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Research Article
Pioglitazone Mitigates the Toxic Effect of Doxorubicin-Induced Nephrotoxicity

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Abstract

Background and Objective: Doxorubicin (DXR), a widely prescribed chemotherapeutic agent, is given to patients for the treatment of different types of cancer. The adverse effects of this substance are well-documented and can lead to harm in various organs such as the liver, kidneys, nervous system and bone marrow. A study found that pioglitazone (PIO) has demonstrated promising results in managing diabetes mellitus and Alzheimer's disease by effectively lowering blood sugar levels and reducing neurotoxicity. The current research focuses on investigating the potential protective effect of co-treatment with PIO on nephrotoxicity induced by DXR. **Materials and Methods:** Forty rats weighing 230-255 g were split into four groups, with ten animals. These groups were divided into control and three therapies. Control animals received saline. The DXR animals were administered intraperitoneal four doses (5 mg/kg). The PIO-treated animals got 2 mg/mL mixed in their drinking water one day before DXR administration and continued until the last dosage. The remaining group received four DXRs and a daily PIO in drinking water. The animals were observed for mortality and blood samples were obtained to quantify BUN and creatinine. **Results:** It was found that the animals who received DXR had a higher mortality rate compared to the control group. In addition, the survival rate is improved when DXR and PIO are combined. In addition, there was a notable rise in the levels of BUN and creatinine, along with their ratio, in the animals that received DOX. However, this increase was reversed when PIO was combined with DXR. **Conclusion:** The study's findings indicate that DXR can cause nephrotoxicity, increasing BUN and creatinine levels. However, co-treatment with PIO appears to counteract this elevation, suggesting that PIO may have a beneficial effect in reducing DXR toxicity in the kidney.

Key words: Doxorubicin, pioglitazone, nephrotoxicity, BUN, creatinine, rats

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Acute kidney injury is clearly defined as a sudden decrease in renal function that results in structural alterations[1]. Measuring the levels of BUN and creatinine, along with their ratio, is a common method for assessing renal function[2]. Chemotherapy drugs like doxorubicin and cisplatin have been found to cause an elevation in BUN and creatinine levels, as well as their ratio[3]. The doxorubicin (DXR) is a well-known and effective anticancer anthracycline antibiotic that has been widely used to treat various types of cancer, such as breast, prostate and lung cancers[4]. Regrettably, the use of DXR in chemotherapy is limited due to its toxic effects on important organs like the heart, liver and kidney, which are dependent on the dosage[5]. While the production of free radicals by NADPH-dependent reductase and non-enzymatic reactions, such as the reaction between DXR and iron, have been reported by Gaytan *et al.*[6], the exact cause of DXR-induced nephrotoxicity remains unclear. The free radical can undergo redox cycling, resulting in the production of O_2 and H_2O_2[7]. When iron is present, DXR can create DXR complexes[7]. These complexes then play a role in accelerating the conversion of H_2O_2 into different types of ROS species, including hydroxyl radicals[8]. Increased production of reactive oxygen species (ROS) contributes to the degradation of biomolecules such as proteins and lipids, resulting in kidney tissue damage and toxicity[9].

The Peroxisome Proliferator-Activated Receptors (PPARs) are ligand-activated nuclear hormone receptors found in various tissues throughout the body, including the kidney[10]. Studies have demonstrated that PPAR agonists can have beneficial effects on drug-induced kidney toxicity in animal models[11]. Research has demonstrated that activating PPAR in the kidney can help decrease glomerular and tubulointerstitial injury caused by lipotoxicity, potentially preventing renal failure[11].

Pioglitazone (PIO) is a type of medication called thiazolidinedione (TZDs) that is commonly prescribed to help control diabetes mellitus[12]. The PIO has been shown to activate Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ), which is quite stimulating[13]. Recent studies have shown that PIO has properties that help protect the nephron by reducing inflammation and combating oxidative stress[14].

Thus, the present study aimed to investigate the potential protective effect of PIO against nephrotoxicity caused by DXR in rats and to elucidate the underlying mechanisms responsible for these protective effects. It also assessed the effect of PIO on renal function in rats undergoing chronic treatment with DOX.

MATERIALS AND METHODS

Study area: The study was conducted at a laboratory specializing in the field of Pharmacology and Toxicology in the College of Pharmacy at Qassim University, Saudi Arabia, from September, 2023 to October, 2023.

