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Original Article

A Study on the Toxic Effects of Doxorubicin on the Histology of Certain Organs

P. Shivakumar, M. Usha Rani, A. Gopala Reddy, Y. Anjaneyulu[1]

Departments of Pharmacology and Toxicology and [1]Pathology, College of Veterinary Science, Rajendranagar, Hyderabad, Andhra Pradesh, India

ABSTRACT

In the present study, effect of doxorubicin at 2 mg/kg b.wt. (i/p), alone, once in a wk for 4 wks and in combination with vitamin E at 250 and 500 mg/kg b.wt., orally, daily for 4 wks was evaluated on histological alterations, if any, on heart, liver, kidney, and testes of rats. Doxorubicin alone treated group showed marked congestion and degenerative changes in heart, kidney, liver, and testis. Treatment with vitamin E showed marked improvement in all the degenerative changes, though more protection was observed with the dose of 500 mg/kg.

Key words: Doxorubicin, histopathology, vitamin-E

INTRODUCTION

Cancer continues to represent the largest cause of mortality in the world and claims over 6 million lives every year.[1] Chemotherapy of cancer is not found to be safe because of the side effects of the drugs on the healthy tissues. Among the several types of chemotherapeutic drugs, doxorubicin (adriamycin) is commonly used and comes under anthracycline group of antibiotics. It is derived from the algae, *Streptomyces peucetius var. caesius*.[2] It is very active against a wide spectrum of cancers and is mainly used in the treatment of lymphomas, leukemias and other solid tumors like carcinoma of ovaries, breast, lung, thyroid etc.[3] Similar to the adverse effects of other anti-cancer agents, doxorubicin has its own dose-dependent cytotoxicity on heart and other organs.[4] The present work was undertaken in male *Wistar kyoto* rats to study the effect of doxorubicin on histological alterations, if any, in heart, liver, kidney, and testes.

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MATERIALS AND METHODS

Male albino rats of *Wistar Kyoto* strain weighing about 200-250 g were procured from National Institute of Nutrition (NIN), Hyderabad. The animals were housed in solid bottom polypropylene cages. Animals were placed on commercial standard mash feed for rat (NIN, Hyderabad) and provided water *ad libitum*. Experiment was conducted as per the protocol approved by Institutional Animal Ethics Committee.

Four groups of 8 male rats each were maintained in animal house of the Department. Group 1: Sham; group 2: Doxorubicin at 2 mg/kg b.wt. intraperitoneally, weekly once for four weeks; group 3: Doxorubicin at 2 mg/kg b.wt. intraperitoneally + vitamin E at 150 mg/kg b.wt., orally, daily for four weeks; and group 4: Doxorubicin at 2 mg/kg b.wt. intraperitoneally + vitamin E at 500 mg/kg b. wt., orally, daily for four weeks. At the end of 28th day, animals were euthanized and organs were collected in 10% buffered formalin for histopathology.

Address for correspondence: Dr. A. Gopala Reddy, Department of Pharmacology and Toxicology, College of Veterinary Science, Rajendranagar, Hyderabad - 500 030, Andhra Pradesh, India. E-mail: gopalareddy123@rediffmail.com

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RESULTS AND DISCUSSION

Gross pathology

Heart size was reduced in group 2 as compared to control group. Size of the liver was also decreased and edges were rounded in group 2 as compared to control group. In kidney and testis, there were no appreciable gross lesions.

Histopathology

The sections of heart showed interfibrillar hemorrhages, congestion, and focal areas of disrupted cardiac muscle fibers in group 2 [Figure 1]. The sections of heart in group 3 showed moderate hemorrhages and mild disruption of cardiac muscle fibers. Group 4 showed focal areas of mild infiltration [Figure 2], while group 1 did not show any significant lesions of pathological importance. Similar findings of cardiomyopathy were reported by Naiyra *et al*.[4]

The sections of kidney in group 2 showed marked congestion, inter tubular hemorrhages with marked degenerative changes, and disrupted epithelium [Figure 3]. Bertani *et al*.,[5] reported that doxorubicin has the potential to induce renal damage with glomerulosclerosis. Sections from groups 3 [Figure 4] and 4 showed mild and very mild degenerative changes in tubules, respectively, while group 1 did not show any significant lesions of pathological importance.

