Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2018; 6(2): 3035-3037

Received: 10-01-2018
Accepted: 11-02-2018

Guguloth Ramesh
Department of Veterinary Pathology, College of Veterinary Science, P.V. Narasimha Rao Telangana Veterinary University. Rajendranagar, Hyderabad, India

D Madhuri
Department of Veterinary Pathology, College of Veterinary Science, P.V. Narasimha Rao Telangana Veterinary University. Rajendranagar, Hyderabad, India

M Lakshman
Department of Veterinary Pathology, College of Veterinary Science, P.V. Narasimha Rao Telangana Veterinary University. Rajendranagar, Hyderabad, India

A Gopal Reddy
Department of Veterinary Pathology, College of Veterinary Science, P.V. Narasimha Rao Telangana Veterinary University. Rajendranagar, Hyderabad, India

Correspondence
Guguloth Ramesh
Department of Veterinary Pathology, College of Veterinary Science, P.V. Narasimha Rao Telangana Veterinary University. Rajendranagar, Hyderabad, India

Histopathological changes in bone marrow induced by lead and cadmium alone and combined exposure in male Wistar rats

Guguloth Ramesh, D Madhuri, M Lakshman and A Gopal Reddy

Abstract
This study was carried out to study histopathological changes in bone marrow (femur bone) induced by lead and cadmium alone and in combination on rats. Forty eight male albino Wistar rats were divided into 4 groups 12 rats in each group; group 1(control) was given deionized water, group 2 (lead group) was given water with lead acetate @30mg/kg b.wt, group 3 (cadmium group) was given water with cadmium chloride @15mg/kg b.wt, group 4 (combined group) was given water with both lead acetate@ 30mg/kg b.wt and cadmium chloride @15mg/kg b.wt for 28 days. Histopathological changes in bone marrow were recorded at 14th day and 28th day. Results showed group 2, 3 rats showed a progressive increase in adipocytes in bone marrow from 14th to 28th day and cellular portion of bone marrow was reduced. In group 4 most of the bone marrow was replaced by adipose tissue and cellular portion was reduced on 14th and 28th day of experimental period.

Keywords: Albino Wistar rats, lead acetate and cadmium chloride, histopathology, bone marrow, osteotoxicity, myelosuppression

Introduction
Lead and cadmium are well known toxic metals in the environment. The common sources of lead and cadmium are diverse in nature including natural and anthropogenic processes such as combustion of coal and mineral oil, smelters, mining and alloy processing units and paint industries. Constantly increasing environmental pollutants due to increased urbanization, industrialization and through the scientific and technical advances have stimulated interest in the study of toxic substances and its consequences to biological system (Pandya *et al.*, 2012) [10]. Lead inhibits key enzymes in the synthesis of hemoglobin like δ-aminolevulinic acid dehydratase (ALAD), a cytosolic enzyme that catalyzes the formation of porphobilinogen from δ-aminolevulinic acid (ALA), aminolevulinic acid synthetase (ALAS) which is necessary for the synthesis of hemoglobin (Piomelli, 2002) [11]. Lead considered as potent toxicant which can cause osteotoxicity and myelosuppression. Cd depletes glutathione and protein-bound sulfhydryl groups, which lead to enhancement of reactive oxygen species generation (ROS) such as superoxide ion, hydroxyl radicals and hydrogen peroxide. Lead and cadmium are well known potent toxicants which cause tissue injury creating oxidative stress. In majority of animal studies, single metal was used in high concentration, however in environment, population receives multiple exposure, indicating the need for experimental work with combination of toxicants (Yuan *et al.*, 2014) [15]. Heavy metals like lead and cadmium have been reported to induce anemia in experimental animals (Deur *et al.*, 1981and Tephly *et al.*, 1978) [2, 14]. The myelosuppression and inhibition of erythropoiesis was also noticed by Lutton *et al.*, (1983) [8]. Purpose of the present study was to evaluate the effect of lead and cadmium on bone marrow.

2. Materials and Methods
2.1 Chemicals
Lead acetate and cadmium chloride were procured from Thermo Fisher Scientific India. Pvt. 1973 Ltd. Mumbai.

2.2 Experimental animals
Adult male albino rats (*Wistar* strain*)* weighing 250-280g were procured from Sanzyme laboratories Ltd., Hyderabad.

