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Intramuscular Single Dose one Compartmental Toxicokinetics of Lead in Duttaphrynus Melanostictus.

KEYWORDS: Lead, Toxicokinetics, Area under curve, Volume of distribution, elimination,

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ABSTRACT *Lead continues to receive as much attention as any modern environmental health risk, despite years of intensive research, educational efforts, and remedial measures. The present study examines toxicokinetics of Pb in Indian Common Toad after an intramuscular injection at 15 mg/kg.Samples of the blood, were obtained from Indian Common Toad at times between 2 to 16 h at even hour. The concentrations of Pb in the blood and tissues were determined by atomic absorption spectrometry. Toxicokinetic parameters such as MRT, Vd , Vss, kel, t1/2ß, Tmax, Cmax, CL, AUC0-∞ , AUMC0-∞ of Pb were calculated from the mean metal concentrations in the blood.The highest concentration of Pb in the blood, appeared 2 h after the injection.The concentration of lead in blood ranged from 0.90-3.48 µg/ml. The Vss of 12.40 L/kg in blood, CL of 0.73 L/h/kg in Blood and t1/2ß of 10.43 h in Blood, The Appar-*

Introduction:

Lead is a stable, silver-gray, ubiquitous heavy metal and is detectable in all .Lead can form a number of salts. (WHO 1995, WHO 1996). It can enter the human body through uptake of food (65%), water (20%) and air (15%). Lead in the air has come from a variety of sources. They are leaded gasoline. Concentration of lead is from 76 pg/m^3 in remote areas and above 10 µg/m^3 near stationary point sources such as smelters, with an average annual concentration below 1.0 µg/m^3 for urban areas. (WHO 1995, WHO 1996, ATSDR 1999).

The rate of deposition of air borne lead is 30-50% & is affected by certain factors such as particle size & ventilation rate where as the gastrointestinal absorption after ingestion is influenced by the physiological state of an exposed person (ex- age, fasting, nutritional calcium & iron status) & the physical-chemical properties of the lead ingested (e.g. particle size, mineralogy, solubility, lead species) (ATSDR, 1999). A study of rats showed that lead carbonate was absorbed more relative to other form of lead and metallic lead was absorbed the least (Davidson, 1994). A study of rats showed that lead carbonate was absorbed more relative to other form of lead i.e lead acetate , lead thallate, lead sulphide, lead naphthenate and lead octoate, lead chromate and metallic lead was absorbed the least (Davidson, 1994). Absorbtion by injestion of lead is found to be more significant than in case of dermal absorption (ATSDR, 1999). Lead can be mobilized from bone to blood & thus be once again available. This happens especially in case of pregnant women & the elderly (WHO, 1995). Lead poisoning continues to be of interest in current research. Lead poisoning (also known as plumbism, colica pictorum, saturnism, Devon colic, or painter's colic) is a medical condition in humans and other vertebrates caused by increased levels of the heavy metal lead in the body. Lead continues to receive as much attention as any modern environmental health risk, despite years of intensive research, educational efforts, and remedial measures. The present study examines toxicokinetics of Pb in Indian Common Toad after an intramuscular injection at 15 mg/kg.

Materials & Methods

The test species that was used to perform the experiment is Indian Common Toad (*Duttaphrynus melanostictus*) which has Kingdom: Animalia, Phylum: Chordata,Class: Amphibia,Order: Anura,Family: Bufonidae,Genus: Duttaphrynus, Species: D. melanostictus and Binomial name: Duttaphrynus melanostictus. (Schneider)Toads of both sexes obtained from a local area were kept in an aquarium for 7 -10 days with constant lighting & proper food. Injectable solution of Pb at 15ppm was prepared. All the chemicals and reagents used in the study is of analytical grade and pure .Doubly distilled demineralized water is used for all the washings and preparation of solution. Then the solution was injected into the body of the test model & then the blood samples were taken from the test model Duttaphrynus melanostictus. 05 ml of fasting blood serum was drawn by pyrogen free disposal syringe. Blood is allowed to clot for one hour & then centrifuged at 2500 RPM for 15 minutes. Serum thus obtained is refrigerated & stored in contaminated free evacuated tube. Each sample is processed within 72 hours. Toxicokinetic parameters such as MRT, V_d , V_{ss}, k_{el}, $t_{1/2\beta}$, T_{max}, C_{max}, CL, $AUC_{0-\infty}$, $AUMC_{0-\infty}$ of Pb were calculated from the mean metal concentrations in the blood

Results & Discussion

Results:

The highest concentration of Pb in the blood, appeared 2 h after the injection. The concentration of lead in blood ranged from 0.31-1.06 µg/ml. (Table 1)The V_{ss} of 12.40 L/kg in blood, CL of 0.73 L/h/kg in Blood and t1/2ß of 10.43 h in Blood, The Apparent volume of distribution (V_d) was found to be 11.06L.Here the elimination rate constant is 0.07 h-1 in blood

The metal levels in the blood, was found out after injection of lead at the dose rate of 15 mg/kg intramuscularly at time 2-16 hrs. (Table 1). The concentration of lead in blood ranged from 0.31 µg/ml in 14 & 16 hr- 1.06 µg/ml in 2 hr.

