LITHIUM TOXICITY IN TWO DOGS

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ABSTRACT

Two cases of lithium toxicity are reported on in dogs having had lithium hypochlorite chlorinated water as their sole source of drinking water. Clinical signs in one dog included polyuria, polydipsia, loss of body mass, dehydration, diarrhoea and general weakness and in the other case, polyuria, polydipsia, loss of body mass and seizures. Withdrawal of the water resulted in complete recovery.

Key words: Toxicity, lithium, dog, polyuria, polydipsia, seizures, muscle tremors

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INTRODUCTION

Lithium carbonate is used in man to treat a multitude of psychiatric disorders including manic-depressive conditions. Lithium treatment has resulted in the reversal of the long-term prognosis of manic-depressives, effecting total rehabilitation in most cases[12]. The use of lithium to stimulate granulocytopoiesis in humans, has recently been reviewed[2]. In dogs, lithium has been used to stimulate erythropoiesis in aplastic anaemia due to oestrogen toxicity[7 9] and other disorders of erythropoiesis[10]. Cyclic haematopoiesis of grey collies has been controlled with lithium therapy[6 9].

Apart from the medicinal uses of lithium, chlorine and lithium in the form of lithium hypochlorite, form a highly soluble chlorine granule which is used in swimming pool chlorination. Lithium chloride was also used as a table salt substitute in the 1940's, resulting in numerous cases of human toxicity[4 12].

This case report documents lithium toxicity seen in 2 dogs whose sole source of drinking water was swimming pool water, chlorinated with a lithium hypochlorite compound.

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CASE REPORT

Two dogs belonging to the same owner were presented for clinical investigation. Both dogs were fed a normal balanced diet, but the sole source of drinking water for several months, had been the swimming pool.

Case 1:

A 30-month-old pure-bred German Shepherd bitch was presented with a history of severe polyuria, polydipsia, a loss of body mass, intermittent diarrhoea, muscle tremors in the hindquarters and general weakness.

Faecal flotation was positive for *Ancylostoma* sp eggs, and initial laboratory blood tests showed no obvious abnormalities. Urinalysis consistently showed a urine specific gravity (SG) of 1,001. The dog was discharged after deworming with pyrantel pamoate (5mg kg^{-1} Nemex liquid, Pfizer) with a view to performing water deprivation and vasopressin concentration tests at a later stage.

Three weeks later, the animal presented with severe diarrhoea and dehydration. Urine SG was 1,006 in the presence of clinical dehydration. The haematology and blood chemistry tests were repeated with the following abnormalities (normal values for the laboratory used in parentheses): albumin 44g ℓ^{-1} (29-33g ℓ^{-1}), serum potassium 6,5 mmol ℓ^{-1} (3,7 - 5,8 mmol ℓ^{-1}), packed cell volume ,59 (,37-,55), and absolute lymphocyte count 300 x 10^9 ℓ^{-1} (1000 — 4800 x 10^9 ℓ^{-1}). Blood glucose, serum cholesterol, serum alanine transferase, serum alkaline phosphatase, serum creatinine, serum urea, serum calcium, serum inorganic phosphorus, serum sodium and serum chloride concentrations were all within normal limits.

Treatment included intravenous fluid therapy with a polyionic electrolyte solution (Ringers lactate, Labethica) (20 ml kg^{-1}), trimethoprim-sulphadiazine (Tribrissen 24%, Coopers Animal Health) (30 mg kg^{-1}) and prednisolone (Prednisolone, Centaur) (1 mg kg^{-1}). After 3 d of this therapy, the dog started eating but was still clinically dehydrated with a urine SG of 1,015. As serum potassium was still elevated (6,1 mmol ℓ^{-1}), fluorocortisone (Florinef, Bristol-Meyers Squibb) (0,2 mg d^{-1}) was added to the regimen.

At this stage it transpired that the swimming pool water, which was the only souce of drinking water, had been chlorinated with soluble lithium hypochlorite granules (Solchlor, AECI Explosives and Chemicals Limited). This had been the sole method of chlorination for 3 months. Serum lithium levels were determined, using an atomic absorption spectrophotometer (Model 5000 Perkin-Elmer Corp., Norwalk, Conn. USA), and were found to be very high (1,5 mmol ℓ^{-1}). The serum of 2 healthy control dogs showed lithium concentrations of 0,03 mmol ℓ^{-1} and 0,04 mmol ℓ^{-1}. The swimming pool water lithium level was 29 ppm compared to zero in 2 control swimming pools chlorinated with sodium hypochlorite granules. As the dog had not been exposed to lithium medication, it was assumed that the swimming pool water was the source of the abnormal lithium levels detected in the serum.

