DOI Number: 10.37506/v14/i1/2020/ijfmt/192954

Treatment of Induced Lead Toxicity by using DMSA in Puppies

Omar-Althani Shareef Saed[1], S. M. A. AL-Kubaisi[2], Jassim Mohamed Suleiman[1], Mustafa Salah Hasan[2]

[1]Department of Internal and Preventive Veterinary Medicine, College of Veterinary Medicine, University of Tikrit, Iraq, [2]Department of Internal and Preventive Veterinary Medicine, College of Veterinary Medicine, University of Fallujah, Iraq

Abstract

To determine efficacy of DMSA in treatment of sub-chronic lead exposure in dogs, fifteen puppies aged 2-4 months from both sexes were used for experimental induction of lead toxicity. These puppies were adapted for two weeks and divided randomly to three groups , each group contain five puppies; Group 1 which was regarded as negative control; Group 2, this group was drenched 15mg/kg of lead acetate daily for sixty days; Group 3, this group was drenched 15mg/kg of lead acetate daily for sixty days then were treated with DMSA 10 mg/Kg twice daily orally for one week. These animals were clinically examined daily till the end of experiment, then whole blood, bone, liver and brain were collected for estimation the lead concentrations. The results showed presence of several signs after 15 days of exposure which included depression, diarrhea, tremor then these signs subsides after 7 days of treatment with DMSA. Also, the results presented a significant increasing in the concentrations of lead in liver, blood, bone and brain in group 2 as compared with control group, after treatment with DMSA, group 3 showed a significant decrease in lead concentrations in liver , blood, bone, and brain as compared with group 2. In conclusion, DMSA is an effective therapy for clinical cases of lead toxicity.

Key words: *DMSA, Puppies, Lead, Toxicity.*

Introduction

Lead is a toxic type of heavy metal causes an adverse effects on the GIT, nervous system, also, cardiovascular, urinary and hematological systems, the main mode of action is interrelation of lead affinity with proteins [(1)].

Lead poisoning affects thousands to millions of children in many countries which may lead to many biochemical and some neurological dysfunctions [(2)], and it is commonly occurs via oral route by consumption a contaminated water, leaded paint and ingestion of leaded particles mainly the young dogs that have strange eating habits [(3)].

The dose of lead that can do the adversarial effects in dogs fluctuates, but 1 mg/kg bw/day of lead acetate can be regarded as a LOEL causing increase in blood pressure after ten days from exposure [(4)].

Rosenman *et al*. [(5)] stated that colic may combine with other signs such as constipation, vomiting, abdominal pain, cramping, nausea, anorexia, sometime diarrhea and weight loss.

Succimer (DMSA) is one of the most antidotes that used in cases of poisoning by heavy metals especially lead. The main advantage of DMSA is its high effectively when used orally because it is solvable in water [(6)].

Due to importance of lead toxicity in dogs, this study was aimed to induction of lead toxicity in dogs and evaluate the efficacy of DMSA in treating the lead toxicity.

Materials and Method

A Fifteen healthy puppies with same age (2-4 months) and both sexes were adapted for 2 weeks. before initiation the experiment. These fifteen dogs were divided into 3 groups, each group have 5 animals:

a. Group 1 (Control): this group regarded as control negative.

b. Group 2 (Pb): this group was drenched orally with lead acetate at 15 mg/ kg per day for sixty days according to Faustman *et al.* [7].

c. Group 3 (DMSA+ Lead): this group was drenched orally with lead acetate at 15 mg/ kg/ day according to Faustman *et al.* [7] for 60 days then was treated orally with 10 mg/ Kg DMSA twice daily for one week.

Clinical examination

Clinical examination was carried out along the period of experiment for all dogs every day for any changes in appetite, presence of diarrhea or any other symptoms and every 2 weeks the pulse rate, rectal temperature and respiratory rate were examined.

Lead level measurement:

Specimens were taken for lead level measurement including whole blood, bone, liver and brain of all animals at the end of experiment (day 68), the tissues preserved by freezing immediately after collection, Lead analysis done by adding 20 ml of nitric acid and one ml of concentrated H_2SO_4 to digest 1g of tissues then heated at hotplate until foams appeared then 3 ml of nitric acid and 1ml of $HClO_4$ were added without roasting the sample then the volume was completed to 100 ml by using deionized water then the concentration was estimated by Atomic Absorption Spectrophotometer according to [8].

Statistical Analysis

All data were examined according to [9].

Results

Puppies were monitored daily for development of some clinical signs such as depression, diarrhea, dehydration and other signs. All lead treated puppies showed different degrees of depression appeared after day fifteen till to the end of experiment. Lead treated puppies showed slight decrease in appetite and many lead treated animals showed mild diarrhea and some showed tremor and aggressive behavior after 30 days of lead exposure. After treatment with DMSA, all puppies improved after 7 days of treatment and showed a normal signs. All puppies showed a normal temperature, pulse and respiratory rates before and after lead exposure till the end of experiment.

