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ORIGINAL ARTICLE

Effect of Glucocorticoids Receptor Ligands on Renal Functions of mice induced by Nephrotoxic Poison Concanavalin-A

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ABSTRACT

Background: According to international society of nephrology about 2 million people die with AKI every year.
Aim: To evaluate the effect of GR ligands on renal functions of mice induced by nephrotoxic poison Concanavalin-A.
Study design: Experimental study.
Methodology: The study was conducted at Agriculture University of Faisalabad-Pakistan following approval from ethical committee. Mice having age around 10 weeks, weighing 25 to 30 grams, kept under observation at animal house facility at University of Agriculture for 9 days. Subject animals (n=12) were equally divided into 3 groups, 1st was control group, 2nd was treated group and 3rd was untreated group. Renal markers, creatinine, urea and BUN were estimated from blood sample by using serum analyzer. The collected data was analyzed by using SPSS version 20. ANOVA ware applied with P-value< 0.05 as significant.
Results: Analysis of kidney function test showed significance increase in creatinine, urea and BUN level in Con-A induced toxic group. They were normalized in pretreated groups receiving GR ligand (Dexa).
Conclusion: It was concluded that glucocorticoids ameliorated the Con-A induced nephrotoxicity by significantly reducing the elevated kidney biomarker levels including creatinine, urea and BUN in mice serum.
Keywords: Glucocorticoids, Serum Urea, BUN and Concanavalin-A.

INTRODUCTION

Literature review showed that renal defects are the leading health issue among humans due to many reasons and ultimately leading to death with renal failure[1]. Renal failure has high (10-20 folds) mortality in comparison to general population[2,3]. Drug metabolites and waste material excreted through kidney can cause renal impairments[4] as kidney receive more blood that may be a reason of about 25% acute renal failure by means of reno-toxic materials. Renal impairments through free radical production & its binding to cellular components cause cellular necrosis, proteinuria & lysosome enzyme urea and reduce glomerular filtration rate by toxic chemicals[5]. Kidney problems including acute renal failure, chronic renal failure, nephrotoxicity & end stage renal disease is increasing day by day[6]. Literature review showed that ROS plays an important role in inflammation by activating T cells that damage other cells & stimulate inflammation[5]. Previous studies showed that various pathological factors produce ROS due to an imbalance between oxidant and antioxidant defense system[6,7].

According to international society of nephrology about 2 million people die with AKI every year. Elder patients and pediatrics have less immunity due to which concurrent administration of medication may damage the nephrons[1]. Many endogenous and exogenous factors disturb the physiology of the kidney and reduce its normal functions like detoxification and excretion of waste materials[4].

Concanavalin A is extracted from *Canavalia ensiformis*. At toxic concentration by activation of T cells it causes the release of inflammatory mediators[8]. ROS are associated with activation of T cells that cause damage of cells & mediate inflammatory processes[9]. Glucocorticoid receptors have 2isoforms GRα and GRβ[10]. Dexamethasone exhibits anti-inflammatory effect by inhibition of pro-inflammatory mediators including interleukin[11,12]. Kidneys are refined reprocessing machines[13].

The objective of the study was to evaluate the effect of GR ligands on renal functions of mice induced by nephrotoxic poison Concanavalin-A.

METHODOLOGY

The study was conducted at Agriculture University of Faisalabad-Pakistan following approval from ethical committee. Subject animals (n=12) were equally divided into 3 groups, 1st was control group, 2nd was treated group and 3rd was untreated group. Total serum protein profile, albumin, globulin and A/G ratio were estimated from blood sample by using serum analyzer.
Chemical and drugs: Concanavalin-A (99% purity) and Dexamethasone were purchased from Sigma Aldrich. Phosphate buffer saline sachets (10X) were also purchased.
Reconstitution of Con.A:15mg of con-A per 5 ml of phosphate buffer saline was dissolved carefully then added 1 drop of 0.1mM Manganese chloride and 1 drop of 0.1mM calcium chloride solution.
Experimental Design: Twelve animals equally divided in 3 groups. All groups kept on routine diet + vehicle (100 µl of ethanol diluted 1:10 in sesame oil) + normal saline for 7 days. Then subjected for treatment of con.A separately in 2nd and 3rd group.
Blood samples collection: Blood sample collected at ninth day, centrifuged & stored at -20^{0}C.
Biochemical parameters: Serum used for estimation of RFTs that include creatinine, urea & blood urea nitrogen by kits. To convert urea into BUN, the serum urea value is multiplied by 0.47.
Statistical analysis: SPSS version 20 was used to analyze the data. ANOVA ware applied with P-value< 0.05 taken as significant.

