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Residual effects of Lithium in Muscle and Organ Tissues of Sheep Post-Ingestion of Lithium Chloride

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Abstract

Conditioned taste aversions (CTA) occur when animals associate gastrointestinal distress with a particular food source. CTA strategy can be used to reduce animal consumption of an undesirable feedstuff. Lithium chloride (LiCl) has been used in wild ungulates as a CTA and could be used in white tail deer (WTD) as a potential CTA. Consumption of LiCl by WTD may leave residue in meat which may be consumed by a human. The objectives of this study were to examine the effect of dietary LiCl on kinetics and depletion of lithium in muscle, kidney, and liver tissue in adult domestic sheep (model for WTD). In experiment1, eleven adult sheep orally received either 150 mg LiCl/kg BW (n = 8) or placebo (n = 3). Using aseptic procedure, muscle biopsies were taken at 4,8,12,24,48,96,192, and 240 hours post LiCl ingestion and lithium concentrations were measured. In experiment2, sixteen adult sheep received either 450mg LiCl/kg BW (n = 14) or placebo (n = 2). In experiment3, nine adult sheep orally received a single dose of 150mg/kg BW. Three-animal groups were euthanized at 7,24, and 96 hours post-LiCl ingestion and muscle, liver, and kidney samples were harvested to measure lithium concentrations. Low dose of LiCl reached a maximum level in muscle 24 hours post-ingestion and returning to basal levels (P = 0.72) by 192 hours. High mortality (12 of 14; 86%) occurred following high dose administration resulting in an inability to determine maximum concentration levels or appreciate differences between muscle, organ tissue types and over time. Lithium concentrations were greater (P<0.01) in liver and kidney compared to muscle at 7 and 24 hours post ingestion, but no difference in lithium concentration was detected in the three tissues at 96 hours (P > 0.05). It appears that a withdrawal period in muscle tissue for low dose LiCl in domestic sheep is 192 hours. The toxic threshold for domestic sheep, and likely other small ruminants, occurs between 150-450mg LiCl/kg body weight.

Keywords: Crop depredation, Deer, Lithium chloride, Lithium chloride toxicity, Small ruminants, Taste aversion

Abbreviations: CTA: Conditioned Taste Aversion; WTD: White-tailed deer; LiCl: Lithium Chloride

Introduction

White-tailed deer (Odocoileus virginianus; WTD, hereafter) are one of the most widespread large mammal species of North America, with correspondingly large impacts on society, both positive (e.g., hunting, wildlife viewing) and negative (e.g., car collisions, crop depredation). White-tailed deer inhabit a variety of areas, occurring almost where digestible forage is available and accessible habitat cover is nearby. In recent years, population numbers have drastically increased in many areas of the Western United States, potentially due to their extreme adaptability and versatility [1]. High population densities have been thought to increase dispersal and movement rates, likely causing them to travel further across the landscape in search of available resources [2]. As deer movement and dispersal rates increase, more encounters with agricultural fields containing nutritious crops occur [2], resulting in an increase in crop depredation rates.

To mitigate costs associated with abundant deer while maintaining recreational and economic benefits, there is a pressing need to find effective deer deterrents. In the past, multiple deterrent methods targeted at reducing deer damage have been tested, including propane exploders and other frightening devices, fencing, and lethal removal [3-5]. Although previously tested deterrents have resulted in a wide range of effectiveness, wildlife managers are still searching for a deterrent method that is cost-effective with high efficacy rates across a multitude of wildlife

species. One promising method yet to be tested in an open field setting for deterring WTD is the use of lithium chloride (LiCl), a gastrointestinal toxicant that has successfully been used to create taste aversions to specific food items in both carnivores and ruminants.

Previous studies have shown high efficacy in reducing the amount of food consumed after LiCl was ingested as treated animals associated targeted food sources with gastrointestinal distress [6-9]. However, most of these studies were conducted in controlled, captive feeding trials where ruminants, as well as carnivores, were given the choice to consume food items pre- and post-ingestion of LiCl [8-11]). Due to LiCl creating strong taste aversions across multiple species, it has a potential of being a successful deterrent method in reducing WTD crop depredations.