The experiment was carried out according to the guidelines and prior approval of the Institutional Animal Ethics Committee (IAEC) (No.18-2017 SA).

2.3 Experimental design

A total of 48 male albino Wistar rats were randomly divided into 4 groups consisting of 12 in each group. Group 1(control) was given deionized water, group 2(lead group) was given water with lead acetate @30mg/kg b.wt, group 3(cadmium group) was given water with cadmium chloride @15mg/kg b.wt and group 4 (combined group) was given water with both lead acetate @ 30mg/kg b.wt and cadmium chloride @15mg/kg b.wt for 28 days respectively.

2.4 Methods

To study the histopathology bone marrow, six rats from each group were sacrificed on 14th and 28th day of experimental period. Detailed necropsy was conducted and femur bones were collected, decalcified and fixed. Samples were processed, sectioned (5µm) and stained with Hematoxylin and Eosin (H&E) as per the standard protocol given (Luna, 1968) [7].

3. Results

Section of femoral bone of group 1 showed normal histological architecture of bone with bone marrow and normal adiposity on 14th day (Fig.1) and 28th day (Fig.2). Group 2 rats showed a progressive increase in adipocytes in bone marrow from 14th to 28th day and cellular portion of bone marrow was reduced (Fig.3) when compared to the control group.

Section of bone of group 3 rats on 14th and 28th day showed increased adipocytes in bone marrow (Fig.4).

In group 4 most of the bone marrow was replaced by adipose tissue and cellular portion was reduced on 14th day (Fig.5) and 28th day (Fig.6) of experimental period when compared to the control group. The potentiated effect of lead and cadmium toxicity on bone marrow was notice after histopathological study of bone.

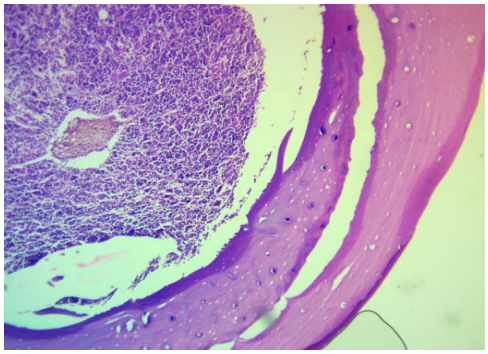

Fig 1: Microphotograph of Group 1 normal bone and bone marrow on 14th day. H&E×100.

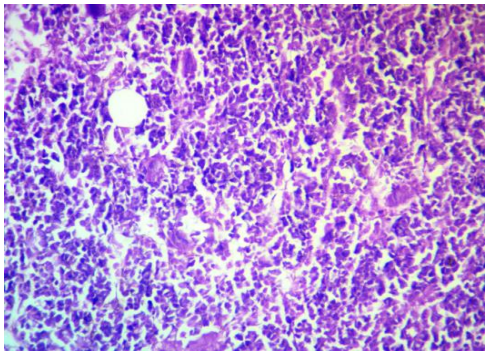

Fig 2: Microphotograph of Group 1 showing normal bone marrow on 28th day. H&E×400.

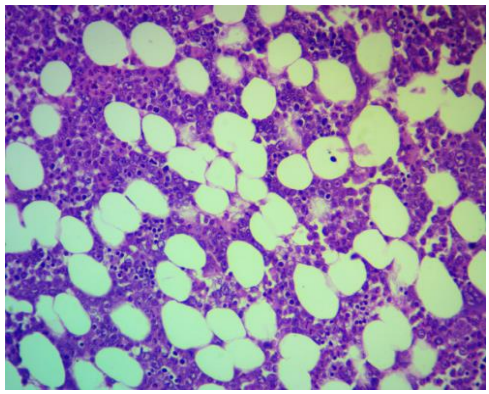

Fig 3: Microphotograph of Group 2 bone marrow increase in adipose tissue in bone marrow on 28th day. H&E×400.

