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Research Article
Comparative Analysis of the Cardiotoxic Effects Induced by Various Chemotherapeutic Agents

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Abstract

Background and Objective: Chemotherapeutic drugs like doxorubicin, cyclophosphamide, fluorouracil and cisplatin are frequently prescribed for the treatment of various types of cancer. However, these medications can have adverse effects. This study was conducted to evaluate the impact of different chemotherapeutic agents on heart toxicity in a rat model. In addition, this study delved into the underlying mechanisms behind these effects. **Materials and Methods:** A group of fifty rats received a single dose of DOX (25 mg kg^{-1}), 5-FU (100 mg kg^{-1}), cisplatin (8 mg kg^{-1}) and CYP (200 mg kg^{-1}) through intraperitoneal injection. The mortality rate was monitored on a daily basis and the cardiac performance of rats was assessed by measuring troponin I, creatine kinase (CK) and creatine kinase MB (CK-MB) levels using ECL. **Results:** This study revealed notable variations in survival rates, with a 50% rate for DOX, 30% for cisplatin and 20% for CYP. In the DOX group, there was a significant increase in troponin I, CK and CK-MB levels. However, there were no significant changes observed in the 5-FU, cisplatin and CYP-treated groups. **Conclusion:** The various chemotherapy drugs can lead to heart damage by increasing the levels of certain cardiac markers, such as troponin I, CK and CK-MB.

Key words: Chemotherapy, cardiotoxicity, survival rats, troponin I, creatine kinase

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

INTRODUCTION

There were approximately 19.3 million new cancer diagnoses worldwide, with Saudi Arabia reporting over 27,000 cases in 2020[1,2]. By 2040, it is projected that the number of cancer cases worldwide will increase to 28.4 million. However, in 2022, there were over 40 million cancer survivors worldwide[3]. In addition, thanks to advancements in early detection and cancer treatments, experts predict that this figure will rise[4]. In spite of advancements in cancer management, the treatment of cancer has been found to have an impact on the functioning of the heart. The precise mechanisms through which cancer treatment leads to cardiotoxicity are still not fully understood. However, it is suggested that it may be due to the induction of inflammation and oxidative stress. Chemotherapy is a commonly employed approach in the treatment of cancer[5]. Chemotherapeutic agents are capable of eliminating cancer cells by specifically targeting different phases of the cell cycle[6]. Various groups can be formed to categorize these chemotherapeutic agents, taking into account their mechanisms and chemical structures. Anthracyclines, like doxorubicin (DOX), belong to antibiotics, which work by disrupting enzymes responsible for DNA transcription and RNA synthesis[7,8]. Alkylating agents like cyclophosphamide (CYP) and cisplatin have the potential to directly harm the DNA structure[9]. Certain drugs like 5-fluorouracil (5-FU) and methotrexate disrupt the process of DNA or RNA synthesis[10].

Although chemotherapeutic agents are highly effective in treating various cancers, they can also lead to side-effects and toxicity due to the activation of inflammatory responses and oxidative stress[5,7]. Chemotherapeutic agents often focus on cells that divide quickly, like bone marrow, hair follicles and the cells in the digestive system lining. As a result, they can cause various side effects[11]. While cardiac cells do not undergo rapid division, they have the potential to cause cardiotoxic damage[11], which can have a direct or indirect impact on various symptoms that can significantly affect one's quality of life[11,12]. Chemotherapeutic agents can have serious cardiological effects, such as myocardial infarction and heart failure.

Given these findings, it was hypothesized that different chemotherapeutic agents may differ in their potential to cause cardiotoxicity. Therefore, study was conducted to examine the impact of DOX, 5-FU, cisplatin and CYP on cardiotoxicity. The levels of troponin I, CK and CK-MB were assessed which are biomarkers associated with cardiac damage, in order to gain insights into the underlying molecular mechanism of this toxicity. Current research findings may provide additional insights into the mechanisms of heart toxicity in rat models, which could be valuable for the development of protective strategies.

MATERIALS AND METHODS

Study area: The investigation was carried out at the College of Pharmacy at Qassim University in the Kingdom of Saudi Arabia between the 1st and the 30th of March, 2023.

Drugs: The drugs DOX, 5-FU and cisplatin were acquired from EBEWE Pharma Ges.m.b.H. Nfg.KG in Austria, while CYP was attained from Baxter in Mumbai, Maharashtra, India.