Before implementation of LiCl as a depredation deterrent in an open field setting can be utilized, key issues regarding toxicity and accumulation in deer tissues needs to be addressed. One challenge with using LiCl is that crop depredation season overlaps with hunting season in many parts of WTD habitat range (i.e., late summer through fall). As a result, it is important to first understand withdrawal factors in different types of animal tissues that may be consumed by humans. Information regarding LiCl and pharmacokinetic data in small ruminants to LiCl is lacking, which compelled the need for this study prior to using LiCl as a deterrent in an open field setting.

Although the eventual intent is to use LiCl as a deterrent on WTD, domestic sheep were used in this study as a surrogate due to logistics and cost. Domestic sheep have been used in a variety of feeding trials to test the efficacy and necessary dosage needed of LiCl to create an effective aversion [12-14]. Higher dosages often result in a greater aversion effect [15], but toxicity levels and tissue withdrawal times have yet to be reported. Thus, we addressed the following research questions:

1) What are the concentration levels of LiCl over time in differing body tissues at a realistic dose range that may be consumed by a deer in an open field setting based on LiCl withdrawal in the sheep model?

2) What is the maximum realistic dosage that could be consumed in a field setting and is this toxic for small ruminants?

Material and Methods

Animal use and protocols were approved by the Institutional Animal Care and Use Committee at the University of Idaho (IACUC-2017-70). The kinetics and toxicity of LiCl was tested using adult domestic sheep located at the University of Idaho Sheep Center in Moscow, Idaho. Suffolk, Targhee, and Targhee/Polypay crossbred sheep were used in this study, and all experiments were conducted at the University of Idaho Sheep Center. All animals were housed in an indoor/outdoor covered barn; feed and water were available ad libitum. Grain was provided once a day after biopsy samples had been collected.

Before each experiment began, sheep were weighed on an electric platform scale (+/- 1 kg), so that the appropriate dosage of LiCl for each experiment and animal could be determined on a per-kg of body weight basis. Subsequently, the appropriate amount of LiCl was dissolved in 240 mLs of cold water, and administered via drenching (i.e., orally inserting a lubricated stomach tube to the level of the abomasum). Control animals were drenched only with 240mLs of cold water minus the LiCl. Three experiments were conducted to analyze and compare lithium concentration in kidney, liver, and muscle tissues at a low (150 mg/kg) and high (450 mg/kg) dosage. In all experiments animals were visually observed for behavioral changes. All tissue samples were analyzed at the University of Idaho toxicology lab.

In the first experiment, eleven adult sheep were used to assess the kinetics and depletion of LiCl in muscle tissue at a 150mg LiCl/kg of body weight dosage, which was considered a low dose [7,9,16]. On the first experimental day each treated sheep (n = 8) was weighed and orally drenched with a single dose of LiCl [7,9]. Controls (n = 3) received a drench of water only. Muscle biopsy samples (~1g per sample) were extracted from the triceps and upper thigh muscle (biceps femoris, vastus lateralis, and semitendinosus) for lithium concentration analysis. Animals were physically restrained during muscle biopsy. Once restrained, the area of biopsy was surgically prepared, and a local anesthetic (Lidocaine 1%) was administered within the area to affect. The skin was incised, and a punch biopsy tool (Miltex® 6mm, Princeton, NJ.) was used to remove approximately 1g of muscle sample. Each 1g sample of muscle tissue was placed into a sterile, labeled Whirl-Pak® and frozen until analyses for lithium quantification.

It has been reported that the maximum level of lithium in blood occurs 4-8 hours post-ingestion [17,18], and animals were completely cleared of lithium after 240 hours [18]. Collection of muscle biopsy samples were made at 4, 8, 12, 24, 48, 96, 192, and 240 hours post LiCl ingestion to cover the entire time span between maximum peak levels and complete lithium metabolism.