Chemicals and drugs: The doxorubicin injection (2 mg/mL) and pioglitazone hydrochloride (Glados®) were sourced from EBEWE Pharma Ges.m.b.H. Nfg.KG in Unterach am Attersee, Austria and Tabuk Pharma. Manufacturing Co., Tabuk, Saudi Arabia, respectively.

Animals: Forty rats, ranging in age from ten to twelve weeks, obtained from the animal house in the College of Pharmacy, Qassim University were housed in individual chambers inside an environment that rotated between light and dark cycles lasting 12 hrs, with the lights being turned on at 6 O'Clock in the morning. Pelletized food and water were available to the animals at all times throughout the day. The survival rate of the experimental rats was monitored daily. The research adhered to the institution's ethical standards for animal experiments.

Experimental design and treatment protocol: As part of this investigation, the animals were divided into four groups, each containing ten animals. Normal saline is administered intraperitoneally as the control. Administration of treatment 1 involves intraperitoneal delivery of DXR at a concentration of 5 mg/kg, four times per day, with a three-day interval between each administration. The second treatment involved the administration of PIO (2 mg/mL) dissolved in drinking water over 12 days. The fourth treatment involved a combination of medications. The PIO was taken for 10 days and on the first day of PIO induction, DXR was given in four doses, with each dose administered every third day. After the treatments were completed, the animals were euthanized and blood samples were collected from six animals in each group. The experimental rats were closely observed daily to ensure accurate documentation of their survival or mortality rates. After that, the animals underwent biochemical assays[15].

Electrochemiluminescence (ECL): On the 12th day, the rats were executed humanely by decapitation after being subjected to hypnosis using Carbon Dioxide (CO_2). This occurred after the ultimate delivery of the medication. Subsequently, blood samples were obtained from both the control/untreated group and the treatment groups, which encompassed individuals who were administered PIO, DXR

and DXR in combination with PIO. The gathered samples were subsequently inserted into tubes that contained Ethylenediaminetetraacetic Acid (EDTA). Following the procedure, the vials containing the blood samples were subjected to centrifugation at a speed of 12,000× g for 10 min. Through this process, the plasma component was successfully isolated. Biomarkers like BUN and creatinine were measured using an automatic analyzer that utilizes electrochemiluminescence (ECL) technology. The ECL is a highly sensitive technology used to detect and quantify biomolecules, such as proteins, through the use of immunoassays. The task was conducted following the procedures outlined by Roche Diagnostics, a company based in Germany[16].

Statistical analysis: The findings of the *in vivo* study were subjected to a One-way Analysis of Variance (ANOVA) test. The results of the investigation were presented as the Mean±SEM (Standard Error of the Mean). Consequently, a Tukey's analysis was implemented to compare the data on an individual basis, with statistical significance values set at a p-value of less than 0.05.

RESULTS

DXR and PIO impact on the survival rate in rats: A rat model was established to gain a better understanding of whether PIO improves the survival rate of rats that were administered with DXR. This was achieved by using a Kaplan-Meier test. Based on the results of the survival rate analysis conducted on rats treated with different combinations of medications, it was observed that the findings indicated that the use of DXR resulted in a higher mortality rate in animals, approximately 60%. However, when combined with PIO, the survival rate improved to around 80%. Thus, the study's results indicated that adding PIO to DXR may have a protective effect. Both the saline and PIO groups achieved a 100% survival rate (Fig. 1).

Impact of DXR and PIO on BUN concentrations: The results of the ECL test showed a significant increase in BUN concentrations in the DXR group. However, when PIO was combined with DXR, this increase was reduced compared to the control group. Thus, this outcome suggests PIO. It appears that PIO had a positive effect on the concentrations of BUN (Fig. 2).

Impact of DXR and PIO on creatinine concentrations: According to the results of the ECL study, it was found that there was a significant increase in creatinine concentrations in the DXR group. However, this increase was reduced when PIO was combined with DXR compared to the control group. Thus, this outcome suggests PIO. It seems that PIO had a beneficial impact on the levels of creatinine (Fig. 3).

Impact of DXR and PIO on BUN/creatinine ratio: According to the results of the ECL study, it was found that there was a significant increase in BUN/creatinine concentrations in the DXR group. However, when PIO was combined with DXR, this increase was reduced compared to the control group. Thus, this outcome suggests PIO. It seems that PIO had a beneficial impact on the levels of BUN/creatinine ratio (Fig. 4).