After 3 d of treatment with fluorocortisone, the serum potassium returned to normal (4,8 mmol ℓ^{-1}) and the dog was discharged. The owner was instructed to prevent the dog from drinking the pool water. The mineralocorticoid therapy was discontinued after 10 d.

Serum lithium concentration 2 months later, had decreased to 0,13 mmol ℓ^{-1} with serum sodium and potassium concentrations within the normal range. The dog was healthy and showed no further signs of weakness or polyuria. The urine SG returned to within normal limits 3 mon-

ths after the source of lithium had been withdrawn. Subsequent faecal examinations were negative for helminth eggs.

Case 2:
A 2-year-old sterilised Labrador crossbreed bitch was presented with a history of polyuria, polydipsia and loss in body mass of several months duration. She had also experienced 2 seizures during this period. Prior haematological and blood chemistry tests performed by the referring veterinarian, had detected no abnormalities. Urine SG was consistently lower than 1,010. A renal biopsy had been performed and no histopathological abnormalities had been found.

On initial examination, the patient showed no obvious clinical abnormalities. The urine SG was consistently 1,005. Serum sodium and potassium levels were within the normal range. A faecal flotation was negative for helminth ova. Because the dog belonged to the same owner as did Case 1, and as it also had lithium hypochlorite treated water as its sole source of drinking water, serum lithium concentration was determined and found to be 1,1 mmol ℓ^{-1}. A diagnosis of chronic lithium intoxication was made and therapy consisted of providing the dog with alternative drinking water.

After 2 months, the serum lithium concentration was 0,41 mmol ℓ^{-1}, urine SG was 1,019 and the dog showed none of the previous clinical signs. Seizures have not been reported in the 3 years since the lithium treated water was withdrawn as the source of drinking water.

DISCUSSION

The methods by which lithium achieves its therapeutic effects are complex. In the body, lithium exists as a small ion with a positive charge[4]. Lithium competes with sodium, potassium, magnesium and phosphorus, and displaces these minerals from bone and other intracellular sites[12]. The half-life of lithium in man and dogs is approximately 29 h[12] and 22 h[8] respectively. Muscle and bone act as reservoirs for lithium, due to sequestration in these sites[3].

Lithium is excreted unchanged in the urine, and 80% of excreted lithium is reabsorbed in the proximal and distal renal tubules[2 4 12].

Neutrophilia is induced by lithium, following the stimulation of a granulopoietin[1 6], leading to increased neutrophil output. Although lithium has been used in aplastic anaemia therapy[9], in vitro experiments with human bone marrow show that lithium decreases the generation of erythrocytes[1]. Lithium might also inhibit a population of suppressor T-lymphocytes which usually limits haematopoiesis[1].

Lithium has a narrow therapeutic index, and toxicity can arise even at levels within the normal therapeutic range[12]. Lithium poisoning can arise after a single massive overdose, or after cumulative overdose following low dose ingestion. Decreased lithium excretion due to renal disease in a patient on therapeutic doses may also cause toxicity as may decreased sodium or water intake[4 12].

Most cases of lithium intoxication in man occur with long-duration lithium therapy, and small increases in dosage may induce toxicity[12]. The typical signs of lithium intoxication in man include central nervous system manifestations, gastrointestinal signs, cardiovascular signs, neutrophilia, lymphopaenia, skin lesions and renal signs[4 12].