In the second experiment, sixteen adult sheep were used to assess the kinetics and depletion time at 3x the recommended 150mg LiCl/kg body weight dosage. On the first day of the experiment each sheep was weighed and orally drenched with 450mg LiCl/kg body weight in cold water (n = 14) or just cold water (n = 2). Muscle biopsies were once again collected following the protocol previously described for experiment 1. If an animal died during the trial a necropsy was immediately conducted and 1g of kidney, liver, and muscle samples were each collected from the deceased animal. During the necropsy all other major organs and muscle groups were observed by a veterinarian to determine if the ingested LiCl had resulted in reportable necropsy findings.

In the third experiment, nine adult sheep were used to analyze lithium concentrations within kidney, liver, and muscle tissues, at time intervals surrounding the peak lithium concentration for low dose (150 mg/kg) ingestion. Based on the results from

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experiment 1, the peak lithium concentration occurred ~25 hours post-ingestion. On day one all sheep were weighed and orally received a single dosage of 150 mg LiCl/kg body weight mixed with 240 mL of cold water. Sheep were terminated using a penetrating cap and bolt system with exsanguination at intervals surrounding peak lithium concentration times. Group 1 (n = 3) were terminated 7 hours post LiCl ingestion, group 2 (n = 3) 24 hours post LiCl ingestion, and group 3 (n = 3) 96 hours post LiCl ingestion. Tissue samples (1g) from the kidney, liver, and muscle were collected from each animal. Field necropsies were conducted to assess any notable findings that may have been related to LiCl ingestion.

To measure lithium concentrations in tissues, a Perkin Elmber® Optima 8300 Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) was used. The ICP-OES equipment determined the lithium concentration within each tissue sample using plasma and a spectrometer (operating conditions; plasma: 15 L/min, auxiliary: 0.2 L/min, nebulizer: 0.73 L/min, flow rate: 1.5 mL/min, and wash rate: 2.00 mL/min) [19]. Equipment was calibrated with concentrated redistilled trace metal grade nitric acid and water [19]. Tissue samples were frozen until all samples for the trial had been collected and all samples were tested consecutively to avoid recalibrating equipment multiple times. All samples were analyzed on a wet weight basis, and 1g of tissue sample was added to, and mixed with, 3 mL trace metal grade nitric acid in a 10 mL test tube [19]. The tubes were then heated for 6 hours at 30 °C, then 1 hour at 70 °C, and finally for 8 hours at 120 °C [19]. The tubes were then cooled, vortexed, and centrifuged as needed to produce transparent solutions to prevent clogs from occurring within the nebulizer [19]. If particles remained within the solution a 0.45 Acrodisc filter was used to eliminate the remaining particles [19].

Data on the effects of LiCl on tissue lithium concentration were analyzed using a general linear model (GLM) procedure in SAS [20]. The model included the fixed effect tissue types (muscle, live, kidney), time and their two-way interaction with significance declared at $P < 0.05$. Using SAS GLM, the effect of low dose LiCl on muscle tissue concentration was also analyzed using GLM. The model included the effect of time.

Results and Discussion

Experiment 1:

Feeding low dose (150 mg/kg) of LiCl caused an increase ($P < 0.01$) in muscle Lithium at hours 4, 8, 12, 24, 48, and 96 as compared with baseline lithium concentrations. At hours 192 and 240 the muscle concentration of lithium was not different from baseline levels at ($P \leq 0.9$). Lithium concentration in muscle tissue peaked at (~24 hours post-ingestion (7.8 μg/g, Figure 1). Lithium concentrations declined thereafter and reached baseline level at 192 hours post-ingestion.

