DOI: 10.14260/jemds/2015/1305

ORIGINAL ARTICLE

EFFECT OF CISPLATIN ON LIVER OF MALE ALBINO RATS

Narinder Singh[1], Rachna Magotra[2], Ashwani K. Sharma[3], Mustaq Ahmed[4], Vijay Khajuria[5]

HOW TO CITE THIS ARTICLE:
Narinder Singh, Rachna Magotra, Ashwani K. Sharma, Mustaq Ahmed, Vijay Khajuria. "Effect of Cisplatin on Liver of Male Albino Rats". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 52, June 29; Page: 8993-8998, DOI: 10.14260/jemds/2015/1305

ABSTRACT: The study was conducted on forty adult male albino rats weighing 150-200 grams in Government Medical College Jammu. The albino rats were obtained from Animal house of Department of Pharmacology Government Medical College Jammu. The aim of the study was to observe histomorphological effects of cisplatin on the liver of albino rats. The rats were divided into four groups of ten rats each. The first group of ten albino rats was the control group to which no drug was given. The rest of the three groups were given varied doses of cisplatin by intra peritoneal (I. P) route. These rats were dissected after anaesthetizing and their liver was exposed, taken out and subjected to standard histological proceedings by paraffin embedding method. About 5 micro meter thick sections were prepared followed by H & E staining. The macroscopic as well as microscopic changes in the liver of all the four groups were observed. Toxic effects of cisplatin were seen in liver of albino rats in all the three groups, who were given the drug. So, it was inferred from this study, that cisplatin has toxic effect on liver of albino rats. Therefore careful liver function monitoring is required in patients who are on cisplatin therapy. So our study has important clinical utility.
KEYWORDS: Albino rats, Cisplatin, Hepatotoxicity.

INTRODUCTION: The term cancer originated from the Greek word 'karkinos' meaning crab. Although cancer encompasses a large set of diseases with complex causes, we can expect significant progress in its management as our knowledge base continues to expand. Today, approximately 50% of all cancers are curable through the judicious application of surgery, radiation and chemotherapy or a combination of them. Important development includes not only the availability of an increasing number of effective drugs, but also a better understanding of drug pharmacology, dose intensity and therapeutics.(1) Cisplatin is a platinum containing compound and is currently used as one of the most effective anticancer drug. The drug has been used for many decades and was first described in 1845 as 'Peyrones Chloride'. Observations were made by Rosenberg in the mid-1960s when he was studying the effects of electric currents on the growth of bacterial cultures. He observed that alternate voltage lead to decrease in growth of bacteria.(2)

These effects were because of formation of platinum complexes by the dissolution of platinum from the electrodes. Due to this effect neutral platinum complexes (Including cisplatinum) were tested as anticancer agents.(3) Several side effects were observed with cisplatin. The dose limiting side effects were seen in kidney but repeated higher doses of cisplatin cause massive hepatic toxicity including dissolution of hepatic cords, focal inflammatory lesions & necrosis.(4) A large amount of data is available on the renal effect of cisplatin but very limited data is available on the effect of this drug on liver. Therefore this study was done to observe histomorphological side effects of cisplatin on liver of albino rats and compared with previous studies.

MATERIAL AND METHODS: Forty healthy male albino rats weighing between 150 to 200gms were taken for this study. They were divided into four groups as follows:

DOI: 10.14260/jemds/2015/1305

Group I = Normal control (10 animals) who were not given cisplatin but only the vehicle in which drug was dissolved i.e. sodium chloride intraperitoneally.

Group II = Low dose (10 animals) who were given single daily dose of 0.2 mg/kg body weight of cisplatin intraperitoneally for 7 days.

Group III = Therapeutic dose (10 animals) who were given daily dose of 1mg/kg body weight of cisplatin intraperitoneally for a period of seven days.

Group IV = High dose (10 animals) who were given single dose of 45 mg/kg body weight of cisplatin intraperitoneally.

Animals of three groups i. e., I, II & III were sacrificed on the 8th day while the animals of group IV were sacrificed after 16 hours of exposure, after anaesthetizing them with Ether. A midline incision was made on the skin extending from jugular notch to xiphoid process. The sternum was lifted by cutting the ribs along the side of the sternum and the liver of the animal was removed. The liver was cut into small pieces (Approximately 5mm in size), placed in a tissue capsule and put in a jar containing 10% formalin solution for 24 hours. Paraffin wax embedding method was used for preparing the tissue for section cutting, 5 to 7 micrometer thick sections were cut by a Rotary microtome, fixed on a slide and stained by Harris Haematoxylin and Eosin stain. The slides so formed were observed under a light microscope.