The sections of liver in group 2 showed marked central vein congestion, marked bile duct hyperplasia, and dilation of sinusoidal spaces, and some sections showed marked degenerative changes [Figure 5]. Kalender *et al*.,[6] reported the hepatotoxic potential of doxorubicin. Group 3 showed mild bile duct hyperplasia and mild central vein congestion [Figure 6]. The sections of group 4 showed mild parenchymatous degeneration, while group 1 did not reveal any significant lesions of pathological importance.

The sections of testis showed marked sub-capsular hemorrhages and disrupted basement membrane and

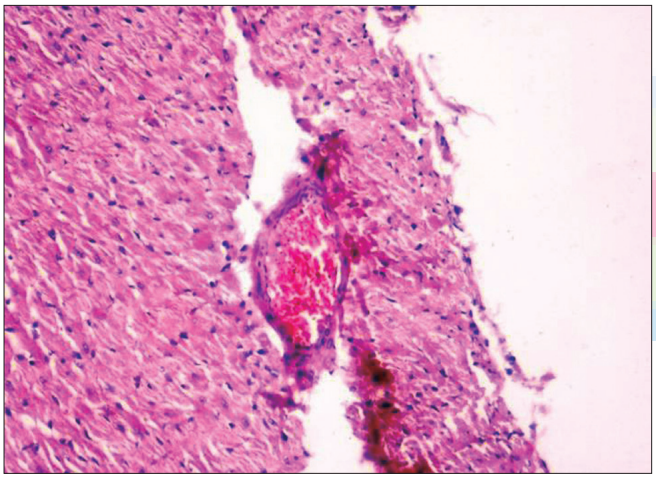


Figure 1: Photomicrograph of heart showing interfibrillar congestion (H and E, X200) (group 2)

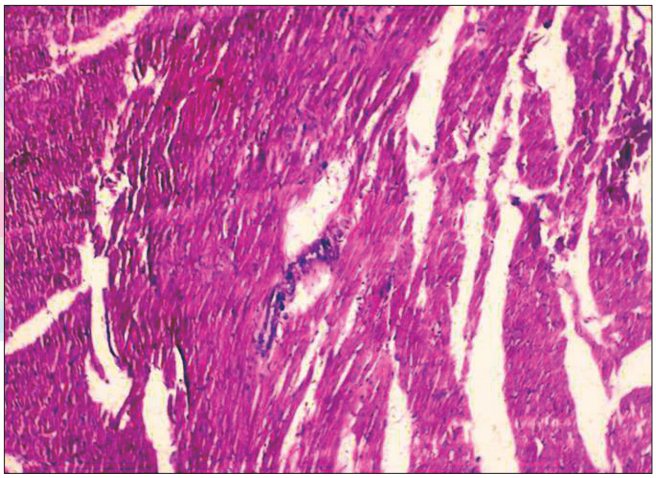


Figure 2: Photomicrograph of heart showing focal areas of mild infiltration (H and E, X100) (group 4)

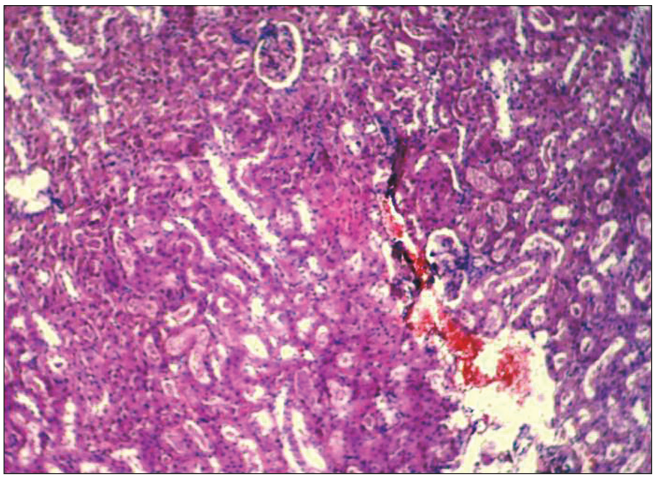


Figure 3: Photomicrograph of kidney showing intertubular hemorrhages (H and E, X100) (group 2)