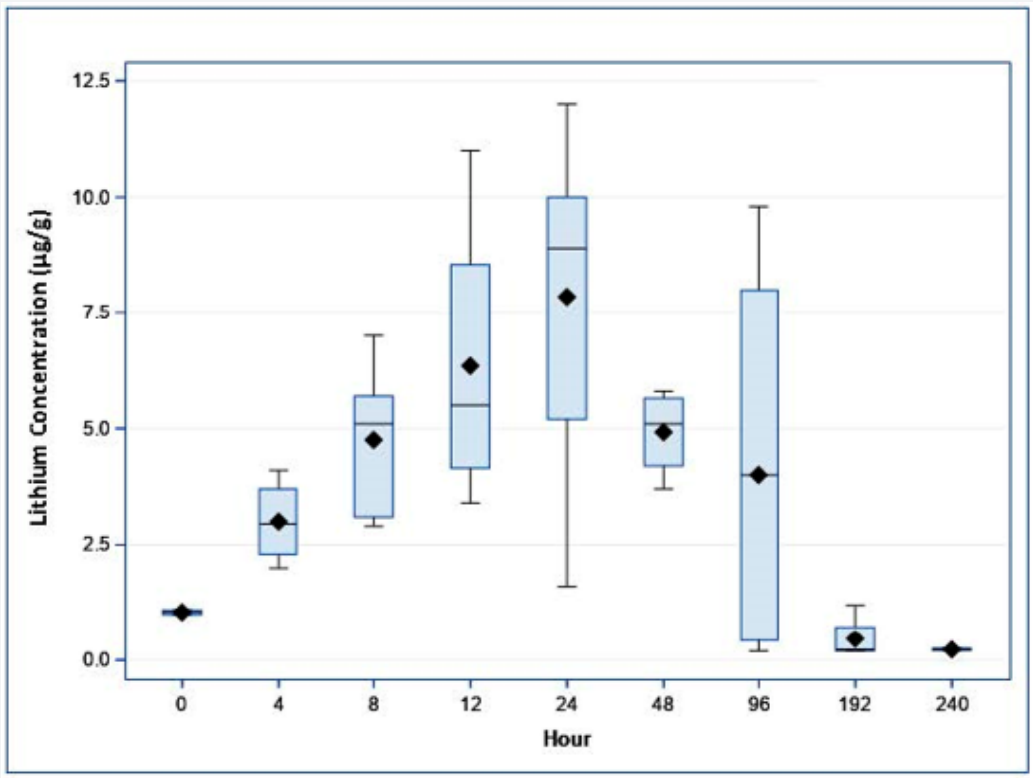

Figure 1: Effect of feeding low dose of lithium chloride (150 mg/kg body weight) on lithium concentration in muscle tissue of sheep (n = 11) over time.

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Experiment 2:

Based on the predicted lithium concentration in the muscle tissues after feeding a high dose of LiCl (450 mg/kg), lithium concentration peaked at approximately 100 hours post-ingestion (Figure 2). Lithium concentrations slowly declined thereafter, and never reached basal level by the end of the experiment (240 hours). A high mortality rate at this dosage was observed (12 out of 14 total treated, ~86% mortality) with most of the mortalities occurring after 73 hours post-ingestion. Approximate death times post ingestion of 450 mg/kg LiCl were as follows; 48h - 1 dead; 73h - 2 dead; 97h - 2 dead; 145h - 2 dead; 169h - 5 dead. Kidney, liver, and muscle tissue samples were obtained from all the animals that died. Behavioral observations were once again recorded for treated animals following LiCl ingestion. Treated animals appeared unaffected until 24 hours post-ingestion when they stopped eating, drinking, and moving around the containment area. Because of the high mortality rate, we were unable to construct a complete depletion curve for this concentration.

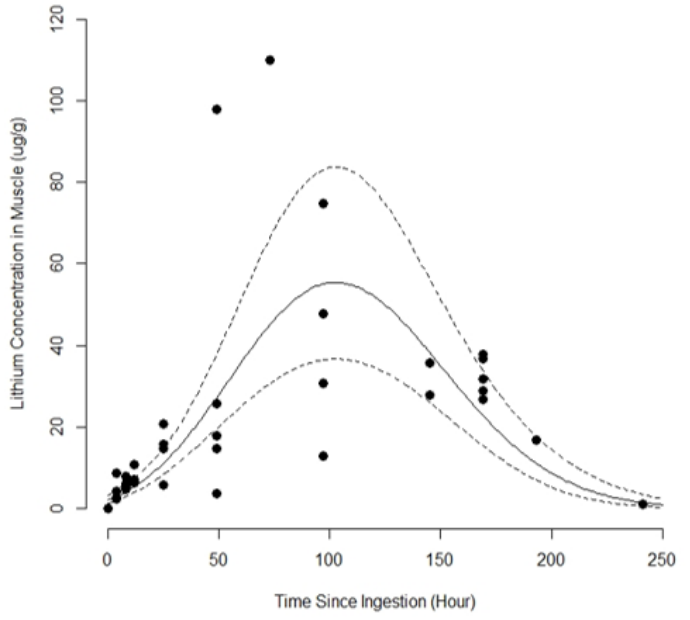

Figure 2: Predicted concentration of lithium in sheep muscle tissue after receiving a single dose of 450 mg /kg body weight of lithium chloride. Each data point represents a muscle sample from one individual and dashed lines represent a 90% confidence interval.