OBSERVATION: Macroscopic and Microscopic changes were looked for in all the four groups. The changes observed on macroscopic & microscopic examination were classified as per the severity and were graded as:

MILD (+)
MODERATE (++)
SEVERE (+++)

GROUP –I: No Macroscopic as well as Microscopic changes were seen. (Fig. 1)
GROUP –II: No Macroscopic changes were seen.

Microscopic Changes were as follows:

1. Hepatic cord pattern was preserved. No dissolution of cords was seen.
2. Hepatic sinusoids showed mild dilatation (+) & congestion (+).
3. Focal fatty change (+) present. Occasional hepatocytes showed fatty change (+).
4. Vacuolization was present (+++).
5. Pyknosis of nuclei (++).
6. Apoptosis not seen.

GROUP –III: Macroscopically no change seen in the liver.

Microscopic Changes were as follows:

1. Hepatic cord pattern was preserved.
2. Sinusoidal dilatation (++).
3. Fatty change (++).
4. Vacuolization of hepatocytes present (++).
5. Pyknosis (++), Occasional Portal triad showed infiltration.
6. Apoptosis not seen.

DOI: 10.14260/jemds/2015/1305

GROUP – IV: Macroscopically no gross change were seen in the liver.

Microscopically the Cut Section of Liver showed:

1. Hepatic cord pattern was preserved.
2. Sinusoidal dilatation (+++).
3. Fatty change (+).
4. Vacuolisation of hepatocytes (++).
5. Pyknosis (++).
6. Apoptosis not seen.

DISCUSSION: Hepatotoxicity is an undesirable side effect of cisplatin. However, little work has been done for evaluation of hepatotoxicity. Therefore present study was undertaken to evaluate hepatotoxicity with different doses of cisplatin. Efforts were made to elucidate gross (macroscopic) and histopathological (microscopic) changes in liver in detail. In the current study, we observed hepatotoxicity in all the three groups treated with cisplatin, while control group remained unaffected as no histomorphological change was observed. Hepatotoxicity was manifested in the form of acute sinusoidal dilatation with congestion, vacuolisation and pyknosis of hepatocytes and fatty infiltration. However, no apoptosis or dissolution of hepatic cords was observed in these groups. The sinusoidal dilatation was more marked in Group IV (+++) but vacuolisation and pyknosis of hepatocytes was equally present in all these groups. Liu J et al 1998[5] observed cisplatin induced liver injury in rats which was found dose and time dependent. Liver injury was evaluated at 3-16 hours after drug administration (150-200mmol/kg) in which apoptosis was observed as a major lesion. However, we could not demonstrate apoptosis in the present study.

Some authors like Huang Q et al 2001[6] studied cisplatin induced side effects on rats (0.2mg/Kg body weight daily for 7 days) but no findings suggestive of hepatotoxicity was observed by them. Al Majed A A 2007[7] suggested that hepatotoxicity of cisplatin is due to induced oxidative stress damage to liver. Aslihan A V C I 2008 et al[8] in their histological study of cisplatin treated rats with a single dose of 10mg/Kg by I P route showed sinusoidal congestion, vacuolardegeneration, disorganization of hepatocytes and significant fibrosis around central vein. Their study is a recent one and is in accordance with our observations. Kamble P R and Bhiwgade D A 2011[9] studied hepatotoxicity by long term treatment of cisplatin and observed increased vacuolisation in hepatocytes and change in perilobular connective tissue with expanded portal spaces. They concluded that dose up to 0.4mg/Kg day caused least damage to liver.

This is in accordance to our study as we observed less hepatic damage with small doses of cisplatin. Rana M A and Jawary A H 2011[10] demonstrated cisplatin induced hepatotoxicity in rats which was manifested as severe fatty changes, congestion, and dilatation of portal vessels & central veins along with multiple necrotic foci. Similar changes were seen in our study. El-Sayeed et al 2009[4] studied albino rats who were given cisplatin (0, 2mg/Kg body weight) for a period of 20 days and showed dissolution of hepatic cords and focal inflammatory cells in hepatic tissue. The Hepatocytes of liver also showed pyknotic nuclei and densely collected inflammatory cells composed of mainly macrophages and lymphocytes. They suggested that liver accumulates significant amount of cisplatin which lead to hepatotoxicity. We observed similar changes in our study but hepatic cord pattern was maintained. From results of our current study we conclude that liver is damaged even with small doses of cisplatin given over a longer period but liver changes are more marked with higher doses (45mg/Kg body weight).