The central nervous signs described in human patients include initial fine hand tremors, followed by spastic or choreiform muscle tremors, parkinsonism, anxiety, seizures, delirium and coma[12]. In the more common chronic cases of human intoxication, nervous signs develop gradually, starting with fine hand tremors and progressing to severe, protracted impairment of consciousness[4]. Lithium affects nerve excitation, synaptic transmission and neuronal metabolism in many ways. The lithium ions substitute for sodium ions, leading to altered electrical conductivity and increasing the excitability of the nerve due to the raised number of positive ions in the cell[4]. The inhibition of adenylate cyclase, which decreases cylic AMP production, is an important pharmacologic and toxicologic mechanism[4 12]. Cyclic AMP acts as a "second messenger" for a multitude of hormones, including the catecholamines, adrenocorticotrophic hormone, vasopressin, parathyroid hormone, calcitonin, glucagon, gastrin and others[5]. Serotonin release in the hippocampus is stimulated by chronic lithium therapy[12], and the release and re-uptake of noradrenalin at nerve endings is inhibited[12]. The beneficial effects of lithium in the treatment of mental disease are probably due to these varied neuroendocrine effects. During lithium intoxication, the lithium ion may also lower the seizure threshold[4]. Case 1 presented with muscle tremors and Case 2 showed seizures.

Severe gastroenteritis has been seen in acute human lithium overdoses[12]. Signs which have been recorded include nausea, vomition and diarrhoea. The exact pathophysiological mechanisms by which lithium causes these signs are not well defined, and several mechanisms have been implicated. Lithium enters the mucosal cell with sodium, but the sodium ions are then actively pumped out whilst lithium remains in the cell[4]. Instead of sodium moving along its concentration gradient from the intestinal lumen into the cell, it is then retained in the gut. This leads to decreased absorption of glucose because glucose usually moves along the same concentration gradient as sodium[5], and an osmotic diarrhoea results. Lithium may also cause gastrointestinal signs due to direct irritation of the gastrointestinal mucosa[12], or by interference with gastrin[4]. The diarrhoea in Case 1 could also have been caused by concurrent hookworm infestation.

The electrocardiographic signs which have been recorded in humans, include T-wave inversion and S-T segment depression. These changes are due to lithium ion interaction with intramyocardial sodium and potassium, and are reversible[4]. Electrocardiographic examination was not performed on the 2 cases seen. Thoracic auscultation revealed no obvious cardiac problems.

Neither of the 2 patients showed the neutrophilia which has been reported in human cases of lithium toxicity. The severe lymphopaenia (lymphocyte count of 300 x 10^{-9} ℓ^{-1}) seen in Case 1, is consistent with human cases of lithium poisoning[12].

Skin lesions which have been recorded in human cases include acne, exacerbation of psoriasis, rashes and alopecia[12]. The 2 canine cases described, showed no skin lesions.

Lithium has multiple effects on the kidneys. The lithium ion competes with sodium and potassium at the renal tubular level, and may also directly decrease the normal hypothalamic thirst response to dehydration[12]. The main renal effect is nephrogenic diabetes insipidus, possibly caused by the inhibition of adenylate cyclase[4 12]. In dogs, the mechanism may involve morphologic changes in the distal tubules with less effect on the renal adenylate cyclase[3]. Under normal circumstances, water intake is greater than the water needs of the body. During lithium intoxication, water intake is decreased and dehydration develops, leading to decreased renal excretion of lithium. The resultant increased serum lithium concentration causes further inhibition of water absorption in the kidneys, exaggerating the dehydration.

Both dogs presented with severe polydipsia, polyuria and decreased urine specific gravity. Case 1 also showed severe dehydration in the presence of hyposthenuria. Polyuria and polydipsia are regarded as early signs of lithium poisoning in man[12]. Water deprivation and vasopressin tests were not performed to confirm the presence of the suspected nephrogenic diabetes insipidus. The increased serum potassium seen in Case 1, is not a sign of lithium toxicity in man,

but lithium therapy has been reported as a possible cause of hyperkalaemia in dogs[11].

The serum lithium concentrations seen in these dogs were at the upper human therapeutic range (0,6 mmol ℓ^{-1} to 1,6 mmol ℓ^{-1}) of serum lithium at the laboratory used (I J Van Wyk 1990 Du Boisson and Partners, Sandton, personal communication). Levels of 1,5 mmol ℓ^{-1} have been associated with tremors, weakness, ataxia, agitation, fascicular muscle twitching, vomition and diarrhoea in man[4 12].

Recommended therapy for lithium intoxication in human patients, includes hospitalisation to control seizures, withdrawal of the drug, saline infusion to restore fluid and electrolyte balance, forced diuresis and haemodialysis[4 12]. It is worth noting that permanent renal and neurological defects have been noted in about 10% of human lithium poisoning cases[12].

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