Experiment 3:

Mean lithium concentrations were different among muscle, kidney, and liver tissues within 7 hours after ingestion. Mean lithium concentrations in both liver and kidney tissues were greater than muscle at 7 and 24 hours post ingestion ($P < 0.01$; Table 1). There was no difference in lithium concentrations between the three tissues at 96 hours ($P > 0.05$) (Table 1). Mean lithium concentrations remained elevated ($P < 0.01$) in both liver and kidney in the first 24 hours after LiCl ingestion but returned to basal level at 96 hours after ingestion. Although, the overall concentration of lithium was less in muscle tissue, lithium concentrations remained elevated ($P < 0.01$) in muscle in the first 24 hours after LiCl ingestion and returned to basal level at 96 hours after ingestion (Table 1). There was not a tissue type by time interaction effect on Lithium concentrations.

Table 1: Effect of feeding low dose of LiCl (150 mg/kg body weight) of lithium chloride on lithium concentrations (ug/g of tissue)- in three different tissues over time in sheep.

TISSUE	HOUR		
	7	24	96
KIDNEY	18.6 ±2.9^{ax}	18.4 ±2.9^{ax}	2.1 ±2.9^{ay}
LIVER	14.3 ±2.9^{ax}	13.6 ±2.9^{ax}	1.04 ± 2.9^{ay}
MUSCLE	5.5 ±2.9^{bx}	5.5 ±2.9^{bx}	0.51 ±2.9^{ay}

^{a,b} Means with different superscripts within a column differ ($P< 0.05$)

^{x,y} Means with different superscripts within a row differ ($P<0.05$)

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A 150 mg LiCl/kg body weight was selected as the low dose based on previous reports of effectiveness in creating taste aversion in domestic sheep, cattle, and caribou [9,22,23]. Administering LiCl dosages greater than 300 mg/kg body weight is rare within the literature, and an exact toxic dosage in small ruminants has yet to be determined. The LiCl toxicity in mice occurred at a 600 mg LiCl/kg body weight [24], and to avoid exceeding the toxic threshold for ruminants the high dosage was reduced to 450 mg LiCl/kg body weight in the current study. However, with the multiple mortalities occurring post-ingestion the toxic threshold apparently was exceeded in the sheep indicating the LiCl toxic threshold maybe even less than 450 mg LiCl/kg body weight.

Maximum lithium concentration levels and withdrawal periods within muscle tissue may vary by dosage, and among animals to an extent. Most notably in experiment 1, one sheep at 96 hours had a greater Lithium concentration (9.8 μg/g) causing a larger variation in the data at that time point (Figure 1). Interestingly, mean muscle lithium concentration at 96 hours post ingestion was similar to the pre-ingestion concentration when the data from that sheep was not included in the data analysis. As indicated, at the low dosage, lithium concentration increased within muscle tissue starting with the first biopsy samples taken at 4 hours and continued to increase until the maximum concentration value occurred at approximately 24 hours. Following the peak, lithium concentrations quickly declined and returned to basal levels by 192 hours. (Figure 1) Although lithium in kidney and liver samples did not return to baseline concentrations from the low dose, at 96 hours post-ingestion, there was not a difference between lithium concentrations among the three different tissues suggesting most of the lithium had been metabolized and excreted leaving behind small residual amounts in all tissues. These results are similar to withdrawal periods of lithium in different types of excreta in sheep and goats previously reported [18].

