Lithium Nephrotoxicity: A Review*

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ABSTRACT

Lithium, a group I alkali metal, is widely used for treatment of manic-depressive psychosis. A number of toxic side effects have been reported, among which the most common ones are nephrogenic diabetes insipidus, distal tubular acidosis, and impairment of renal concentrating ability. The proposed mechanisms in the literature of these renal complications of lithium salt therapy are reviewed. None of the proposed mechanisms can be definitively established. Recently reported observations contradict the causative role of lithium in the pathogenesis of renal complications. More careful selection of control subjects is required for further investigation of the nephrotoxic effects of lithium.

Introduction

Lithium has no known vital function in man. Biological interest in this element developed following its introduction for the treatment of various hyperactive states12 in 1949. During subsequent clinical trials performed primarily in Scandinavia, Great Britain and Switzerland, the medicinal use of lithium in the treatment of manic-depressive psychosis was established.25,61,65 Lithium carbonate is used in manic-depressive disease in the therapy of both the acute manic episodes and for the prevention of recurrent psychosis.49 The medical literature dealing with the therapeutic use of lithium has been reviewed recently.6,8,9,10,24,37,38,63 These reviews have stressed the broad range of biological and pharmacological properties of lithium. They also reveal our lack of knowledge about the mechanism of lithium action and indicate the necessity for further research efforts.

Chemistry and Biochemistry of Lithium

Lithium is a group I alkali metal with an atomic number of 3 and an atomic weight of 6.94 and which is widely distributed throughout the geosphere and biosphere. The commonality of some physical and chemical properties of the alkali metals, such as water solubility and high ioniza-
tion potential, with the biologically important sodium and potassium elements, accounts for many of the biologic characteristics of lithium. However, owing to its small ionic radius, it has a significantly higher surface charge density than its congeners. This accounts for some of the anomalous properties of lithium when compared with its congeners, such as its high degree of solvation in solution, the high lattice energy of its salts with small anions, and its relative unstable salts with large anions.\textsuperscript{14} The diagonal relationship of the periodic table identifies similar properties for lithium, magnesium, and calcium. These three elements have very similar atomic radius, hydrated radius, electronegativity, and polarizing power.\textsuperscript{33} These characteristics of lithium make it a unique element. Similar relationships of lithium to its congeners, magnesium and calcium, also exist with regard to their biochemical properties.\textsuperscript{8}

Many enzymes are known to be activated or inhibited by sodium, potassium, calcium, and magnesium. Owing to their similarities in physico-chemical properties, lithium affects a large number of metal dependent enzymes. For example, magnesium is a required cofactor for many enzymatic activities.\textsuperscript{30} The magnesium-dependent enzymes affected by lithium include: aconitase, succinic dehydrogenase, pyruvate kinase, hexokinase, glucokinase, enolase, fructose 1, 6-diphosphatase, tyrosine aminotransferase, tryptophan oxygenase, alkaline phosphatase, acid phosphatase, aryl sulfatase, cholinesterase, acetylcholinesterase, ribonucleic acid synthetase, deoxyribonucleic acid polymerase, etc.\textsuperscript{6,8,38} The inhibitory effect of lithium on these enzymes has been demonstrated in many cases both in \textit{in vitro} and \textit{in vivo} systems.\textsuperscript{8}

It has also been shown that lithium alters the activities of several enzymes associated with the biosynthesis and metabolism of biogenic amines.\textsuperscript{53}

One important enzyme system affected by lithium is the adenylate cyclase-cyclic adenosine monophosphate system. Owing to the involvement of this system in mediating the cellular effects of several hormones and neurotransmitters, the influence of lithium is manifested in many physiological events.\textsuperscript{58}

Another important property of lithium is its effect on membrane adenosine triphosphatase (ATPase). Lithium has been reported to cause stimulation of the magnesium activated ATPase.\textsuperscript{22} Glen has proposed that lithium, when present as an external cation, exhibits potassium-like stimulation and, when present as an internal cation, competes with sodium for membrane ATPase.\textsuperscript{23} Since ATPases have specific orientation within membranes, correlations with the different effects of lithium dependent on its intracellular or extracellular localization exist and, thus, may be of importance with regard to lithium action in nerve cells.\textsuperscript{21}

Lithium also affects other subcellular systems such as microsomes and mitochondria.\textsuperscript{6} In mitochondria, lithium inhibits potassium uptake and stimulates substrate-linked respiration to a greater extent than potassium.\textsuperscript{26,44} However, there is no effect on the uptake of calcium by mitochondria.\textsuperscript{74}

**Metabolism of Lithium**

Lithium occurs in all tissues and fluids of the body in low concentrations, and some evidence has identified low concentrations in brain, thyroid, and ovaries.\textsuperscript{77} The naturally-occurring concentration of lithium in human tissues is not well established.\textsuperscript{75}

