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Effect of Lithium Toxicity in Broiler

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ABSTRACT

Lithium concentration in surface and underground water, in some instances is higher than the standard level in places where lithium-rich brines and minerals occur, and in places where lithium batteries disposed of. This metal has numerous effects on human and other organisms, but there is no evidence about its effects on birds. For the first time we evaluated the effects of experimental lithium consumption in birds. The broiler chicks received daily 200 ppm lithium carbonate in their water, for 20 days and control group received water without lithium. At the end, blood samples collected for chemical analyses and the chickens were then euthanized and samples from brain, kidneys, gastrointestinal tract, heart and liver were collected for histopathological studies. Gross and microscopic lesions in organs were evaluated. Serum Glutamate Pyruvate Transaminase (SGPT), Serum Glutamate Oxaloacetate Transaminase (SGOT) and Uric acid also measured. The significant differences ($P<0.05$) between experimental group and control group were seen.
Keywords: Lithium, Toxicity, Bird, Histopathology, Clinical pathology

INTRODUCTION

Lithium is the lightest metal that has an atomic weight of seven and closely resembles sodium chemically. Compared with other alkali metals, it is less reactive than sodium and much less reactive than potassium. Lithium is generally found naturally in the aquatic and terrestrial environment but in small concentrations (Aral and Vecchio-Sadus, 2008) According to the Australian Capital Territory Environment Protection Regulation (EPA), lithium is listed as a pollutant that causes environmental harm in irrigation water supplies. Since lithium is found in natural brines and lakes, therefore it can be considered as a main source of lithium poisoning for birds, especially for wild birds. Another source of lithium poisoning impact to the environment, especially for pet birds, is spent because the consumers routinely dispose of batteries along with other garbage in the municipal solid waste. Because lithium has many industrial applications (Meshram et al., 2014) therefore, professional intoxications from the industrial applications are possible and environment can be considered as a source of pollution with lithium in such circumstances. This metal has numerous effects on human and other creatures (Haussmann et al., 2015; Moore and Committee, 1995; Phiel and Klein, 2001). Denoted that prolong administration of lithium resulted in significant inflammatory and hyperemic changes in kidneys, liver and brain in rats (Dimitrova et al., 2013) (Socaciu and Leucuta, 1999). There are limited evidences concerning the effects of this metal on different organs of birds. It has been reported that lithium can be accumulated in the organs of birds, and the rate of lithium accumulation is higher in the terrestrial birds than in the aquatic ones (Horai et al., 2007).

Since lithium is poorly absorbed across the skin, so dermal contact and inhalation are not likely to be significant routes of exposure to this metal and ingestion appears to be the most popular route of exposure. When ingested in excessive amounts, lithium primarily affects the gastrointestinal tract, central nervous system, liver and kidneys. Although it can be life threatening, but unfortunately, no studies have quantified the risk of lithium toxicity in birds. Most of the toxicity information has been obtained from the ingested lithium salts by humans (Hardman and Lant, 1996). Therefore, the present study investigated the pathological and clinic pathological effects of experimental lithium poisoning in broilers.

MATERIALS AND METHODS

Ethical approval

All experiments in this study were performed in accordance with the guidelines for animal research from the School of Veterinary Medicine, Shiraz University, Shiraz, Iran. Also, we used the recommendations of European Council Directive (2010/63/EU).

Experimental design

Twenty eight day old broiler from both sexes were purchased from a local hatchery and were kept at 32±1^{o}C, 40-50% humidity, controlled electrical heating batteries and at12/12h light-dark cycle. They were maintained as a flock and were provided with commercial diet and water ad-libitum. After 20 days they were randomly divided into two control (A) and experimental (B) groups, each having 14 chickens. Each group was then divided into two subgroups A1, A2 and B1, B2, each having 7 chickens. The chickens of the experimental group (B) received daily 200 ppm lithium carbonate in their water, for 20 days, which was calculated on the base of the producer recommendation and our previous experiences.

The animals of the control group received water without lithium. At the end of the experiment, blood samples were collected for chemical analyses of the Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyrovic Transaminase (SGPT) enzymes (Reitman and Frankel, 1957) and uric acid. The animals were then euthanized and all organs were carefully examined and samples from brain, kidneys, gastrointestinal tract, heart and liver were collected for histopathological examination. After fixation in 10% neutral buffered formalin, the tissue samples were washed, dehydrated by graded ethanol, cleared, embedded in paraffin wax, sectioned at 4-5 µm, stained with haematoxylin and eosin and examined by a light microscope (Olympus, Tokyo, Japan).

Statistical analysis

Statistical analysis of the blood SGOT, SGPT and uric acid between the lithium treated and control groups was done by the independent sample *t-test*. Data were analyzed by SPSS 21 using one-way ANOVA.