The results of estimation lead concentrations in different tissues showed that the concentrations of lead in liver, blood, brain and bone were increased significantly in group 2 as compared with control group (G1) , after treatment with DMSA, the group 3 showing a significant decreasing in the concentration of lead in bone, blood, brain and liver as comparing with group 2 (Table 1; Fig. 1,2,3,4).

Table 1: Lead concentration (ppm) in different tissues of all groups at the end of experiment (Mean ± SE)

Tissues Groups	Blood	Bone	Liver	Brain
G1 Con.	0.1460± 0.020C	0.1420± 0.018C	0.1100± 0.029C	0.1420± 0.031C
G2 Tox.	1.0540± 0.099A	13.1040± 0.815A	12.0440± 0.439A	11.1480± 0.3212A
G3 DMSA	0.4600± 0.039B	8.3140± 0.301B	5.1580± 0.403B	6.0500± 0.379B

Capital letters mean a significant differences ($p<0.05$) between groups

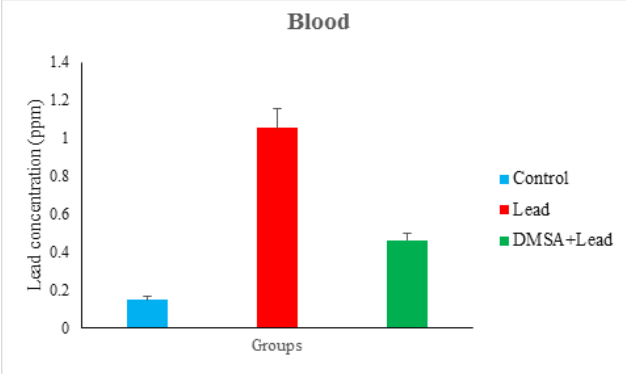


Figure 1: Lead concentration (ppm) in blood of all groups at the end of experiment

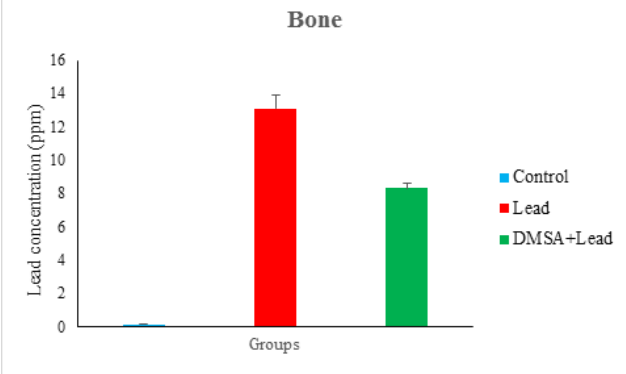


Figure 2: concentration of Lead (ppm) in bone of all groups at the end of experiment

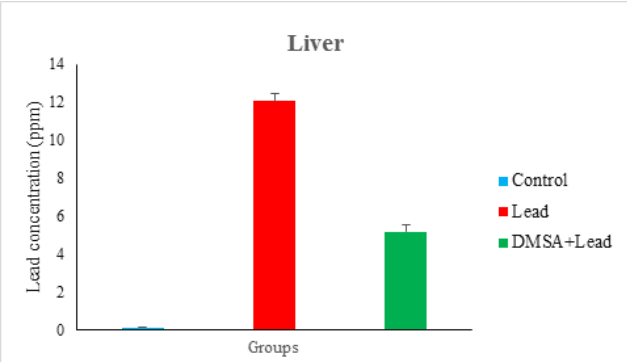
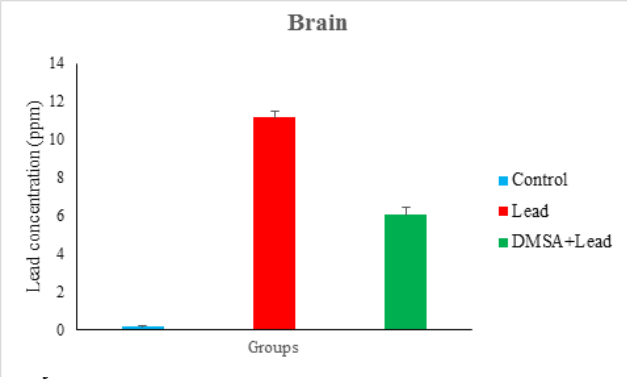


Figure 3: Lead concentration (ppm) in liver tissues of all groups at the end of experiment



The presented study showed that all lead treated animals exhibit different degrees of depression which appeared after day fifteen and extended to the end of experiment. The presented results were in compatible with results of Fewtrell *et al.* [10] who showed that lead interfering with neurological functions in all stages of the life at low levels, and may cause many signs ranged from blindness to encephalopathy that causing dullness, muscular tremor and headache). Puppies showed slight decrease in appetite and eight out of twenty lead - treated animal showed mild diarrhea after 30 days of lead exposure. The current results were similar with results of Rosenman *et al.* [5] which showed that colic may combine with other symptoms such as pain of abdomen, constipation, vomiting, cramps, anorexia, nausea, sometime diarrhea and loss of weight. GIT signs happen at blood lead concentration of 100-200 µg/dL, but sometimes associated with level between 40-60 µg/dL.

