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ORAL TREATMENT OF AVIAN LEAD INTOXICATION WITH MESO-2,3-DIMERCAPTOSUCCINIC ACID

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Abstract: The efficacy of meso-dimercaptosuccinic acid (DMSA) (succimer) in treating avian lead intoxication was studied in a retrospective, nonrandomized, longitudinal study. Nineteen birds with moderate to high blood lead concentration and neurologic signs compatible with lead toxicity were treated with DMSA (30 mg/kg p.o., b.i.d.; $n = 15$) for a minimum of 7 days. In cases with severe neurologic signs, DMSA was supplemented with a single dose of edetate calcium disodium (<50.0 mg/kg of body weight i.m.; $n = 4$). Blood lead concentrations were measured two or more times (before and after treatment). Median blood lead concentration decreased (87%), neurologic signs were resolved, and there were no apparent adverse secondary effects.

Key words: Birds, lead toxicity, meso-dimercaptosuccinic acid, DMSA, succimer.

INTRODUCTION

Lead intoxication remains one of the most common toxicities in free-ranging birds, despite the ban of lead shot in the United States in 1991.[2,9,18] Despite efforts to reduce lead concentration in the immediate environment, captive birds may be exposed to lead that persists in paints, soil, and other compounds. Although environmental abatement efforts have been undertaken in avian exhibits at the Wildlife Conservation Society (Bronx, New York 10460, USA) during the last 20 yr (primarily through paint and soil removal), occasional cases of avian lead intoxication occur in areas where lead paint was used previously or where foraging behavior of birds results in ingestion of lead particles.

Standard treatment of avian lead intoxication usually consists of parenteral administration of edetate calcium disodium (CaEDTA; Versenate, 3M Pharmaceuticals, Northridge, California 91324, USA).[17,18] Although CaEDTA removes lead from body stores effectively, it has many disadvantages. Because of poor gastrointestinal absorption, it must be given parenterally.[18] When injected i.m., CaEDTA causes severe and painful reactions.[4] Manual restraint during administration may cause problems, particularly with birds in large naturalistic enclosures. Neurologic signs caused by redistribution of lead to the brain also may follow CaEDTA use,[5] as may depletion of essential metals (i.e., zinc).[11]

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Meso-dimercaptosuccinic acid (DMSA) or succimer (Chemet®, McNeil Consumer Products Co., Fort Washington, Pennsylvania 19477, USA) is the first oral chelating agent for treatment of lead toxicity that was approved as an investigational new animal drug by the Food and Drug Administration's Center for Veterinary Medicine[19] since CaEDTA was approved more than 40 yr ago.[16] When used at its recommended dose regimen, DMSA reverses the adverse metabolic effects of lead on heme synthesis and increases urinary lead excretion rate without increasing essential mineral excretion rates. Hypersensitivity and idiosyncratic reactions have not been noted.[16] In addition, DMSA can be coadministered with CaEDTA.[16] Meso-dimercaptosuccinic acid has been used experimentally in many species including primates, dogs, cats, rabbits, guinea pigs, rats, mice, sheep, and birds.[6,7,17,18]

MATERIALS AND METHODS

Lead intoxication cases were identified in the medical records of birds maintained at the Wildlife Conservation Society from 1994 to 2001. Birds included in the study had blood lead concentrations higher than 0.53 μmol/L (11 μg/dl) and neurologic signs compatible with lead intoxication, such as lethargy, depression, weakness, ataxia, paresis, paralysis, loss of voice, head tilt, blindness, circling, and seizures. Nineteen birds of nine species completed the study. Thirty birds suffering from lead toxicity and belonging to 13 different species were initially treated with DMSA. Eleven were excluded from the study despite recovery from neurologic signs because their blood lead concentrations were not determined after treatment.

