure in aminoglycoside treatment and alternative studies should be conducted on this subject.

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