During lead exposure period, all puppies showed no shafting change in body temperature, pulse rate and respiration. Due to continues low dose of sub chronic exposure of lead there is no shafting change in temperature , pulse rate and respiration and these results are in agreement with those of [11] which showed that signs occur in association with higher doses or increasing the exposures length. The lead toxicity doesn't related to the route of exposure and it is depending on blood lead levels.

DMSA is non-toxic, water-soluble, when orally-administered may act as metal chelator, so that it can be used as antidote for heavy metal toxicity [12].

Ramsey *et al.* [13] showed that in dogs that treated with succimer (10 mg/kg B.W., PO, q 8 h) for 10 days, mean blood lead concentrations decreased 53.6, 76.2, and 60.9% from pretreatment value on days 3, 7, and 20, respectively, while, mean urine lead concentrations on days 0, 3, 7, and 20 were 70.0, 485.4, 254.3, and 28.3 micrograms/dl, respectively, they concluded that dogs with lead poisoning, when treated orally with DMSA for ten days it effectively reduced the lead concentrations in blood and absence of lead poisoning signs.

Studies in human with lead poisoning showed that DMSA rapidly increase the urinary excretion of lead, also in persons with low exposure to lead it give a significant improving [14]. An increasing the excretion of lead in urine is due to chelation therapy of DMSA. In a study of Graziano et al. [15] which done to establish the DMSA therapeutic dose, it showed a 28-fold increase was seen in excretion of urinary lead after the first five doses.

In a study done to estimate blood and brain lead after DMSA treatment, they concluded using of DMSA to reduction of lead concentrations in brain [16].

In conclusion, DMSA is a good therapeutic agent for treatment lead toxicity in human and animals.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: Self-funding

References

1. Høgåsen H R, Ørnsrud R, Knutsen H K and Bernhoft A. Lead intoxication in dogs: risk assessment of feeding dogs trimmings of lead-shot game. BMC veterinary research, 2016; 12(1): 152.
2. Xiao X, Zhang C, Liu D, Bai W, Zhang Q, Xiang

Q, ... & Su Z. Prevention of gastrointestinal lead poisoning using recombinant Lactococcus lactis expressing human metallothionein-I fusion protein. Scientific reports, 2016; 6:23716.

3. Berny P J, Cote L M and Buck W B. Relationship between soil lead, dust lead, and blood lead concentrations in pets and their owners: evaluation of soil lead threshold values. Environmental research, 1994; 67(1): 84-97.
4. Fine B P, Vetrano T, Skurnick J & Ty A. Blood pressure elevation in young dogs during low-level lead poisoning. Toxicology and applied pharmacology, 1988; 93(3): 388-393.
5. Rosenman K D, Sims A, Luo Z & Gardiner J. Occurrence of lead-related symptoms below the current occupational safety and health act allowable blood lead levels. Journal of occupational and environmental medicine, 2003; 45(5): 546-555.
6. Volans G N, Karalliedde L & Wiseman H M. Review of Succimer for treatment of lead poisoning. prepared for the World Health Organization 18th Expert Committee on the Selection and Use of Essential Medicinesm, 2010.
7. Faustman E M, Omenn G S & Klassen C. Em Casarett and Doull's Toxicology: The Basic Science of Poisons. CD Klaassen (Ed.), 2008.
8. Berman E, Valavanis V and Dubin A. A micromethod for determination of lead in blood. Clinical chemistry, 1968; 14(3): 239-242.
9. Snedecor G and Cochran G. Statistical Methods, Eighth Edition, Iowa State University Press, 1989.
10. Fewtrell L J, Prüss-Üstün A, Landrigan P and Ayuso-Mateos J L. Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure. Environmental Research, 2004; 94(2): 120-133.
11. WHO. Environmental Health Criteria 165: Inorganic Lead. Geneva, 1995: 29-220.
12. Miller A L. Dimercaptosuccinic acid (DMSA), a non-toxic, water-soluble treatment for heavy metal toxicity. Alternative medicine review: a journal of clinical therapeutic, 1998; 3(3): 199-207.
13. Ramsey D T, Casteel S W, Faggella A M, Chastain C B, Nunn J W & Schaeffer D J. Use of orally administered succimer (meso-2, 3-dimercaptosuccinic acid) for treatment of lead poisoning in dogs. Journal of the American Veterinary Medical Association, 1996; 208(3):371-375.
14. Hoet P, Buchet J P, Decerf L, Lavalleye B, Haufroid V & Lison D. Clinical evaluation of a lead mobilization test using the chelating agent dimercaptosuccinic acid. Clinical chemistry, 2006; 52(1), 88-96.
15. Graziano J H, Siris E S, Lolacono N, Silverberg S J & Turgeon L. 2, 3-Dimercaptosuccinic acid as an antidote for lead intoxication. Clinical Pharmacology & Therapeutics, 1985; 37(4): 431-438.
16. Stangle D E, Strawderman M S, Smith D, Kuypers M & Strupp B J. Reductions in blood lead overestimate reductions in brain lead following repeated succimer regimens in a rodent model of childhood lead exposure. Environmental health perspectives, 2004; 112(3): 302.