Before treatment, whole blood samples from af-

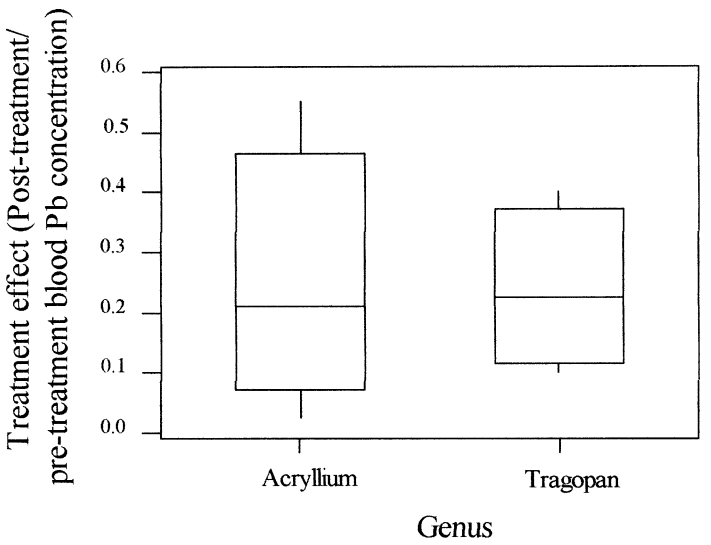

Figure 1. Response to meso-dimercaptosuccinic acid treatment (30 mg/kg) of birds of the genera *Acryllium* (n = 5) and *Tragopan* (n = 4) (Phansianidae) that were clinically diagnosed with lead intoxication as expressed by the posttreatment–pretreatment ratio of blood lead concentration. The horizontal line of each box plot represents the median. The lower and upper vertical lines present the 5th and 95th percentiles, respectively.

fected birds were collected in lead-free syringes, transferred to lithium heparin lead-free tubes, and shipped by overnight delivery to the New York State Diagnostic Laboratory (College of Veterinary Medicine, Cornell University, Ithaca, New York 14852, USA). Blood lead concentration was quantitated by furnace atomic absorption spectrophotometry with a 0.12 μmol/L (2.5 μg/dl) detection limit by using a transverse heated graphite furnace spectrophotometer (Perkin Elmer Inc., Norwalk, Connecticut 06484, USA).

Meso-dimercaptosuccinic acid was administered at 30 mg/kg p.o., b.i.d., by sprinkling the contents of capsules over food for a minimum of 7 days, usually for 10 days. Birds were monitored continuously for adverse effects or behavioral abnormal-

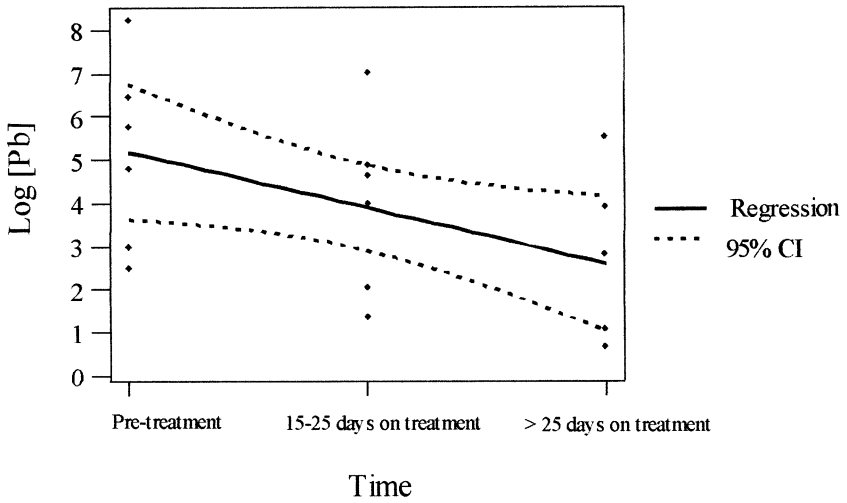

Figure 2. Effect of meso-dimercaptosuccinic acid treatment over time in six birds clinically diagnosed with blood lead intoxication as expressed by blood lead concentration. Solid line represents the fitted regression line. Broken lines represent the lower and upper limits at the 95% confidence intervals, respectively.

Table 1. Pretreatment and posttreatment blood lead concentration in birds orally treated with DMSA (30 mg/kg) or DMSA + CaEDTA (<50 mg/kg).