RESULTS

The chickens of the control group remained healthy and active throughout the experiment, but those in the experimental group were lethargic and drowsy and some of them started to perish about 10-12 days after receiving lithium and after necropsy, the hydropericard lesions were seen. No pathological changes were noticed on gross and microscopic examinations of the organs of chickens of the control group; however, the cell lining in the tubules of the kidneys of the chickens in the experimental group showed degenerative and necrotic changes. The epithelium of proximal convoluted tubules was vacuolated and, in some sections, showed necrotic and sloughing changes (Figure. a). Proteinaceous casts and cellular debris were present in some of the degenerated or necrotic tubules (Figure b and c). The basement membrane, epithelial cells and lumen of some of the necrotic tubules showed mineralization (Figure a).

The glomeruli showed hyperemia, glomerular atrophy and dilatation of the urinary spaces. The blood vessels were hyperemic and foci of hemorrhages were evident in the interstitial tissue of these organs (Figure. b). The hepatocytes of the experimental animals showed different extents of fatty infiltration and in some instances focal necrosis (Figure d). The portal area showed chronic portal hepatitis and were infiltrated with lymphocytes, plasma cells and macrophages (Figure e and f). The blood vessels were hyperemic and multifocal or diffused hemorrhages were seen in the parenchyma of the liver of the experimental animals. The white matter of cerebrum showed cellular vacuolation and spongiosis (Figure g and h). The submucosa and lamina propria of different parts of the gastrointestinal tract were infiltrated by lymphocytes, plasma cells and macrophages. Hyperemia and hemorrhages were other consistent changes in the submucosa and lamina propria of intestine.

The Serum Glutamate Pyruvate Transaminase (SGPT) and Uric acid levels between the two groups showed significant differences ($P<0.05$), but there was no significant difference ($P>0.05$) between the Serum Glutamate Oxaloacetate Transaminase (SGOT) values among the groups (Table 1).

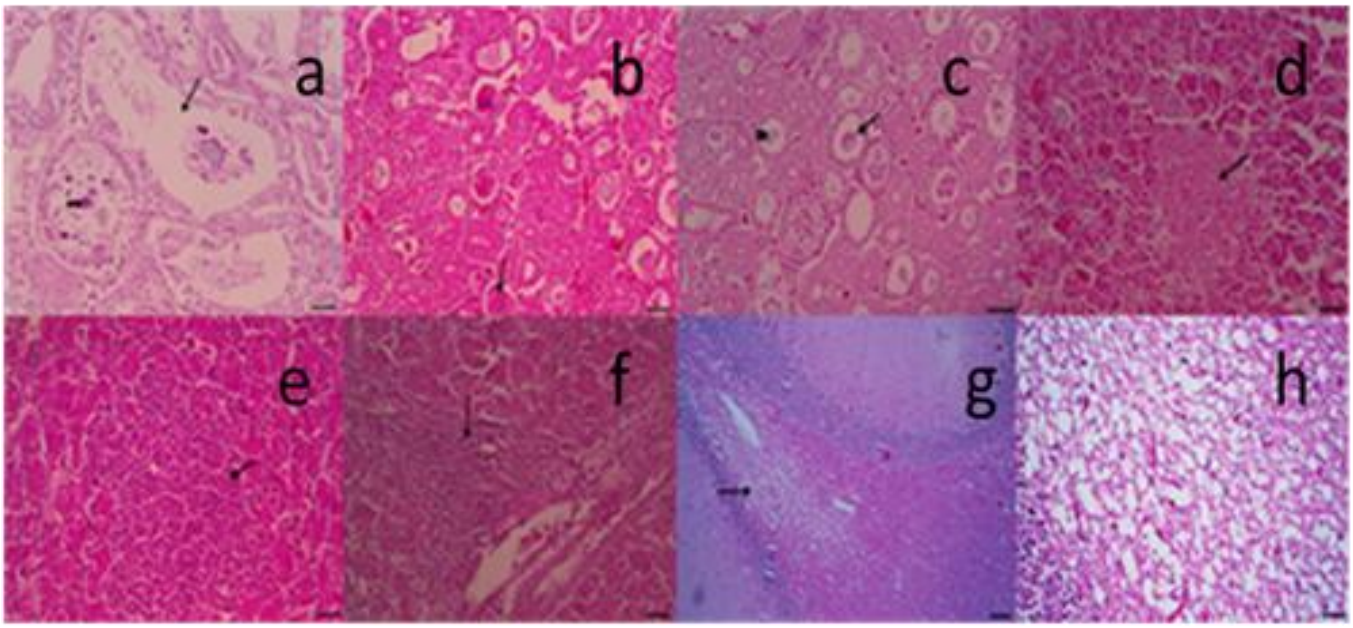

Figure 1. Microscopic lesions of kidney, liver and brain in broilers under lithium toxicity