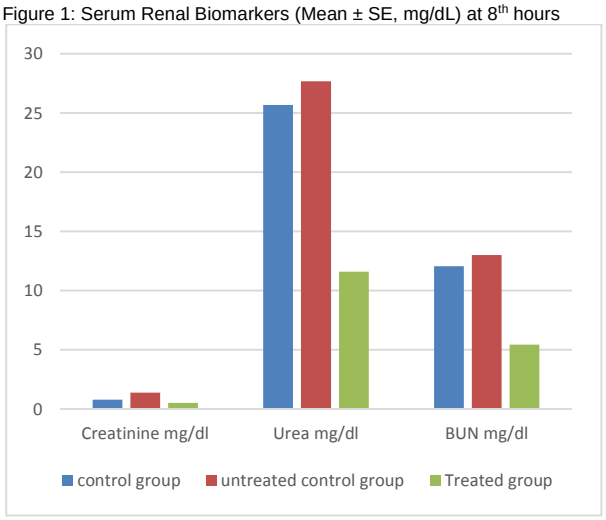
RESULTS

Kidney biomarkers as expected elevated in untreated control group receiving toxicant Con-A 15mg per kg revealed acute renal injury in mice model. Mean± SE of serum creatinine, urea and blood urea nitrogen were shown in table-1 and figure-1 among different groups.

Table-1: Serum renal biomarkers at 8th hours among both groups

Groups	Treatments	Creatinine (mg/dl)	Urea (mg/dl)	BUN (mg/dl)
Control group	Normal saline	0.785±0.146	25.682±6.66	12.070±3.132
Untreated control group	Vehicle + Con-A.	1.380±0.157	27.677±4.915	13.008±2.310
Treated group	Dexamethasone	0.526±0.181	11.605±3.38	5.454±1.589

Figure 1: Serum Renal Biomarkers (Mean ± SE, mg/dL) at 8th hours



DISCUSSION

One of the major health issues all over the world is kidney disease that's increasing day by day. There is significant progress in therapy but the mortality rate is still increasing due to which less than 40% of patients remain alive after 5 years of dialysis. The main cause of kidney problem is nephrotoxicity, toxicant and drugs induce nephrotoxicity by initiation of inflammatory process, membrane disruption, vascular regulation disturbance and production of free radical by oxidative stress[14,15].

Homeostasis of water and mineral ions are regulated by kidneys. Kidney diseases are developed by accumulation of waste products that disturb normal functioning of kidneys[16]. In present study, Concanavalin-A induced nephro-toxicity among mice at 15 mg/kg dose. It activates T cells alongwith cytokines release at dosage of 10-30mg/kg as revealed by previous study[17].

Drugs like steroids (Glucocorticoids) plays a role as anti-inflammatory agent and inhibits production of cytokines as well as transforming growth factors [3,18]. Con-A treated mice induced renal impairment rises the level of creatinine[19]. In case of renal impairment there is imbalance between rate of production and rate of excretion of BUN and urea[20].

Results depicted that intravenous Con-A in subjects caused renal impairment by significantly elevating the kidney biomarkers in comparison to normal control group. In pathological state there's increase muscular metabolism which produces high conc. of creatinine. There is elevation in serum level of biochemical markers in stress[20]. In current study pretreatment with GR ligand (Dexa) significantly diminished the serum levels of renal bio-markers in comparison to Con-A treated group.

Limitations: Sample size was too small for the study. Resources were limited with financial constrains.

CONCLUSION

Analysis of kidney function test showed significant increase in creatinine, urea and BUN level in Con A-induced toxic group that were normalized in pre-treated groups receiving Dexa. Our study showed acute kidney damage induced by Con-A which was ameliorated by protecting with Dexa.

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