Bird no.	Spe--cies[a]	Treat-ment[b]	Blood lead concentration by collection day (μmol/L, μg/dl)								
			Day 1	Day 10	Day 14	Day 15	Day 19	Day 23	Day 25	Day 26	Day 27
1	Aaa[d]	Sca	1.5, 31.1			1.3, 28.5					
2	Af	S	1.3, 27			0.5, 10.4					
3	Av[d]	S	2.3, 47.7						1.8, 38.2		
4	Av	S	2.6, 54							1.4, 29.9	
5	Av	S	7.3, 151		1.5, 32						
6	Av	S	7.2, 150							1.5, 32	
7	Av	S	90.7, 1,880								2.3, 48.9
8	Gs	S	4.5, 93						0.8, 15.8		
9	Gs	S	33.8, 700			1.6, 34.3					
10	Gv	Sca	36.2, 750			0.1, 2.66					
11	Pi	S	2.6, 55			0.1, 2.5					
12	Tb	S	14.0, 291				1.4, 29.2				
13	Tb	S	6.6, 136						1.9, 39.7		
14	Pi	Sca	5.8, 120	2.6, 55							
15	Pr	S	0.6, 11.9								
16	Ts	S	0.9, 19.6		0.4, 8.3						
17	Ts	S	184.3, 3,820	54, 1,120					12.3, 255		
18	Tb[e]	S	31.4, 650								
19	Gs[e]	Sca	15.5, 322				6.3, 132	9.7, 202			

[a] Aaa, Malay great argus pheasant, *Argusianus argus argus*; Af, Fischer's lovebird, *Agapornis fisheri*; Av, Vulturine guineafowl, *Acryllium vulturinum*; Gs, Junglefowl, *Gallus* sp., Gv, Victoria crowned pigeon, *Goura victoria*; Tb, Blythi's tragopan, *Tragopan blythi*; Pi, Mountain peacock pheasant, *Polyplectron inopinatum*; Pr, Red bird of paradise, *Paradisea rubra*; Ts, Satyr's tragopan, *Tragopan satyra*.

[b] Type of treatment: S, DMSA only; Sca, DMSA + CaEDTA. DMSA, meso-dimercaptosuccinic acid; CaEDTA, edetate calcium disodium.

[c] Number fraction of posttreatment–pretreatment blood lead concentration (or percentage).

[d] Outliers.

[e] Birds with oscillating blood lead concentrations. Several courses of treatment were given.

ities during treatment. Birds with severe neurologic signs received an initial i.m. injection of CaEDTA (25.0–50.0 mg/kg). Blood was collected from all treated birds 7–30 days after treatment was completed. Although all birds were tested before and after treatment, six of them also were tested during treatment.

The significance of differences between pre- and posttreatment blood lead concentrations was tested with the Wilcoxon's rank test. The median postreatment blood lead concentration was compared with the median pretreatment blood lead concentration by using the Mann–Whitney test. The relationship between initial blood lead concentration and treatment efficacy (posttreatment–pretreatment ratio) and the temporal effect of treatment (when more than two postreatment observations were available) were assessed by regression analysis. Results were considered significant at $P < 0.05$.

RESULTS

Mean blood lead concentration of all the 19 treated birds was significantly reduced after treatment. As shown in Table 1, mean pretreatment blood lead concentration for the 19 birds was 23.6 μmol/L (490 μg/dl), with a range of 0.5–185 μmol/L (11.9–3,820 μg/dl), whereas mean postreatment blood lead concentration was 1 μmol/L (22.7 μg/dl).

Mean blood lead concentration in the 19 treated birds was significantly reduced after treatment. The median posttreatment/pretreatment difference was −11 μmol/L (−226 μg/dl; $P < 0.0001$). The mean posttreatment reduction in blood lead concentration was 87%. The distribution of data indicated two possible outliers (No. 1 and No. 3), with values >3 SD > the mean. The removal of these birds increased treatment efficacy to 90%. The treated birds also showed remission of neurologic signs. There was no significant difference between the median efficacy of birds treated with DMSA + CaEDTA (96%) and that of birds treated with DMSA alone (87%). Treatment efficacy based on improvement of clinical signs and reduction of blood lead concentration was not significantly associated with pretreatment blood lead concentration ($P > 0.23$). No

Table 1. Extended.

Blood lead concentration by collection day (μmol/L, μg/dl)										Tx efficacy[c] (%)
Day 30	Day 35	Day 36	Day 40	Day 45	Day 54	Day 60	Day 75	Day 89	Day 90	Day 128	
											0.08, 8
											0.62, 62
											0.2, 20
											0.45, 45
											0.79, 79
											0.79, 79
											0.98, 98
											0.84, 84
											0.95, 95
											0.99, 99
											0.96, 96
											0.90, 90
											0.71, 71
	0.1, 2.5										0.98, 98
0.2, 4.2			0.1, 2.7								0.78, 78
0.1, 2.5											0.88, 88
	0.9, 18.8			0.6, 12.9							0.99, 99
5.0, 103				37.2, 770		13.5, 280	4.44, 92		2.5, 51		0.93, 93
		7.3, 150			7.3, 152			34.7, 720		0.8, 17	0.95, 95

difference in treatment efficacy was noted between the two genera tested (Fig. 1).