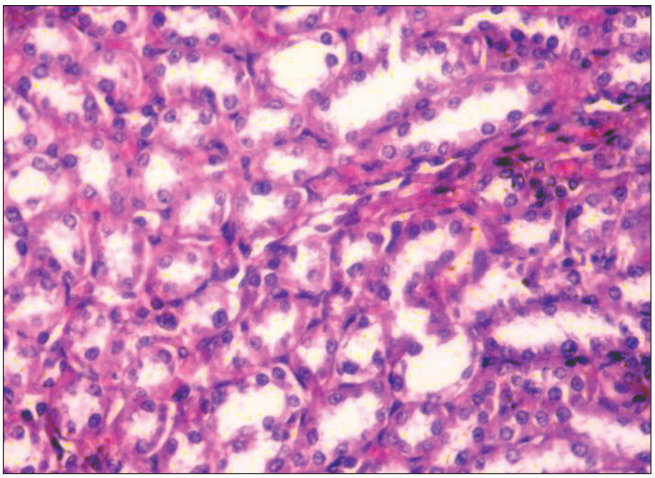


Figure 4: Photomicrograph of kidney showing few tubules degenerative changes (H and E, X400) (group 3)

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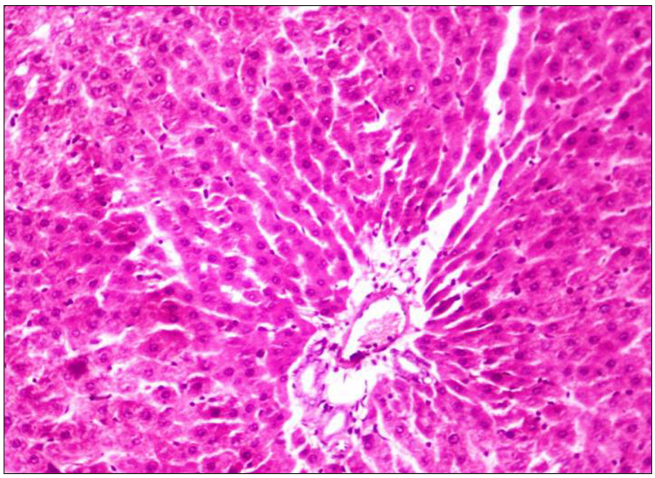


Figure 5: Photomicrograph of liver showing mild centralvein congestion, moderate bile duct hyperplasia and dilation of sinusoidal spaces (H and E, X100) (group 2)

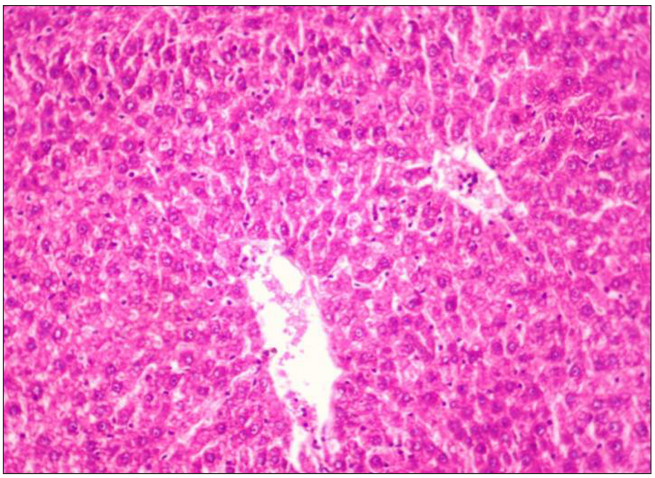


Figure 6: Photomicrograph of liver showing mild central vein congestion (H and E, X200) (group 3)

