Introduction

Since its introduction several decades ago for the occasional treatment of “psychotic excitement”, lithium is still a mainstay in the treatment and prophylaxis of manic-depressive disorders [1]. The biologic basis for the clinical efficacy of lithium is not completely known. Interestingly, the agent relieves both mania and depression, states which appear to be opposites. Its therapeutic range, however, is narrow, and even at the lowest effective dosage, some unwanted side effects may occur [2]. Serum levels above 1.5 mEq/L often result in acute intoxication, which may be severe. The therapeutic range varies, depending on methodology, but it is advisable to target a level of about 0.5 mEq/L, with an upper range at 1.0 mEq/L. Values above this level signify a warning range of impending toxicity.

An equation to predict daily lithium dose has been suggested:

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\text{Daily lithium carbonate dose (mg)} = 100.5 + 752.7 \times \text{desired lithium concentration (mEq/L)} - 3.6 \times \text{age (years)} + 7.2 \times \text{weight (kg)} - 13.7 \times \text{blood urea nitrogen [BUN] (mg/dl)} \]

[3].
Lithium is one of the smallest elements, between H and Na in the Periodic Table of elements, and is always ionized (Li\(^+\)) in watery solutions [1]. In living organisms it has strong pharmacologic and toxic activity. Lithium occurs in two isotopic forms of mass number 6 and 7, with natural abundances of 7.4 and 92.6\% respectively [4]. Pharmaceutical lithium is prepared from the isotope mixture [4]. The smaller \(^6\)Li has higher charge to mass and radius ratio. This can produce differences in the isotopes’ electrostatic interactions with water molecules and negatively charged membranes. An increase in the rate of \(^6\)Li transport, compared to \(^7\)Li transport, across membranes is expected [4]. Accordingly, elimination or reduction of \(^6\)Li from pharmaceutical preparations may merit further evaluation as a way to develop potentially less nephrotoxic form of lithium [4].

The red blood cell, which is a convenient model, shows a cell-to-plasma lithium ratio of 0.3-0.6, whereas the Nernst equation would predict a 1.6 ratio. When red blood cells are loaded with lithium \textit{in vitro} its extrusion is accomplished by a Na\(^+\)/Li\(^+\) countertransporter (SLC), the physiological role of which is unclear, but some believe it represents a mode of operation of the Na\(^+\)/H\(^+\) exchanger. Interestingly, a recent paper suggested that red cell SLC may be a marker of the activity of Na\(^+\)/H\(^+\) exchanger-3 the isoform expressed in the kidney proximal tubule rather than the ubiquitous Na\(^+\)/H\(^+\) exchanger-1 isoform [5].

Because lithium is cleared from the body by the kidneys, its blood level at a given dosage depends critically on renal excretion, which is subject to various physiological and pathological influences. An insight into renal “lithium handling” is a prerequisite for effective prevention of complications and treatment of lithium intoxication when it occurs. Another reason why lithium is of interest to nephrologists is that its clearance has been used as a tool to investigate segmental tubular function [6-9].

With the widespread use of lithium in the treatment of affective disorders, many questions have centered on its long-term effect on the kidneys. Of particular interest is the action of lithium at distal nephron sites where it inhibits water transport, hydrogen secretion, and possibly potassium secretion as well [10, 11]. The most common side effect of chronic lithium therapy is an impairment of renal concentrating ability [11]. Lithium therapy is also associated with side effects related to hormonal alterations and changes in calcium metabolism.

Lithium transport along the nephron

Lithium is freely filtered by the glomeruli, whereas excretion into the urine is 20-30\% of that amount [2]. Thus, at least 70\% of the filtered load undergoes tubular reabsorption. Lithium clearance closely parallels changes in natrium delivery from the proximal tubule (Figure 1).

a. Proximal tubule. Early micropuncture studies reported Lithium concentration at the end of the convoluted proximal tubule to be close to unity [12]. Subsequent recent studies [13-19] using lower lithium plasma concentrations and more sensitive methods all found filtrate-to-plasma ratios to be definitely higher, the average value being 1.14. This value was not influenced by various manipulations such as natrium depletion, osmotic diuresis, prostaglandin inhibition, or infusion of acetazolamide, furosemide, or angiotensin [13, 14, 16]. Lithium can enter the cells via the

![Figure 1. Scheme of Li\(^+\) transport along different nephron segments.](image-url)