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Original Research Article

Study of Histopathological Effects of Doxorubicin on Git of Wistar Albino Rats

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Abstract:

Background and Objectives: Ideal anticancer drugs should eradicate cancer cells without harming normal tissues. Unfortunately, no currently available agents meet these criteria, and clinical use of these drugs involves a weighing of their benefits against their toxicity in search for a favorable therapeutic index.

Methods: Experimental animals were divided into 4 groups, control, low dose, therapeutic and high dose respectively. After giving respective doses and sacrificing the animals organs were taken and observed grossly and on under light microscopy.

Result: Microscopic changes were observed in all groups except control group. Low dose group showed less change while therapeutic group showed most of the changes which were observed by other authors. High dose group showed marked toxic changes.

Conclusion: The present study showed that the toxicity pattern is almost same in low and therapeutic doses of doxorubicin, and this could be of immense value while treating the carcinoma patients while in high doses it cause severe toxicity on GIT.

Keywords: Doxorubicin, Histopathological.

Introduction

The problem of cancer is universal. In developed countries, cancer is ranked as the second commonest cause of death, while in developing countries; it is third next to infectious and cardiovascular diseases. The systemic treatment of cancer has its roots in the initial work of Paul Ehrlich, who coined the term chemotherapy. The use of in vivo rodent model systems to develop antibiotics for treating infectious diseases led to the development of inbred rodent lines bearing transplanted tumors to screen potential anticancer drugs. This in vivo system provided the foundation for mass screening of novel compounds. [1] Anticancer drugs are widely used against variety of human tumors. However, while they generate acceptable outcome in chemotherapy of some cancers, they also exhibit severe toxicity and undesirable side effects.

An extensive investigation has been conducted on general organ toxicity of doxorubicin. These are demonstrated by light and electron microscopic study of various organs. However in our set up there is very limited information on effects of doxorubicin on histopathology of GIT. Our aim is to determine the various histopathological changes induced by DXR on stomach and intestines of albino rats at low, therapeutic and toxic doses so that appropriate dose adjustments and combination therapy may be considered in future treatment of cancer to ensure better patient safety.

Materials and Methods

Albino rats (Wistar strain) of either sex, weighing 125-160 grams were used for current experimental studies. They were procured from animal house, at Darbhanga medical college and Hospital Laheriasarai Darbhanga, Bihar. The clearance for the use of animals for experimental purpose was obtained from Animal Institutional Ethical Committee constituted for the before purpose. Animals were housed in polypropylene cages (6/cage) with dust free rice husk as bedding material under laboratory conditions with controlled environment of temperature of 25±2^{O}C , humidity (16% ± 10%) and 12 hours light/dark cycle (16- 18) as per Committee for the purpose of Control and Supervision of Experiment on Animals (CPCSEA), Indian guidelines. They were provided standard rodent chaw/feed and water ad-libitum. Subjecting them for experimentation, animals were given a week's time to acclimatize with laboratory conditions. Animals were fasted for 24 hours before experimentation. The principal of Rationalization, Refinement and Re-

duction (3 "R's") was strictly followed while undertaking the following experiment.

The animals were divided into 4 groups with each group consisting of 6 animals.

GROUP 1 was administered weekly intraperitoneal injections of 3ml of sterile distilled water and it served as a healthy control.

GROUP 2 was administered a weekly low dose of doxorubicin (0.2 mg/kg body weight) intraperitoneal injection.

GROUP 3 was given a weekly therapeutic dose of doxorubicin (1mg/kg body weight) intraperitoneal injection.

GROUP 4 received a single intraperitoneal toxic dose of doxorubicin (20mg/kg body weight).

The above dosing schedules were adapted after going through studies conducted by El-Sayyed H et al. [2], Sule A et al., [3] and Shivakumar P et al. [4] The animals were sacrificed after 48 hours of the administration of final dose of drugs as per the prescribed methods by CPCSEA.

After sacrificing the animals, hearts were isolated and fixed in 10% buffered formalin solution and processed to prepare 5 micron thick paraffin sections. Paraffin sections were stained by using H&E/other relevant staining. Histological sections were examined by light microscopy to assess the degree of toxicity. The histopathological findings among the 4 groups were compared to achieve relevant conclusions.

Result

In *control group* no gross and microscopic changes were observed. Under light microscopy, stomach showed normal architecture in the form of simple columnar epithelium lining the cavity. Numerous gastric glands were seen in the lamina propria. Submucosa contained loose connective tissue with blood vessels. In muscularis externa three muscular layers having inner oblique, middle circular and outer longitudinal layers were observed. Outermost adventitial layer was also seen. In small intestines, normal architecture in the form of lining epithelium covering luminal surface. Numerous villi were seen projecting in the lumen. Lamina propria contained intestinal glands with lymphoid tissue. In submucosa loose connective tissue with blood vessels were seen. Muscular wall consisted of inner circular and outer longitudinal muscle layers which were covered on externally with adventitia. In the *low dose group* there were no gross changes present. In the *therapeutic dose group* no gross change was seen. Histologically, necrosis and ulceration of mucosa with infiltration of inflammatory cells were seen.

In high dose group no gross changes were detected. Under light microscopy, necrosis and desquamation of mucosa along with infiltration of mononuclear cells was seen.

Discussion

The purpose of the present study was to evaluate at our best the toxicity profile of the drug doxorubicin histologically in Wistar albino rats in order to suggest whether to modify the present therapeutic dosage of this drug for avoiding its toxicities on GIT. The Wistar albino rats were selected as they are very close species among mammals with humans and toxicity in them with this drug may reflect the same toxicity pattern in humans with per kilogram dosage formula.

There were no gross changes seen. On light microscopy Inflammatory cell infiltration with mononuclear cells was the only finding. At therapeutic doses, in addition to above findings, there was necrosis and desquamation of mucosa. These findings are also similarly reported by Baba H et al., [5] .

Summary

Histological study was done on the sections of stomach and intestines from different groups of animals under study viz control group, Low dose group, therapeutic dose group and high dose group. The control group was given only normal saline, low dose group was given doxorubicin at a dose of 0.1 mg/kg body weight, therapeutic group 1 mg/kg body weight which were given weekly for a total period of 4 weeks while a single stat dose of 15 mg/kg body weight was given in the group no 4. It was observed that the doxorubicin toxicity at low dose and therapeutic dose was running almost parallel with each other while the drug which was given in high dose exhibited severe toxic changes. It is therefore concluded from the present study that the toxicity pattern is almost same in low and therapeutic doses of doxorubicin, and this could be of immense value while treating the carcinoma patients while in high doses it cause severe toxicity on stomach and intestines.

Conclusion

The present study showed that the toxicity pattern is almost same in low and therapeutic doses of doxorubicin, and this could be of immense value while treating the carcinoma patients while in high doses it cause severe toxicity on GIT.

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