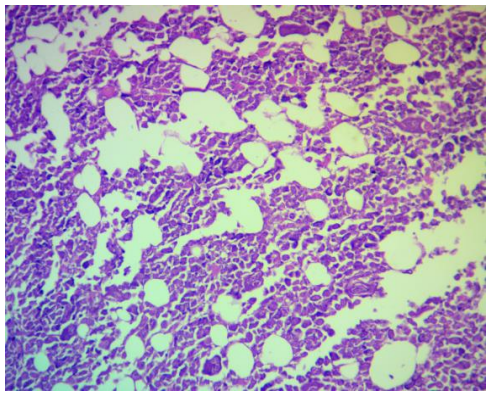

Fig 4: Microphotograph of Group 3 bone showing mild increase in adipose tissue in bone marrow and decreased cellular portion on 28th day. H&E×400.

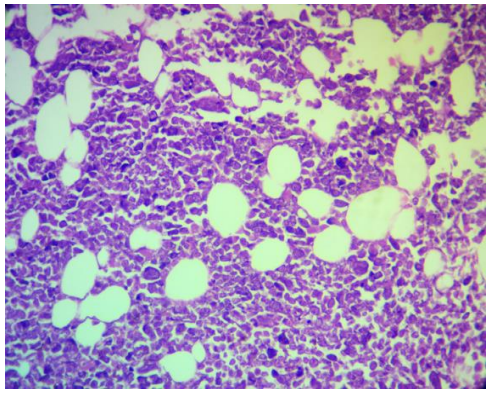

Fig 5: Microphotograph of Group 4 bone showing progressively increasing adipose tissue and decreasing cellular portion on 14th day. H&E×400.

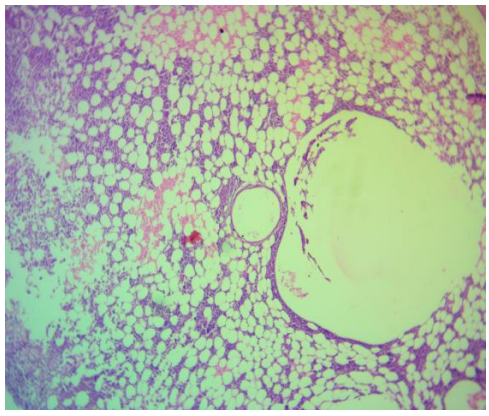

Fig 6: Microphotograph of Group 4 bone showing total cellular portion of bone marrow is replaced by adipose tissue on 28th day. H&E×400.

4. Discussion

Bone section of lead intoxicated rats showed increase in adipocytes in bone marrow, and cellular portion of bone marrow was reduced. Present study lesions in bone were related to the findings of Ochiai *et al*., (1992) [9] and Kumar and Reddy *et al*. (2012) [5].

Group 3 rats, section of bone on 14th and 28th day also showed increased adipocytes in bone marrow and thinning of bone, similar changes were also noticed by Kumar and Reddy *et al*. (2012) [5]. These changes might be attributed to cadmium which can act directly on bone cells in bone organ and cell culture systems to decrease bone formation and increase bone resorption (Bhattacharyya, 2009) [1]. In Group 4 rats, most of the bone marrow was replaced by adipose tissue and cellular portion was reduced on day 14th and 28th day of experiment. This indicates lead and cadmium co- exposure has additive toxic effect on bone. Myelosuppression was also observed in lead intoxicated mice by Queiroz *et al.,* (2003) [12] and Li *et al.*,(2006) [6]. These changes in bone marrow might be due to oxidative stress caused by release of lead and cadmium ultimately led to myelosuppression. Pb toxicity in man was familiar clinical problem in urban areas due to its ability to inhibit the sulphahydral dependent enzymes of the heme biosynthetic pathway, aminolevulinic acid dehydratase (ALAD) and ferrochelatase (Sassa *et al.*, 1973; Granick *et al.*,1973) [13, 4]. Lead toxicity ultimately resulted in anemia due to bone marrow depression (Freyburg, 1972) [3].

5. Conclusion

In conclusion, this study shows that lead and cadmium are the potent toxicant which can cause histopathological changes in bone marrow. Lead and cadmium administered in combination has a potentiated effect in causing myelosuppression. It is also concluded that lead and cadmium are the potent inducers of oxidative damage of bone marrow. The present study therefore provides investigatory evidence of supporting lead and cadmium toxicity in albino Wistar rats.

6. Acknowledgement

Authors are thankful to Associate Dean, College of Veterinary Science, Rajendranagar, Hyd. For providing necessary facility to carry out the investigation.

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