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Effects of Doxorubicin Administration at Different Doses and Durations on the Body Weight of Rats

Zeynep ÇELİK KENAR [1*] Ertan ORUÇ [1]

[1] Selçuk University, Faculty of Veterinary Medicine, Department of Pathology, Selçuklu-Konya, Türkiye

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ABSTRACT

This study examines the impact of varying doses of Doxorubicin (DOX) on body weight in rats, with a focus on the drug's cachexia-inducing properties. While DOX is a widely used anticancer drug, it is associated with significant side effects, including cardiotoxicity and cachexia, which occur through mechanisms such as reduced insulin sensitivity, impaired glucose uptake, and decreased adipogenesis. In this study, 12-week-old male Wistar albino rats were divided into four groups: Control (C), low-dose DOX (DOX-L, 3 mg/kg), high-dose DOX (DOX-H, 12 mg/kg), and cumulative-dose DOX (DOX-C, 3 mg/kg every 24 hours for 4 days). The rats' weights were measured after administering various doses of DOX. Results indicated that the DOX-H group, which received a single high dose of DOX, experienced greater body weight loss compared to the other groups. The DOX-C group, which received the same total dose of DOX in cumulative doses, showed less weight loss compared to the DOX-H group. This suggests that single high-dose DOX applications lead to more significant body weight loss than cumulative dosing. The similarity in body weight loss between the DOX-L group (receiving a single low dose) and the control group indicates that DOX dosage is more influential than exposure duration. Given the potential for DOX to exacerbate cachexia in cancer patients, it is concluded that administering DOX in lower or cumulative doses may be preferable to a single high dose. In light of this information, we recommend further studies to determine the optimal dosage and duration of DOX administration, and to explore potential protective agents that could reduce DOX-related side effects on treatment.

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***Corresponding Author:** Zeynep Çelik Kenar, *zeynep.celik@selcuk.edu.tr*

INTRODUCTION

Chemotherapy administration, while being a potentially curative or survival-extending treatment for many types of cancer, can also lead to severe cachexia and sarcopenia (Evans et al., 2008; Fearon et al., 2011; Cella et al., 2024). Daly et al. (2018) reported in their study involving 225 patients that chemotherapeutic agents used during cancer treatment exacerbate symptoms such as cancer-related cachexia, weakness, and sarcopenia. Cachexia alone accounts for 20% of cancer-related deaths (Ni and Zhang, 2020; Cella et al., 2024). This has led to a need for further research into cachexia induced by chemotherapeutic agents. Doxorubicin (DOX) is a widely used anthracycline derivative in the treatment of various cancers and continues to be employed as an anticancer drug (Schirone et al., 2022). DOX exerts its effects through topoisomerase II, which is involved in DNA replication, and also induces cell death through the production and accumulation of reactive oxygen species within the cell (Rawat et al., 2021). Despite being an effective antineoplastic agent, DOX has had its use restricted since its early years due to its cardiotoxicity (Bachur, 1979). In addition to its cardiotoxic effects, DOX, like many chemotherapeutic agents, also induces cachexia in the organism (Panjrath et al., 2007; Xiang et al., 2009; Arunachalam et al., 2012; Cella et al., 2024; Pandey et al., 2024). It has been reported that DOX induces this effect through mechanisms such as reduced insulin sensitivity, decreased adipogenesis, triggering of hyperglycemia, decreased glucose uptake by cells, and inhibition of lipolysis (Biondo et al., 2016). Literature searches have not revealed sufficient studies on changes in body weight of experimental animals subjected to DOX at various doses and durations. This study was conducted to elucidate the changes in body weight observed in rats subjected to low and high doses of DOX, as well as high-dose treatments administered in divided days.

MATERIALS and METHODS

For the purpose of the study, 24 male Wistar albino rats, each 12 weeks old, were obtained from the Experimental Medicine Research and Application Center of Selçuk University. The rats were randomly divided into four groups, each consisting of six rats (Control-C, low-dose DOX-DOX-L, high-dose DOX-DOX-H, and cumulative-dose DOX-DOX-C), and their weights were recorded using a precision balance. Throughout the study, the rats were provided with ad libitum access to food, unlimited water, and a lighting schedule of 12 hours light and 12 hours dark, with a temperature maintained at 22±3ºC. In the study, the control group received a single dose of 12 ml/kg saline intraperitoneally (ip), the DOX-L group received a single dose of 3 mg/kg DOX ip, the DOX-H group received a single dose of 12 mg/kg DOX ip, and the DOX-C group received 3 mg/kg DOX ip administered four times at 24-hour intervals (a total of 12 mg/kg). On the 7th day after the final DOX injection, the experimental animals were weighed again using a precision balance, and the results were recorded.