Animals: Fifty female rats, weighing between 200 and 290 g and aged 10 to 12 weeks, obtained from College of Pharmacy at Qassim University, were kept in plastic cages with unlimited access to water and food. The animals were closely observed on a daily basis to evaluate their body weights and mortality rate. The animals were divided into groups labeled DOX, CYP, 5-FU and Control, with 10 animals in each group.

Ethical consideration: The ethical requirements and experimental protocol for this study were granted approval by Qassim University represented by the Deanship of Scientific Research (under number 23-27-05).

Drug administration: The rats were administered a single injection of DOX at a dosage of 25 mg kg^{-1}[8], CYP at a dosage of 200 mg kg^{-1}[13], 5-FU at a dosage of 100 mg kg^{-1}[14], or cisplatin at a dosage of 8 mg kg^{-1}[15] via intraperitoneal route. The control group, on the other hand, received saline.

Experimental design: For the purpose of this investigation, the animal house located within the College of Pharmacy at Qassim University provided a total of fifty albino female rats weighing between 200 and 290 g. The rodents were housed in cages with a light-dark cycle that lasted for 12 hrs and a temperature that was maintained at 25.2°C throughout the day. They were never constrained in terms of the amount of food and water that was available to them. The rodents were divided into five groups, each consisting of 10 rats. After a period of 5 days during which the rats were subjected to daily observations during which their body weight and mortality rate in response to treatments were recorded, the rats were then put through a biochemical evaluation.

Electrochemiluminescence immunoassays: After 5 days, the rats were euthanized in a humane manner by cervical decapitation under anesthesia induced by Carbon Dioxide (CO_2) following the last drug administration. Blood samples were promptly obtained and deposited into tubes containing Ethylenediaminetetraacetic Acid (EDTA) from both the control group as well as the groups receiving treatment with DOX, 5-FU, cisplatin and CYP. This was done for all of the participants. After that, the vials that contained the blood samples were subjected to centrifugation for a period of ten minutes at a force that was 12,000 times the acceleration due to gravity (12,000 g). Following the separation of the plasma, it was placed in vials that had a capacity of 2 mL. A temperature of -80°C was maintained during its storage. Following the collection of the blood samples, a painstaking examination was carried out with the assistance of a cutting-edge automated analyzer. This advanced device utilizes a unique electrochemiluminescence technology to conduct immunoassay analysis on a range of biomarkers related to heart toxicity, such as troponin I, CK and CM-MB. The ECL approach was executed utilizing the COBAS INTEGRA 400 plus equipment in accordance with the specifications that were provided by the manufacturer, Roche Diagnostics, Germany.

Statistical analysis: The statistical analysis was done utilizing GraphPad Prism 10 and the findings were displayed as means SEM. Biomarkers of cardiac damage, including troponin I, creatine kinase and cardiac nitric oxide synthase MB (CK-MB), were examined alongside the overall survival rate. The data was analyzed using one-way ANOVA and then Dunnett's test for statistical significance. Those in the therapy group saw their results compared to those in the placebo group. When the $p<0.05$, it was considered to be statistically significant.

RESULTS

Effect of various chemotherapeutic agents on survival rats: The survival rate was monitored on a daily basis throughout the study, which spanned 5 days after the rats were administered various chemotherapeutic agents. The saline and 5-FU groups did not experience any fatalities throughout the duration of the study. At the end of the study, the treatment with DOX resulted in a 50% mortality rate, while cisplatin caused a 30% mortality rate and CYP led to a 20% mortality rate (Fig. 1).

Analyzing the impact of different chemotherapies on troponin I: An evaluation was conducted using ECI to assess the impact of chemotherapeutic agents (DOX, 5-FU, cisplatin and CYP) on the levels of troponin I in rat blood. In comparison to the saline group, the DOX, cisplatin and CYP groups showed an increase in troponin I levels, while no significant changes were observed in rats treated with 5-FU (Fig. 2).

Analyzing the impact of different chemotherapies on CK and CK-MB: The CK and CK-MB concentrations were evaluated 5 days after rats received a single dose of chemotherapy. The DOX- and cisplatin-chemotherapy treated rats showed increase in CK and CK-MB concentrations in the blood samples compared with the saline rats; however, 5-FU and CYP treated groups did not exhibit a notable rise in CK and CK-MB concentrations versus the saline group (Fig. 3a-b).