Mineralization and vacuolation of proximal convoluted tubules (**Figure a**; H & E, scale bar=200 μm), hyperemia, glomerular atrophy and dilatation of the urinary spaces (**Figure b**; H & E, scale bar=250 μm), Proteinaceous casts and cellular debris in some of the degenerated or necrotic tubules (**Figure b** and **c**; H & E, scale bar=250 μm), fatty infiltration and focal necrosis (**Figure d**; H & E, scale bar=250 μm), infiltration of lymphocytes, plasma cells and macrophages in portal area (**Figure e** and **f**; H & E, scale bar=250 μm) and cellular vaccuolation and spongiosis of cerebrum (**Figure g**; H & E, scale bar=370 μm and **Figure h**; H & E, ×40 scale bar=105 μm).

Table 1. Means and standard deviations of serum activities of Serum Glutamate Pyruvate Transaminase (SGPT), Glutamate Oxaloacetate Transaminase (SGOT) and uric acid of broilers at the end of experiment

Group	SGPT (U/L)	SGOT (U/mL)	Uric acid (mg/dL)
Control	5.849±1.727a*	274.09±52.48b	5.2±1.18a
Lithium	14.103±383b	298.95±49.11b	9.5±2.19c

*Different small letters in the same row indicate significant difference among groups (P<0.05).

DISCUSSION

Normally lithium is not present in significant amounts in body fluids and doesn't appear to be an essential element for life (Shahzad et al., 2017; Léonard et al., 1995). Lithium can substitute for sodium or potassium, thus providing a pathway for lithium entry into cell cytoplasm (Timmer and Sands, 1999). The pathways for transporting lithium out of cells are more limited, resulting in lithium accumulating intracellularly (Timmer and Sands, 1999). When lithium is ingested in excessive amounts, it primarily affects the gastrointestinal (GI) tract, central nervous system and kidneys. Lithium is well absorbed from the GI tract (Casarett and Doull, 1975; Ellenhorn and Barceloux, 1997; Schrauzer, 2002). It primarily affects the GI tract. Hyperemia and hemorrhages with infiltration of mononuclear cells in the sub-mucosa and lamina propria of the GI organs in the experimental chickens of the present study indicate that lithium is harmful and results in consistent lesions in GI organs. Lithium is excreted almost entirely by the kidneys (McCartney et al., 2014). Lithium is freely filtered by the glomeruli since it is not bound to serum proteins and in the proximal tubules it is handled similar to sodium (McCartney et al., 2014). Approximately 80% of the lithium that is filtered by the glomeruli is reabsorbed; the remainder is excreted in the urine. Of the filtered lithium 60% is reabsorbed in the proximal tubules and 20% between the loop of Henle and the collecting ducts (Okusa and Crystal, 1994). The nephrotoxic effects of lithium have been divided into three main categories: nephrogenic diabetes insipidus, acute intoxication, and chronic renal disease (Markowitz et al., 2000). Nephrogenic diabetes insipidus (NDI) is the most