Statistical Analysis

The parametric data obtained from the measurements were analyzed using SPSS 22.0 statistical software, employing One-Way ANOVA followed by post hoc Duncan's test. Results are presented as mean ± standard error (mean ± SE). A p-value of < 0.05 was considered statistically significant.

RESULTS

The body weight values obtained from weighing the animals at the beginning of the experiment and prior to necropsy, along with the proportional differences and statistical values, are presented in Tables 1-2 and Figure.

Table 1. The weights of the animals used in the experiment, measured in grams (g) at the beginning (initial) and at the end (final) of the study.

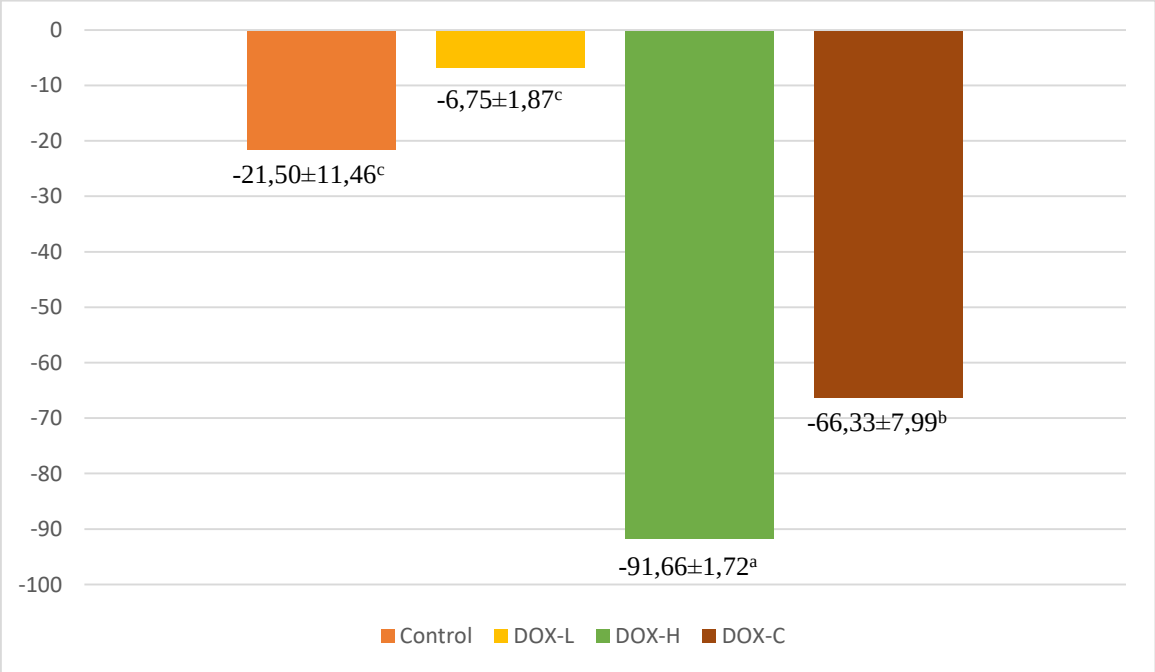
	C initial	C final	DOX-L initial	DOX-L final	DOX-H initial	DOX-H final	DOX-C initial	DOX-C final
1	332	332	445	444	411	316	380	316
2	390	342	438	434	378	288	374	314
3	364	336	347,5	336	353,5	266	338	292
4	473	494	348	342	357,5	270	354	292
5	330	308	433	420	362	270	362	300
6	300	248	277	272	326	228	322	218

Table 2. The mean differences (in grams) between the pre-experiment and post-experiment weights of the rats, categorized by group.