In this study feed and water intake pre- and post-ingestion were not directly quantified, but treated animals were observed for behavioral changes. Although previous studies have observed signs of malaise (head droop and inactivity) [21] and an aversion to food post LiCl ingestion [7,15], we did not observe either of these behavior changes. Treated sheep were consuming provided alfalfa immediately following LiCl drenching and continued to do so throughout the study period. The low dose LiCl may not have been high enough to produce the taste aversion in sheep, and perhaps a greater dose of LiCl (200-300 mg/kg) may produce the taste aversion without producing the toxic effects seen at a LiCl dose of 450 mg/kg.

Only 2 of the 14 individuals that received high dosage (450 mg/kg BW) did not succumb to toxicity, and after 240 hours post-ingestion muscle tissue samples from the surviving animals had yet to reach basal level. Thus, a complete withdrawal time for a dosage of 450 mg LiCl/kg body weight was not determined. Despite supportive treatment for dehydration animals succumbed within a few hours of clinical signs. As indicated, majority of the mortalities occurred between 36- and 193-hours post-ingestion. Multiple symptoms of toxicity were observed including lack of appetite, malaise, severe dehydration, hypoglycemia, muscular tremors, increased heart rate, and extreme diarrhea. Necropsies were conducted by a veterinarian, and cause of death was determined for each deceased animals. In the absence of any additional post-mortem findings, it was determined that all animals had died due to LiCl overdose, and that 450 mg LiCl/kg body weight appears to be a lethal dose for small ruminants.

Although treated animals only received a single dosage of LiCl, the high-level potency of the chemical compound resulted in death as the physiological responses in the body, and especially the kidneys, were not able to process and excrete excess LiCl resulting in accumulation and eventual death [17,25]. Kidneys are the main processing organ that excretes LiCl [17,25], and excess lithium can disrupt the absorption of salt and water, often leading to polyuria [26]. If the kidneys are not able to process and excrete the ingested amount of lithium, excess amounts begin to accumulate in other tissues [17]. This is likely what occurred in the high dose trial and why our results show no difference in lithium concentrations among the tissue types. Once lithium levels in the kidney exceeded maximum intake, surplus lithium may have deposited in the liver and muscle tissues, resulting in all 3 tissue types containing high concentration levels. However, in the low dose, the highest lithium concentrations were in the kidneys, followed by liver, and the least amount of lithium concentration was in muscle tissue. This was likely because of the kidneys being able to function correctly with a manageable intake of lithium. Overdosing was not an issue as the amount of ingested lithium was processed and excreted by the kidneys without excess accumulation.

Conclusion

The muscle concentration of lithium at a low dose of 150 mg/kg body weight of LiCl administration reached baseline lithium in muscle tissues by 192 hours post-ingestion. Although, the withdrawal period within the liver and kidney for this dosage was not established, the lack of difference in lithium concentration between the three tissues (muscle, liver, kidney) at 96 hours suggests lithium concentrations of liver and kidney would not differ from baseline by 192 hours. Likewise, high dose withdrawal periods for all 3 tissue types were undetermined due to 450 mg LiCl/kg body weight being lethal for many sheep. It appeared that kidney tissues retain the greatest amount of lithium, followed by liver tissues, and lastly muscle tissues. It is important to acknowledge the toxic threshold for domestic sheep, and likely for other small ruminants, lies between 150-450 mg LiCl/kg body weight.

Although we didn't notice any instant food aversion after ingesting LiCl, this chemical could be a useful deterrent for lowering WTD crop destruction. Although sheep and deer have

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similar body sizes and rumen capacities, it should be noted that toxicity effects and withdrawal times for each tissue type may differ between species. Based on the results of the current study, a 192-hour withdrawal period in muscle tissue for a low dose of LiCl in domestic sheep may be taken into consideration; however, the analyses for other tissue types at low dosages and for all tissue types at high dosages were inconclusive, hence withdrawal period cannot be recommended.

Therefore, we suggest that before field implementation and human consumption of an animal that has ingested LiCl, more trials are necessary that include using LiCl at a dose range of 200 - 300 mg/kg for longer time periods, with larger samples sizes, and incorporate a variety of ruminant species.

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Conflicts of Interest

No potential conflict of interest was reported by the authors.

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