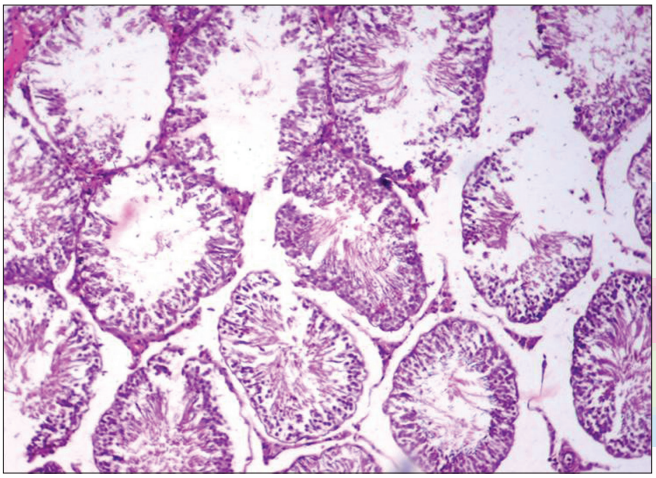


Figure 7: Photomicrograph of testis showing disrupted basement membrane and tubular epithelium (H and E, X100) (group 2)

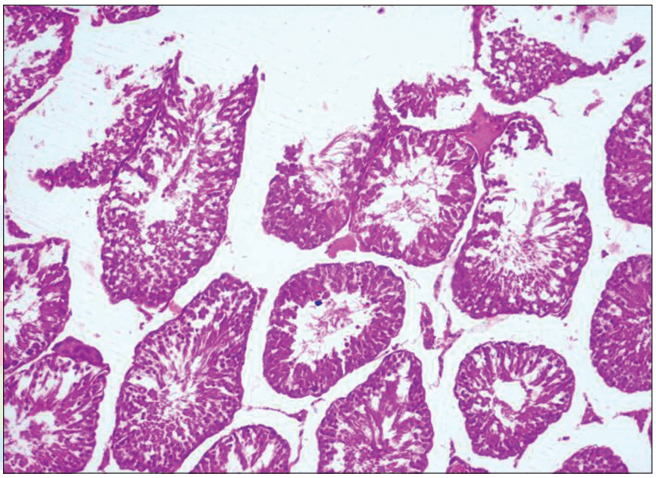


Figure 8: Photomicrograph of testis showing mild damage to tubular epithelium (H and E, X100) (group 3)

tubular epithelium in group 2 [Figure 7]. Patil and Balaraman[7] reported that doxorubicin administration for 5 weeks induces a significant decline in testes weight, sperm count, serum testosterone and increase in serum lactate dehydrogenase (LDH), and increases lipid peroxidation in testis. The sections of group 3 showed moderate sub-capsular congestion and mild damage to tubular epithelium [Figure 8]. Group 4 showed focal areas of congestion, while group 1 did not show any lesions of pathological significance.

The findings of the present study reveal that doxorubicin administered at weekly intervals for 4 wks induced histological alterations in heart, kidney, liver, and testis. The injury to these organs may be due the oxidative stress induced by the reactive intermediates doxorubicin semiquinone formed from doxorubicin. The anthracyclines are reported to form semiquinone radical intermediates, which react with molecular oxygen to for reactive oxygen species that interact with macromolecules of the cells to bring about cytological damage.[8] Administration of vitamin E could successfully reverse the histological alterations in the organs studied owing to its free radical quenching activity.[9] Vitamin E was found more effective at the dose rate of 500 mg/kg b. wt.

It can be concluded from the present study that doxorubicin induces damage to visceral organs and such damage can be prevented by using vitamin E.

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