Groups	Control	DOX-L	DOX-H	DOX-C
Body wight difference	-21,50±11,46^{c}	-6,75±1,87^{c}	-91,66±1,72^{a}	-66,33±7,99^{b}

Values within a row that do not share a common letter ($^{a, b, c}$) are significantly different according to One-Way ANOVA and post-hoc Duncan's test ($p < 0.001$). Results are presented as mean ± SE

Figure. Graphical representation of the statistics for the differences between the initial and final weights of the rats.



DISCUSSION

In addition to their cancer-treating effects, chemotherapeutics are known to exacerbate cancer-related cachexia (Daly et al., 2018). During DOX treatment, cachexia is induced through mechanisms such as reduced insulin sensitivity, decreased adipogenesis, and inhibition of lipolysis (Biondo et al., 2016). In the conducted study, an evaluation of body weight changes in rats after administration of different doses and durations of DOX revealed that the DOX-H group, which received a single high dose of DOX, experienced a greater loss of body weight compared to other groups, with the DOX-C group following. These results suggest that a single high dose of DOX causes more significant body weight loss than cumulative DOX administration. Biondo et al. (2016) administered a single dose of 15 mg/kg DOX to 26 rats and performed euthanasia 72 hours post-administration to examine their adipose tissues. They also assessed parameters such as glucose uptake, adipogenesis, and lipogenesis in cell cultures following DOX administration. Their findings indicated that DOX caused weight loss in rats compared to the control group and negatively affected glucose uptake, adipogenesis, lipogenesis, and lipolysis in both in-vitro and in-vivo trials. Kelishomi et al. (2008) administered a total of 20 mg/kg DOX to rats over four weeks, with weekly injections, and reported a decrease in body weight due to DOX. In our study, the greater weight loss observed in the DOX-H group compared to other groups suggests that a single high dose of DOX has a more pronounced negative impact on body weight. The fact that the DOX-C group, which received the same total amount of DOX as the DOX-H group but in cumulative doses, experienced less weight loss compared to the DOX-H group supports this notion. Although the weight loss in the DOX-C group was not as severe as in the DOX-H group, it was significantly higher than that in the control and DOX-L groups, highlighting the effect of DOX dosage on body weight loss. Interestingly, despite statistical insignificance, the weight loss in the DOX-L group was found to be less than in the control group. The single 3 mg/kg dose of DOX administered to the DOX-L group resulted in an average weight loss of 6.75 grams, underscoring the importance of DOX dosage on body weight. Although the conditions were controlled and consistent, the weight loss observed in the control group may be attributed to individual stress factors.

CONCLUSION

The body weight loss observed in the DOX-H group, which received a single 12 mg/kg dose of DOX, was more severe compared to the other groups. In contrast, the DOX-C group, which received a cumulative dose of 12 mg/kg DOX, experienced significant body weight loss, though not as pronounced as that in the DOX-H group. The statistical similarity between the DOX-L group, which received a single 3 mg/kg dose, and the control group suggests that the dose of DOX is more influential on body weight than the exposure duration. Given that cachexia accounts for approximately 20% of cancer-related deaths and the potential for chemotherapeutics used in cancer treatment to exacerbate cachexia, it is concluded that administering DOX in lower or cumulative doses might be more appropriate than a single high dose. However, to determine the optimal application method and dose, further studies are recommended to investigate the effects of DOX at different durations and doses on body weight, as well as to explore protective agents that might mitigate the adverse effects of DOX on body weight.

Ethical approval

22/11/2021 dated and numbered 2021/60 was given by Selcuk University Experimental Medicine Application and Research Center ethics committee.

Ethical Statement

This study is based on the doctoral thesis entitled “Investigation of Heart Tissue Damage in Doxorubicin-Administered Rats by Molecular and Pathological Methods”, submitted under the supervision of “Thesis defense committee” on 27.06.2024 date.

Author Contributions

Research Design (CRediT 1) Author 1 (%50) – Author 2 (%50)
Data Collection (CRediT 2) Author 1 (%50) – Author 2 (%50)
Research - Data analysis - Validation (CRediT 3-4-6-11) Author 1 (%50) – Author 2 (%50)
Writing the Article (CRediT 12-13) Author 1 (%50) – Author 2 (%50)
Revision and Improvement of the Text (CRediT 14) Author 1 (%50) – Author 2 (%50)

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Conflict of Interest

The authors declare that there is no conflict of interest between the authors.

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Sustainable Development Goals (SDG)

3 Good Health and Well-Being,
15 Life on Land.

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