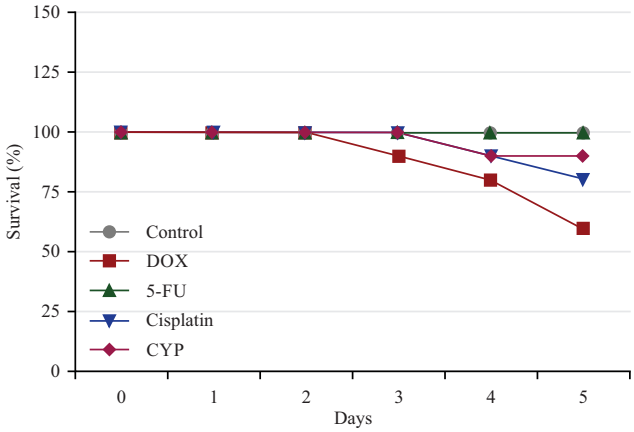

Fig. 1: Effects of different chemotherapy on survival rate

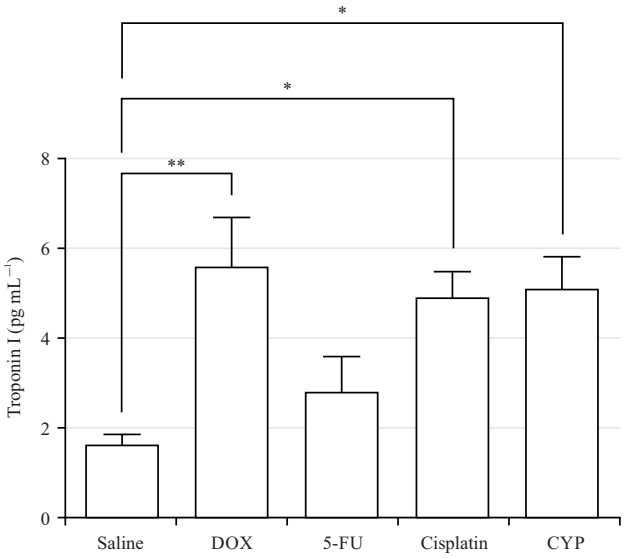

Fig. 2: Impact of various chemotherapeutical agents on Troponin I concentrations in rat serum, ECL analysis showed an increase in Troponin I levels in DOX, cisplatin, and CYP groups related to that in the saline group; however, the 5-FU-treated group did not show significant differences related to the saline group

*p<0.05 and **p<0.01 related to saline rats

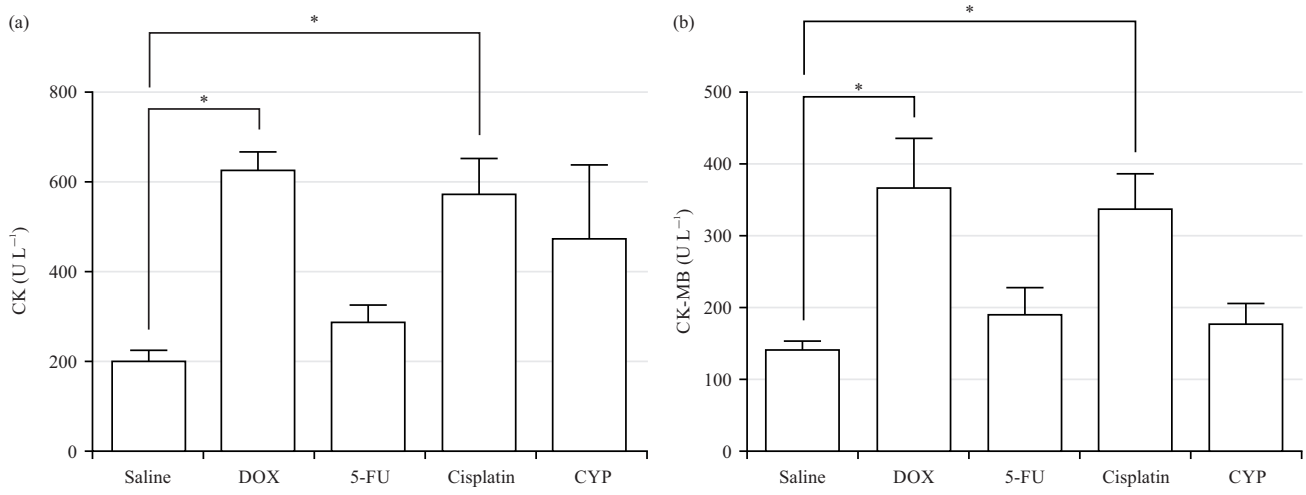

Fig. 3(a-b): Effects of different chemotherapy on CK and CK-MB concentrations in rat serum, (a) ECL analysis showed a significant increase in CK levels following DOX and cisplatin-treated groups related to that in the saline group and (b) Levels of CK-MB were significantly higher in DOX and cisplatin groups