Metabolic behavior of lithium at physiological conditions is not known. Medicinal lithium salts are reported to be efficiently absorbed.\textsuperscript{56,66,70} Peak absorption of an oral dose occurs within 30 minutes. Serum concentrations achieve plateau values in 12 to 24 hours. Absorbed lithium is largely excreted by the renal route. About \( \frac{1}{3} \) to \( \frac{2}{3} \) of a single oral dose is cleared in the urine during the first six to 12 hours, with slow excretion of the remainder over 10 to 14 days. If a constant
therapeutic daily dose is administered, steady-state blood levels (about 1.0 mEq per liter) are achieved within five to six days accompanied by a rapid rise in urinary lithium excretion. When discontinued, lithium is excreted rapidly for the first five to six days and more slowly over the next 10 to 14 days.70

Lithium is not bound to plasma proteins and moves freely across semi-permeable membranes.68 It is freely filtered through the glomerulus of the kidney and 80 percent of the filtered element is reabsorbed along with sodium in the proximal tubule.73 Both these ions are reabsorbed against electrical and concentration gradients.70 Investigators recently reported that a substantial amount of lithium is also reabsorbed in the loop of Henle.29,35 In the more distal portions of the nephron, sodium and lithium are handled quite differently. Lithium reabsorption does not occur in the distal tubule or collecting duct while approximately 20 percent of the filtered sodium is reabsorbed in the distal tubule.9

Clinical Use and Nephrotoxicity of Lithium

The standard dose of lithium used in acute mania is usually 600 mg three times a day. Because of its toxic side effects, serum lithium levels should be monitored closely; when levels reach 1.0 mEq per liter the dosage is reduced to 300 mg three to four times daily. For prophylaxis against depression, the serum concentration should be kept between 0.5 and 1.0 mEq per liter until the end of the attack.57 Toxic manifestations usually begin when serum concentration approaches 2 mEq per liter,68 but toxic symptoms have been reported from concentrations as low as 1.6 mEq per liter.1

Acute lithium toxicity usually presents with a prodromal period in which drowsiness, dysarthria, nausea, and vomiting are the major symptoms. Later, central nervous system symptoms predominate and include increased muscle tone with coarse tremors, impaired consciousness, and asymmetric clonic contractions of large muscle groups.88 Side effects from long term administration have included hypothyroidism with or without goiter64,67 and increased glucose tolerance.76

Clinically, the most commonly reported renal complications of lithium treatment have been polyuria, polydipsia, initial sodium diuresis, and impairment of renal concentrating ability.2,5,42,46,58,71 These symptoms were shown to be pitressin-resistant.2,58 However, the degree of pitressin unresponsiveness and urinary concentrating ability varied considerably in different patients.71 The nephrogenic diabetes insipidus response is fully reversible upon discontinuation of the medication. It has recently been suggested that these side effects (polyuria-polydipsia) were amenable to treatment with thiazide diuretics.20,42

Lithium has been incriminated as a cause of structural renal changes. However, such reports have been inconsistent. Hestbech, et al34 reported that 13 of 14 biopsies, from patients who had received lithium from 1.6 to 15 years, revealed a pronounced degree of focal nephron atrophy and/or interstitial fibrosis as compared with an age-matched control group. All of his patients, however, were referred because of acute lithium intoxication or presumed lithium-induced nephrogenic diabetes insipidus. Burrows, et al11 reported on biopsies from five patients (treated from four months to five years). In their study, a unique tubular lesion was described primarily in the distal convoluted tubule. These same authors39 in a report a year later compared renal biopsy material from 16 patients who had been taking lithium for a mean of 5.5 years with material from nine patients about to start lithium and a group of age-matched donor kidneys used for transplantation. Significant differences were found between the donor kidneys and both the lithium and pre-lithium biopsies. However, there was no difference noted between the pre-lithium and lithium treated patient mate-
rial. In one report of acute renal failure in a patient with lithium intoxication, the renal biopsy showed damage in the proximal tubules with much less marked changes in the glomeruli.40

Histologic changes have been reported after lithium administration in rats.18,19 However, most of the severe ultrastructural changes in these experimental animals have been noted with high dosage lithium treatment. It has been reported that histologic changes indistinguishable from those reported to be caused by lithium treatment develop in some rat strains with aging.36

Proposed Mechanisms of Lithium Nephrotoxicity

The renal complications of lithium salt therapy include nephrogenic diabetes insipidus, renal tubular acidosis, and increased urinary excretion of sodium, potassium, phosphate, and uric acid. None of the mechanisms for these three complications has been definitively proved. Among the three, the most well studied phenomenon is that of nephrogenic diabetes insipidus.