common renal side effect of lithium therapy. Patients present with polyuria and polydipsia due to a urinary concentrating defect that can lead to significant volume depletion. Acute lithium intoxication due to lithium overdose includes acute renal failure and volume depletion and is mostly seen in long-term lithium therapy (Ott et al., 2016). The predominant form of chronic renal disease associated with lithium therapy is a chronic tubulo-interstitial nephropathy (CTIN) that is heralded by the insidious development of renal insufficiency, often in the setting of chronic NDI (Hasegawa et al., 2017). Biopsy findings in patients with lithium-induced CTIN include tubular atrophy and interstitial fibrosis, typically out of proportion to the degree of glomerulo-sclerosis or vascular disease (Aurell et al., 1981; Hestbech et al., 1977; Hetmar et al., 1987; Jørgensen et al., 1984). Majority of studies have shown infrequent and relatively, mild renal insufficiency attributable to lithium therapy (Gitlin, 2016). Much less has been reported about the potential glomerular toxicity of lithium and this particular aspect has been underappreciated. Walker et al. reported occurrence of mild nephrotoxicity in association with lithium therapy and the New Zealand White rabbits treated with lithium developed a pattern of CTIN with tubular cysts that was virtually identical to the human disease, with progressive renal insufficiency (Walker et al., 1986) . In another experiment the male wistar rats treated with lithium developed nephrogenic diabetes insipidus and a distal tubulopathy marked by tubular dilatation (Zardawi et al., 2013). Lithium salts induce renal toxicological symptoms such as sclerotic glomeruli and tubular damage (Chmielnicka and Nasiadek, 2003). In their experiment the inability of the nephrons to concentrate urine during lithium treatment was correlated to the occurrence of histological changes. Chmielnicke and Nasiadeks (2003) showed that oral administration of lithium carbonate induced renal toxicity as well as injurious symptoms which were found to be directly related to the dose effect and to the concentration of this metal in serum and urine in rat (Chmielnicka and Nasiadek, 2003). Walker et al. also reported morphological changes corresponding with Li-NDI induce tubulo-interstitial fibrosis, vacuolation and swelling of the cytoplasm, as well as accumulation of glycogen-like PAS positive material in tubular epithelial cells (Walker et al., 1986). In some instances tubular atrophy and glomerular sclerosis have been observed. The above results were almost comparable to our findings that showed vacuolation and swelling of the cytoplasm resulting in tubular degeneration and necrosis. In addition, in the present study, there was a significant increase ($P<0.05$) in the serum level of uric acid as a marker for renal function. The principal site of uric acid secretion appears to be in the proximal tubules of the cortical nephrons (Thrall et al., 2012) where most portion of the lithium is reabsorbed. Uric acid is the major end product of nitrogen metabolism in birds and evaluation of the serum or plasma uric acid concentration has been widely used in the detection of kidney diseases in birds (Thrall et al., 2012). Liver is the main site of metabolization of xenobiotics. Histopathologic examination of the liver in the lithium group revealed multifocal necrosis and infiltration of inflammatory cells, mainly lymphocytes, plasma cell and macrophages in the portal tracts and hepatic parenchyma. Hepatocellular fatty degeneration, hemorrhages and hyperemia were evident in some of the experimental animals. These findings were comparable to those of Sharif et al. who showed focal infiltration of mononuclear cell infiltration with hemorrhagic areas in the paranchyma and portal tracts in the animals which were naturally exposed to lithium poisoning (Sharif et al., 2011). Measurement of the serum levels of SGOT/AST and SGPT/ALT showed a significant ($P<0.05$) increase in SGPT level and slight but not significant changes in SGOT, from which the hepatic dysfunction can be demonstrated. However, the aminotransferase level has also been recently found in skeletal muscle, heart muscle, brain and kidneys, which makes interpretation of increased plasma AST activity challenging (Thrall et al., 2012). But enhanced serum concentration of the SGPT and SGOT in the lithium group is probably suggestive of liver and intestinal damage as suggested by Sinclair et.al. (1984). Another important organ that can be affected in lithium poisoning is the central nervous system and the toxic effects of lithium salts on the central nervous system have been described for nearly a century (Kjølholt et al., 2003). Persistent neurological deficits have been reported in cases of lithium carbonate intoxication (Nagaraja et al., 1987; Niethammer and Ford, 2007). Previous findings showed that lithium absorption by the central nervous system is not uniform; it may be remain in the plasma and high level in the brain at the therapeutic level (Won and Kim, 2017). The symptoms of lithium neurotoxicity at therapeutic levels are mostly neurological and differ only in the extent of injury from those described in cases of toxicity with high levels. The clinical signs and lesions can occur in both acute and chronic therapy; the most common presentation is one of an encephalopathy. Rarely focal neurological disturbances, motor disturbances, psychotic episodes and specific cognitive deficits may occur (Bell et al., 1993; Sheean, 1990; Verdoux and Bourgeois, 1990). These findings suggest that presence of serum lithium concentrations above the therapeutic levels is not mandatory and that lithium neurotoxicity mechanism seems to be a multifactorial entity. Comparable to the

previous studies, we observed some degenerative lesions in the brain that mainly contained white matter spongiosis and cellular vacuolation. Association between lithium toxicity and cerebral degeneration has similarly been suggested by neuropathological studies which have demonstrated spongiform changes of the white matter and changes in the dentate nucleus. The heart didn't show any lesions. There is no evidence about pathological changes of heart subsequent to lithium toxicity, but some clinical signs have previously been reported. It has been indicated that intravenous lithium salts depressed the heart's action and caused a fall in blood pressure in animals (Good, 1903). The dose of lithium salts necessary to stop the heart has been found to be much larger than the dose of potassium salts necessary to produce the same effect. Leonard et al. indicated that no information on the possible carcinogenic effects of lithium compounds was available. However, this seems unlikely in view of the known biological mechanisms of action of lithium (Mohandas and Rajmohan, 2007). In general, we can say the type and severity of lesions depends on the level of accumulation of this chemical pollutant, that is dependent on the diet, the intensity of exposure, the time spent in a habitat, and various kinds of physiological dysfunctions (Bos et al., 2012; Esselink et al., 1995), and each one can permute the severity of toxicity and consequent lesions.

DECLARATIONS

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Author`s contributions

The authors declare that there is no conflict of interest. R.R., I.S. and M.A. contributed to the conception, design and interpretation of data. A.O, M.S, H.R. was also involved in the collection of data, and drafting of the manuscript. All authors check and approved the final manuscript.

Competing interests

None of the authors of this paper have a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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