DOI: 10.14260/jemds/2015/1305

SUMMARY: The present study was conducted to observe the effect of anticancer drug cisplatin on the liver of 40 adult male albino rats. Hepatic changes were seen in all the three cisplatin treated groups manifested as sinusoidal dilatation, vacuolisation with pyknotic nuclei and fatty infiltration. Apoptosis was not observed in these groups and the hepatic cord pattern also remained unaffected. These changes were of equal magnitude in all the three groups (II, III, IV) except the sinusoidal dilatation which was more in group IV. We conclude from the present study that experimental administration of cisplatin in adult male albino rats was greatly associated with histological changes in liver which were of the same magnitude in group II and group III but were more marked in group IV (45mg/Kg single dose). This has clinical significance as judicious monitoring of the dose of cisplatin as well as liver function tests of the person who is to be given the drug before and during the therapy should be there. This would lead to better compliance and efficacy of the drug.

REFERENCES:

1. Datey K. - API Textbook of Medicine. Bombay association of Physicians of India; 1994: 774-1604
2. Rosenberg B. – Interdisciplinary Science Review.1978; 3: 134-7.
3. Rosenberg B., Renshaw E., Van Camp L., Hartwicj J., Drobnik J., - Platinum induced filamentous growth in E. Coli. Journal of bacteriology.1967a; 93: 716-21.
4. EL – Sayyad Hassan I., Ismail Mohammad F., Shalaby F.M., Abou- El – Magd R.F., Gaur Rajiv L., Fernando Augusta, Ray Madhawa H. G., Ouhtit Allal- Cisplatin, Doxorubicin and 5 FU on the liver of male albino rats. Int. J. Of Biol. Sci. 2009; 5: 466-473.
5. Liu J., Liu Y., Habeebu S.S., Klaassen C.D.- Metallothionein (MT) - null mice are sensitive to cisplatin- induced hepatotoxicity. Toxicol. Pharmacol. 1998; 149 (1) 24-31.
6. Huang Q., Dunn R.T., Jayadev S., Disorbo O., Pack D.F., Farr B, S., StollE.R., and Blanchard T.K., - Assessment of cisplatin induced nephrotoxicity by microarray technology. Toxi. Sci. 2001; 63: 196-207.
7. Al Majeed A. A., -Carnitin deficiency provokes cisplatin- induced hepatotoxicity in rats. Basic and clinical Pharmacology and Toxicology. 2007; 100: 145-150.
8. Avci A., Cetin R., Erguder I. B., Devrim E., Kilicoglu B., Candir O., Ozturk H.S., Durak I., Cisplatin causes oxidation in rat liver tissues: possible protective effects of antioxidant Food supplementation. Turk J. Med. Sci. 2008; 38 (2): 117-120.
9. Kamble R.P. and Dayanand A., Cisplatin induced histological and ultrastructural alterations in liver cisplatin induced histological and ultrastructural alterations in liver tissues of rats. J. Cystol. Histol. 2011, 2; 6 http: //dx.org/10.4172/2157-7099.1000128.
10. Rana M.A. and Al Jawary A. H., - Effect of vitamin C on the Hepatotoxicity induced by cisplatin in rats; Raf.J. Sci., 2012.vol. 23, No. 2 pp 23-33.

DOI: 10.14260/jemds/2015/1305

Site and Effects	Gr. i	Gr ii	Gr iii	Gr iv	Remarks
Hepatic cord pattern	Normal	Normal	Normal	Normal	No effect observed
Sinusoidal dilatation	_	+	++	+++	Marked dilatation in grp iv and in other treated grps
Focal fatty change	_	+	++	+	
Vacuolization of hepatocytes	_	++	++	++	Equal vacuolization in hepatocytes in all grps
Pyknosis of hepatocytes	_	++	++	++	Equal magnitude of damage in all grps
Apoptosis	_	_	_	_	No apoptosis was observed in any grp

Table 1: Table showing comparative hepatotoxic effect of different doses of cisplatin

Fig. 1: T.S. of liver of group I albino rat (control group) showing central vein (a), Hepatic sinusoids (b), Plates of hepatic cells (c). h & e stain x 100.