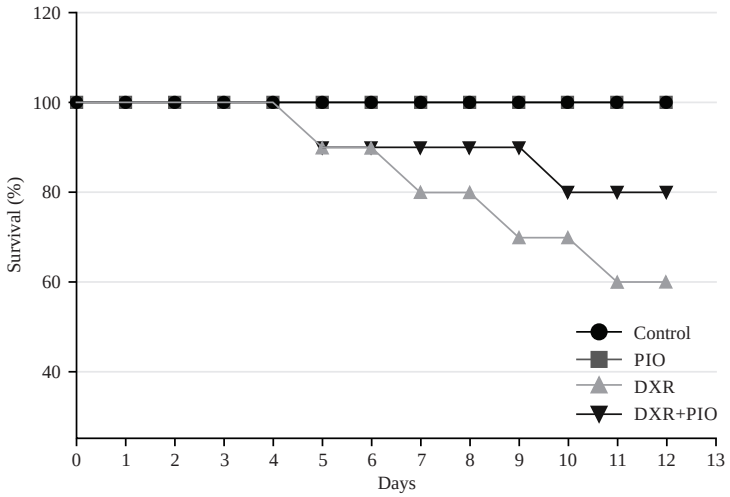

Fig. 1: Effect of DXR, PIO and combination on survival rate

DXR alone resulted in a 40% mortality rate, while the combination of DXR and PIO led to a 20% mortality rate and in contrast, all the control and PIO groups survived throughout the study

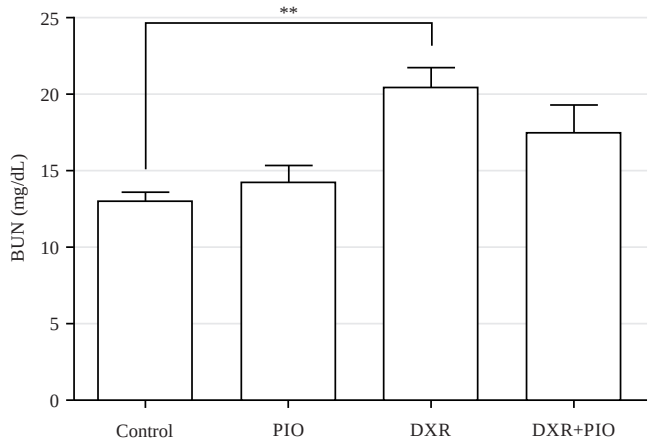

Fig. 2: Effect of DXR, PIO and combination on BUN levels in rats

DXR treatment resulted in an elevation in BUN levels, while PIO combination with DXR provides protection against DXR-induced renal toxicity and a statistically significant representation of the data was the Mean±Standard Error of the mean when $p<0.05$ as equated to the saline **$p<0.01$

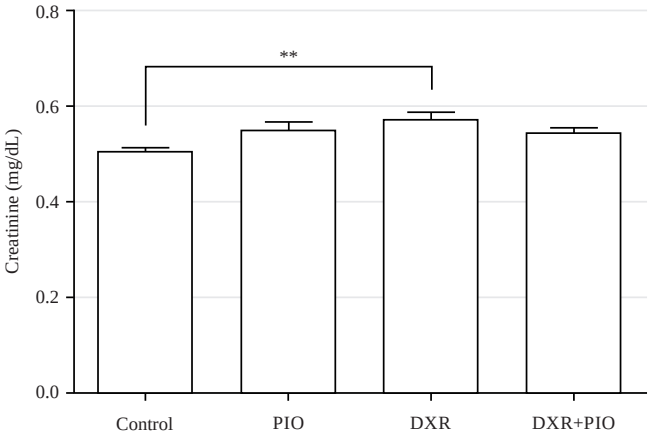

Fig. 3: Effect of DXR, PIO and combination on creatinine levels in rats

DXR treatment resulted in an elevation in creatinine levels, while PIO combination with DXR provides protection against DXR-induced renal toxicity and a statistically significant representation of the data was the Mean±Standard Error of the mean when $p<0.05$ as equated to the saline **$p<0.01$