A significant negative relationship between time and lead concentration (R^2 = 24.2%, n = 6, $P <$ 0.04; Fig. 2) was indicated by regression analysis. Lead concentration did not decrease in a linear fashion in all the treated birds. It increased in two individuals (No. 18 and No. 19) after decreasing initially. After additional treatment, lead concentrations in both birds decreased again, and neurologic signs remitted. No adverse clinical effects were observed after DMSA treatment.

DISCUSSION

This study was based on a longitudinal, nonrandomized, retrospective design. Each individual served as its own control. The design allowed us to observe decreased blood lead concentration and cessation of neurologic signs, which could be attributed to DMSA treatment. These results, however, cannot be compared directly with the results of previous studies[6,7,17,18] because criteria for selection of cases, species treated, mean pretreatment blood lead concentrations, and duration of treatment differed.

Although we did not measure delta-aminolevulinic acid dehydratase activity or reduction in urinary amino levulinic acid and coproporphyrin as in human studies,[10,16] significantly decreased blood lead concentrations and remission of clinical signs in treated birds, regardless of the initial blood lead concentration, were noted.

Treatment of heavy metal intoxication aims to reduce the systemic metal burden below a critical threshold and to eliminate clinical signs with minimal side effects and maximal efficacy before irreversible damage occurs.[18] Meso-dimercaptosuccinic acid is apparently superior to CaEDTA in reducing blood lead concentration.[1,3,4,7,8,14] Our study showed greater reduction of lead levels after DMSA treatment than was observed in another study involving raptors and psittacines.[18] Differences can be explained by the posttreatment blood sampling timeframe and the different avian families involved in that study.[18] Although we provided DMSA in food, the other study used oral gavage.

Interactions between DMSA and CaEDTA did not appear to induce undesirable effects; however, there is a limited amount of data on concomitant CaEDTA and DMSA use in birds. A 13% greater effect was observed when DMSA was used together with CaEDTA. Although there was no statistical difference between the two treatments, the use of both drugs may prove beneficial in the treatment of severe lead intoxication. Other studies have demonstrated that a combined therapy of DMSA and CaEDTA is more effective than either chelator used alone. Meso-demercaptosuccinic acid and CaEDTA together increase urinary and fecal elimination of

lead and reduce hepatic, renal, and femur concentrations of lead in rats and mice.[4,21]

Blood lead levels in two birds (No. 1 and No. 3) did not decrease after chelation therapy (Table 1), possibly because of incomplete DMSA ingestion. Both birds were in naturalistic enclosures where regular ingestion of medicated food was difficult to enforce and control. Blood lead levels in two other birds (No. 18 and No. 19) rebounded after cessation of chelation therapy. This could be related to ongoing lead exposure or to redistribution of lead from other body compartments. Treatment failure in humans, rats, and ducks has been explained by redistribution of lead from bone stores to soft tissue. Lead compartmental kinetics is a function of body lead burden.[13,16,18,20] Rebound in humans can be steep, requiring multiple frequent courses of chelation therapy.[16] In humans, a 2-wk interval between courses of chelation therapy with DMSA has been recommended, unless blood lead concentrations indicate a need for more frequent treatment.[16]

Meso-dimercaptosuccinic acid has been reported to be a good chelator for lead in birds.[6,7,17,18] There appears to be only a twofold difference between a safe and a lethal dosage in cockatiels; therefore, accurate dosing is recommended.[7] In addition, DMSA has been reported to produce side effects such as mucocutaneous eruptions and nausea in humans.[12] Our 30 mg/kg b.i.d. dosage was not associated with toxicity. It is not known if transovarial passage of DMSA occurs or if avian embryos can be harmed.[12] Most DMSA is eliminated by the renal route, so treated birds should be adequately hydrated.[15] Meso-dimercaptosuccinic acid may allow treatment of birds as outpatients, without need for handling.

Orally administered DMSA (30 mg/kg sprinkled over food alone) or DMSA in combination with a single dose of CaEDTA (<50 mg/kg) appears to be a satisfactory treatment of lead intoxication in birds.

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