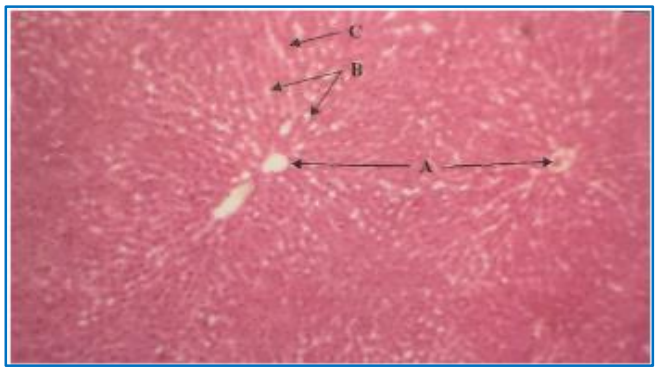

Fig. 1

Fig. 2: T.S. of liver of group ii albino rat showing congestion (a & b), Vacuolization and fatty changes (c), Pyknotic nuclei (d) h & e stain x 400.

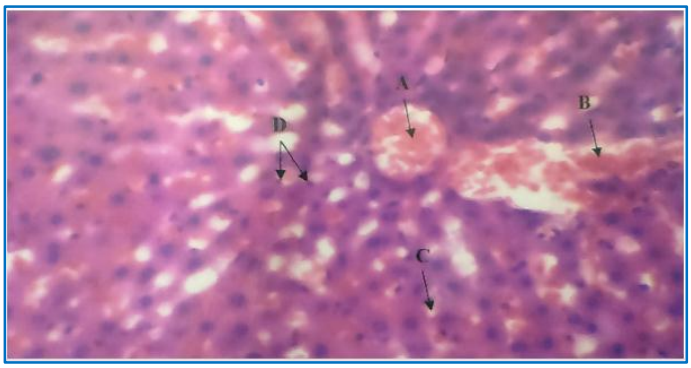

Fig. 2

DOI: 10.14260/jemds/2015/1305

Fig. 3: T. S. of liver of group iii albino rat showing preserved cord pattern (a), Sinusoidal dilatation (b) and fatty change (d) h & e stain x 400.

Fig. 4: T.S. of liver of group iv albino rat showing sinusoidal dilatation (a), Pyknosis (b), Vacuolisation and fatty change (c), Congestion (d). H & e stain x400.

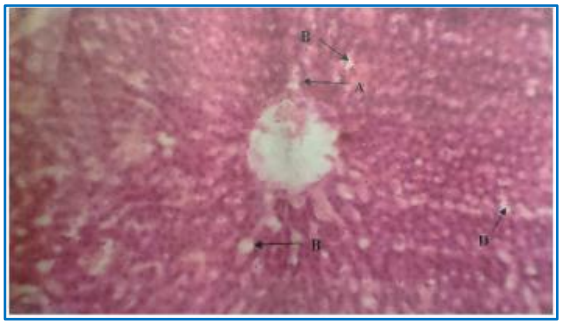

Fig. 3

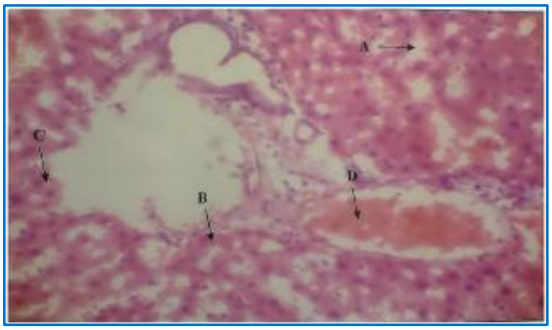

Fig. 4

AUTHORS:

1. Narinder Singh
2. Rachna Magotra
3. Ashwani K. Sharma
4. Mustaq Ahmed
5. Vijay Khajuria

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Anatomy, Government Medical College, Jammu.
2. Assistant Professor, Department of Anatomy, Government Medical College, Jammu.
3. Lecturer, Department of Anatomy, Government Medical College, Jammu.
4. Assistant Surgeon, J & K Health Services.
5. Associate Professor, Department of Pharmacology, Government Medical College, Jammu.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Rachna Magotra,
242/7, Channi Himmat,
Jammu-180015.
E-mail: drmagotrarachna@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None

Date of Submission: 07/06/2015.
Date of Peer Review: 08/06/2015.
Date of Acceptance: 23/06/2015.
Date of Publishing: 26/06/2015.