The mean residence time of Pb was 13.37 h and its area under the concentration-time curve (0-alpha) (AUC) was 16.17 µg.h/ml. Area under the moment curve (AUMC) is

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216.12 µg.h^2/ml. T_{max} is 2 h. C_{max} is 1.06 µg/ml (Table 2) The toxicokinetic parameters of Pb from the mean Pb concentrations in the blood at times 2 to 16 h in ***Duttaphrynus melanostictus*** are depicted in the Table 3. The elimination half-life of Pb was 10.43 h with steady state volume of distribution 12.40 L/kg and total body clearance of 0.73 L/h/kg. The mean residence time of Pb was 13.37 h and its area under the concentration-time curve (0-alpha) (AUC) was 16.17 µg.h/ml. Area under the moment curve (AUMC) is 216.12 µg.h^2/ml. T_{max} is 2 h and the C_{max} is 1.06 µg/ml (Table 3). The Apparent volume of distribution is 11.06 L. The Elimination rate constant (kel) is 0.07 h^{-1}.

Table-1. Lead concentrations in the blood of Duttaphrynus melanostictus after a single intramuscular administration at a dose of 15 mg/kg body weight

Time(h)	Blood
2	1.06 ± 0.22
4	0.79 ± 0.02
6	1.02 ± 0.23
8	0.74 ± 0.10
10	0.42 ± 0.07
12	0.56 ± 0.05
14	0.31 ± 0.05
16	0.31 ± 0.04

Values are mean ± SE of 3 Toads/each sampling time from respective concentrations between 2- 16 hr after the Pb injection

Table- 2: AUC Table for Blood

Time (hr)	Cp (µg/ml)	Cp•t (µg.hr/ml	ΔAUC (µg.hr/ml)	AUC (µg.hr/ml)		AUMC (µg.hr^2/ml)
0	1.36	0.00	Segment	Summation	Segment	Summation
2	1.06	2.11	2.41	2.41	2.11	2.11
4	0.79	3.16	1.85	4.26	5.27	7.38
6	1.02	6.14	1.81	6.07	9.30	16.68
8	0.74	5.95	1.77	7.84	12.09	28.77
10	0.42	4.19	1.16	9.00	10.14	38.91
12	0.56	6.71	0.98	9.98	10.89	49.80
14	0.31	4.36	0.87	10.85	11.07	60.87
16	0.31	4.99	0.62	11.47	9.36	70.23
∞	0.00		4.70	16.17	145.89	216.12

Table 3: Toxicokinetic parameters of lead in Blood of Duttaphrynus melanostictus after a single intramuscular administration at a dose of 15mg/kg.

Variable*	Unit	Blood
Mean residence time [MRT=AUMC/AUC]	h	13.37
Steady state volume of distribution [Vss=Dose.AUMC/ (AUC) ^{2}]	L/kg	12.40
Elimination rate constant (kel= 0.693/ $t_{1/2ß}$)	h^{-1}	0.07
Elimination half-life ($t_{1/2ß}$)	h	10.43
T_{max}	h	2
C_{max}	µg/ml	1.06
Apparent volume of distribution (V_d = Dose/$C_{p\ 0}$)	L	11.06
Total clearance (CL =Dose/AUC)	L/h/kg	0.73
Area under blood concentration-time curve (AUC)	µg.h/ml	16.17
Area under the moment curve (AUMC)	µg.h^2 / ml	216.12

Discussion

Understanding the lead partitioning in the body provides a useful background towards understanding biomarkers of Lead. More than 95 % of circulating lead is bound to erythrocyte proteins after gastrointestinal or pulmonary absorbtion and the remainder is associated with the plasma (Cake et.al 1996; Bergdahl et.al 1997) before reaching the target organs. Lead is distributed widely in the body and can gain access to sites in the central and peripheral nervous, cardiovascular, renal, reproductive, hematopoietic musculo skeletal and other organ system (Hu et.al, 2007; NTP 2012). The persons exposed to lead have a substantial body burden of lead, more than 90 % in bone pool, 2-8% in various soft tissues and 2-5% in blood (Rabinowitz et.al 1976). Non Specific Binding of lead to a variety of a proteins and its involvement in calcium pathways explain in large part its myriad health effects.

The findings of the present study are the first systemic Toxicokinetic report of lead in Indian Common Toad following intramuscular injection at 15mg/kg. The appearance of lead in the plasma within 2 hr correlates with the behavioral changes as reported in Chicks injected with Mn at a dose of 20 mg/kg within 1 hr too(Al- Zubaidy et. al,2012). The C_{max} and T_{max} value shows that lead is relatively rapidly absorbed into systemic circulation of the test species (Indian Common Toad).

The toxicokinetic parameters of the present study suggest that lead is well absorbed and distributed in the body of the toad with a Vss of 12.40 L/kg in Blood, Vss is a reliable estimate of volume of distribution, since it is calculated independent of the Kel (Gibaldi M. et. al 1982, Baggot et. al 2001). The elimination rate constant is 0.07 h^{-1} in blood.

The half-life of lead in these tissues is measured in weeks for blood, months for soft tissues, and years for bone (Karri. et.al ,2008). In human blood half-life of Pb was estimated at 36 days (Rabinowitz, 1991) but in our study Elimination half-life (t1/2ß) was found to be10.43 h in Blood. About 10-15% of intravenously injected lead accumulates in the adult skeleton within a few hours. (Richard W. Leggeff, 1993) Mean residence time (MRT) in the following study was found to be 13.37 h in blood. The AUC value was found to be 16.17

µg.h/ml in blood & the area under the moment curve (AUMC) was found to be 216.12 µg.h^2/ml in blood.

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