*p<0.05 related to saline rats

DISCUSSION

The present work attempted to elucidate the mechanism underlying various chemotherapeutic agents inducing cardiotoxicity. One of the challenges in treating cancer using chemotherapy is the adverse effects, including cardiotoxicity, nephrotoxicity and neurotoxicity[16-18]. Recent studies have indicated that certain chemotherapeutic agents, like DOX and CYP, have been found to potentially cause cardiotoxicity, which can result in heart failure[19-21]. Cardiotoxicity caused by chemotherapy can manifest as arrhythmias, left ventricular diastolic dysfunction and heart failure[22,23]. The objective of the existing study was to explore the impact of certain medications and their potential toxicities on the heart.

Therefore, it was hypothesized that the potential cardiotoxicity may be linked to an elevated in troponin I, CK and CK-MB concentrations after the administration of chemotherapeutic agents. There have been reports indicating that higher levels of pro-inflammatory cytokines, including TNFα, IL-6 and IL-1β, can impact cardiac function. Previous research found that injecting chemotherapeutic agents peripherally can cause increased neuroinflammation in the brain, which in turn affects overall brain function and leads to cognitive dysfunction[24]. Thus, based on current understanding, this study represents the initial examination of the impacts of different chemotherapeutical drugs (DOX, 5-FU, cisplatin and CYP) on heart toxicity. Troponin I, CK and CK-MB concentrations were assessed to gain insights into the underlying mechanisms of cardiotoxicity in patients undergoing chemotherapy.

One popular approach to determining medication safety is keeping track of the number of treated animals that survive[25-28]. In the present study, rats were closely monitored for a period of five days after being given DOX, 5-FU, cisplatin and CYP in a single dose. There was a noticeable difference in the rats' survival rates across the various chemotherapy groups throughout the study. Based on the study, it was discovered that DOX had the highest level of toxicity among chemotherapeutic agents, leading to a survival rate of just 60%. On the other hand, the toxicity of cisplatin was reduced, resulting in a survival rate of 80%. The CYP had the lowest toxicity, resulting in a survival rate of 90%. Interestingly, 5-FU did not show any toxicity in terms of survival rate, as all the individuals in this group survived until the end of the study (Fig. 1).

The exact cause of cardiotoxicity induced by chemotherapeutic agents is still not entirely understood. The findings of this study revealed the harmful effects on the heart caused by certain chemotherapeutic agents like DOX, cisplatin and CYP. This was evident from the notable rise in troponin I, CK and CK-MB concentrations related to the saline group. In addition, there was a notable elevation in troponin I concentrations due to CYP, although this effect was not observed to the same extent in the CK and CK-MB levels. However, 5-FU did not show any notable impact on troponin I, CK and CK-MB concentrations.

The current results were constrained by its *in vivo* design. The results should be validated through future clinical trials. The study's strength lies in the fact that the animals used in the research have identical gender, age, strain and comparable living conditions. In addition, current research unfortunately did not have the opportunity to explore the complex mechanisms that affect cardiac functions, specifically related to DOX, cisplatin and CYP. Future research could explore various dosages and additional mechanisms related to cardiotoxicity, providing valuable insights for practitioners and researchers seeking effective treatments for chemotherapy-induced heart damage.

CONCLUSION

After assessing cardiac biomarkers, it has been established that the administration of different chemotherapeutic drugs resulted in cardiotoxicity in rats. In addition, we have found evidence that certain medications and enzymes can affect the levels of specific cardiac biomarkers. Specifically, DOX, cisplatin and CYP have been shown to increase troponin I levels, while DOX and cisplatin also increase CK and CK-MB levels. However, no changes in cardiac biomarkers were observed with the use of 5-FU. Enhancing our comprehension of the mechanisms behind cardiotoxicity after chemotherapy can lead to the development of novel approaches to alleviate the harmful impacts of chemotherapeutic drugs in individuals with cancer.

SIGNIFICANCE STATEMENT

The current study seeks to evaluate the effects of various chemotherapeutic agents on the development of cardiotoxicity. Various studies have shown that chemotherapy can result in side effects related to the heart. The study revealed that rats treated with various chemotherapeutic agents experienced notable elevations in troponin I, CK and CK-MB levels in their bloodstream, leading to heart toxicity. These findings suggest that certain chemotherapeutic agents showed varying levels of cardiotoxicity, with DOX and cisplatin being particularly powerful.

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