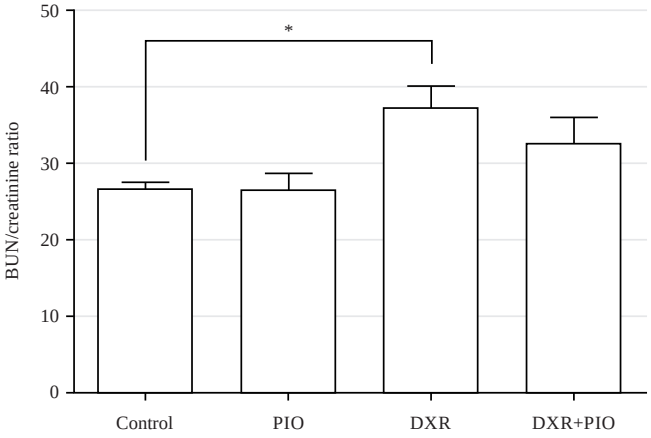

Fig. 4: Effect of DXR, PIO and combination on BUN/creatinine ratio in rats

DXR treatment resulted in an elevation in the BUN/creatinine ratio, while PIO combination with DXR protects against DXR-induced renal toxicity and a statistically significant representation of the data was the Mean±Standard Error of the mean when $p<0.05$ as equated to the saline *$p<0.05$

DISCUSSION

The doxorubicin can interact with DNA by intercalating, which leads to the inhibition of topoisomerase II[17]. This enzyme is crucial for both transcription and replication processes[18]. While the exact cause of renal failure induced by DXR is still unclear, it is believed to be linked to oxidative damage to the renal tissue, resulting in changes to BUN and creatinine levels. Pioglitazone is a Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) agonist that has been shown to have protective effects in diabetic animal models[12]. It has been reported that pioglitazone can help alleviate diabetic nephropathy by addressing various factors such as decreasing renal oxidative stress and inflammation[14]. The PIO has been found to enhance glycaemic control without causing any additional stimulation of the body's natural insulin production[19]. This study provides insights into the potential protective effects of PIO against doxorubicin-induced nephrotoxicity and aims to uncover the mechanisms involved.

This study employed a Kaplan-Meier method to assess the rate of survival. This method plays a crucial role in identifying the toxicities associated with specific medications or illnesses[20]. The recent study demonstrated the safety of using PIO alone, as the survival rate in the treatment group remained at 100%, similar to that of the control group. After administering four doses of DXR to the animals (20 mg/kg), the survival rate of the rats decreased to 60% after 12 days from the first dose. It is worth noting that the combination of PIO and DXR had a significant impact on the survival rate of the animals, resulting in an increase of survival rate to 80% compared to the control group, indicating only 20% death versus 40% in DXR alone. These findings suggest that PIO has the potential to reduce the toxicity of DXR.

The current study found that rats treated with DXR exhibited severe renal damage, as evidenced by a significant increase in blood urea nitrogen and serum creatinine levels, which is consistent with previous research of Afsar *et al.*[21]. Multiple studies have provided evidence of the detrimental impact of DXR on renal health[21]. However, Alsaud *et al.*[13] have shown that combining PIO with DXR in rats can help reduce toxicities like oxidative stress and inflammation. However, the effects on kidney function are still not fully understood. As a result, the current study showed a significant increase in biomarkers for kidney impairment, including blood urea nitrogen (BUN) and serum creatinine, compared to the control. However, these elevations in BUN and serum creatinine were notably alleviated in the co-treatment of PIO against DXR treatment causing renal impairment. Therefore, these findings offer additional support for the current hypothesis that PIO has the potential to alleviate the kidney damage caused by DXR.

This study has both strengths and limitations that need to be considered. Based on current understanding, this study examines the effects of DXR on nephrotoxicity by analyzing the levels of BUN and creatinine. The animals used in this study were of the same strain and age and all experimental procedures were conducted simultaneously across the study groups to minimize the impact of any other factors. To evaluate the direct effects of DXR treatment without any interference from the presence of cancer, cancer-free rats were used. This approach helped to minimize any potential confounding factors. The doses utilized fell within the range typically administered to human patients in clinical settings. To summarize, the administration of DXR leads to a significant impairment of renal function, which ultimately leads to kidney failure.

CONCLUSION

In this work, novel mechanistic evidence was presented that demonstrated that PIO reduces the nephrotoxicity caused by DXR by lowering the levels of BUN and creatinine. This PIO showed a potentially protective effect against the nephrotoxicity that was generated by DXR.

SIGNIFICANCE STATEMENT

This study aims to evaluate the potential therapeutic benefits of pioglitazone in reducing doxorubicin-induced nephrotoxicity. A previous study revealed that doxorubicin significantly increases blood urea nitrogen and creatinine levels, indicating the presence of nephrotoxicity. Based on the research findings, rats treated with pioglitazone experienced a decrease in BUN and creatinine concentrations. Based on the findings, pioglitazone can effectively alleviate the nephrotoxic effects induced by doxorubicin.

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