The physiological basis for the polyuria-polydipsia observed in some patients receiving lithium therapy has been studied using *in vitro* and *in vivo* systems. Forrest et al20 showed that rats receiving lithium (3–4 mEq per Kg per day) developed massive polyuria that was resistant to vasopressin. Infusion of dibutyryl cyclic AMP was ineffective in reversing the polyuria. These investigators proposed that the nephrogenic diabetes insipidus induced by lithium was caused by lithium inhibiting the cellular mediation of vasopressin at a step beyond the formation of cyclic AMP.20,28 The toad urinary bladder, which is similar to the mammalian distal tubule,41 was found to be a useful *in vitro* model for studying lithium-induced nephrogenic diabetes insipidus. Singer and associates69,71 were able to show that lithium significantly inhibits vasopressin (antidiuretic hormone [ADH])-induced water transport in the toad bladder at concentrations similar to those in human urine, but cyclic-AMP-induced water flow is normal. Since ADH stimulates adenylyl cyclase to produce cyclic-AMP51 and since lithium salt directly inhibits ADH-induced adenylyl cyclase in the mammalian kidney at comparable concentrations,16 these investigators suggested that lithium probably exerts its effects by blocking ADH activation of adenylyl cyclase to produce cyclic-AMP.69

Thus, the occurrence of ADH-resistant nephrogenic diabetes insipidus in patients with therapeutic levels is due to the inhibition by lithium of renal adenylyl cyclase and possibly cyclic-AMP action. The site of action of lithium is not definitively proved and the mechanism of the inhibition is not known.

Lithium administration to man and rats induces symptoms similar to distal renal tubular acidosis52,55,59 with alkaline urine. The mechanism of this effect is not well studied. Roscoe et al60 showed that lithium administration in rats caused increased urine pH, increased bicarbonate secretion, and decreased urine PCO2. They concluded that lithium produces a defect in distal nephron H+ secretion. More recently, Nascimento et al,47 using the lithium-treated dog as a model, have shown that lithium administration failed to elevate urinary PCO2 during bicarbonate loading. Sodium sulfate administration, however, resulted in normal urinary acidification in lithium-treated dogs. Under conditions of sodium retention, sodium sulphate stimulates H+ secretion by increasing the negative intratubular potential,47,62 which will restrict the passive back-diffusion of H+. These observations led the investigators to propose that under normal conditions, net H+ excretion is the result of active secretion minus passive back-diffusion of H+. These observations led the investigators to propose that under normal conditions, net H+ excretion is the result of active secretion minus passive back-diffusion of H+. The normal urinary acidification observed is due to the increasing negative intratubular potential which will restrict the back-diffusion of H+. Further studies are
required to elucidate the mechanism responsible for this acidification defect in lithium therapy.

Increased urinary excretion of sodium, potassium, uric acid, and phosphate has been observed in both experimental animals and man after lithium administration.\textsuperscript{3,4,43} On the basis of clearance studies, it was suggested that this phenomenon is caused by depression of proximal reabsorption induced by lithium.\textsuperscript{43} However, recent studies yielded conflicting results. Several laboratories\textsuperscript{45,50,54,72} have failed to demonstrate an appreciable effect of lithium on phosphorus and urate handling by the kidney. Micropuncture studies in lithium-treated animals examining proximal reabsorption in rats also yielded conflicting results. Harris and Dirks\textsuperscript{27} failed to demonstrate changes while Hecht et al\textsuperscript{31} showed depressed proximal reabsorption following lithium administration. These varying observations may have been caused partly by the different amounts of lithium administered by different investigators and partly by the different length of time over which lithium was administered.

Discussion

As indicated by the editorial in a recent issue of \textit{Lancet},\textsuperscript{17} "Lithium and the Kidney: Grounds for Cautious Optimism," the nephrotoxicity of lithium is still an open question.

Recently Miller and associates\textsuperscript{45} reported a well controlled study on the effects of lithium on the kidney. Using the patients as their own controls, these investigators noted that three of their seven subjects had large fluid intakes before lithium therapy. These same subjects also had a vasopressin resistant concentrating defect before lithium therapy. The percentage of patients with major affective disorders who are compulsive water drinkers is not known. However, Noonan and associates\textsuperscript{48} in an investigation of compulsive water drinking leading to water intoxication reported that of 21 cases of water intoxication reported to date, 15 of these patients had psychiatric disturbances. It has been reported that in patients who are known psychogenic water drinkers, a vasopressin resistant diabetes insipidus-like syndrome does occur.\textsuperscript{7,15} In one report of a death owing to water intoxication, post mortem examination revealed cloudy swelling of the more highly differentiated tubular epithelial cells.\textsuperscript{32} This finding is not different from those changes ostensibly owing to lithium intake. Coppen et al\textsuperscript{13} compared the urinary concentrating ability of a lithium-treated group with an affective-disorder control group the members of which were untreated by lithium. They, too, found very little difference between the two. Non-specific structural changes in the kidney similar to those in lithium-treated patients had also been identified in patients who had never received lithium by Kincaid-Smith et al.\textsuperscript{29} All these data seem to suggest that lithium may not be the direct nephrotoxic agent. Further research efforts have to be conducted to either prove or disprove this statement.

References


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