EDITORIAL

Lithium: balancing mood, water, and renal function decline

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Lithia water was first marketed to consumers in the 1800s for its purported therapeutic merits for conditions ranging from gallstones to kidney disease.[1] Although later revealed to be homoeopathically dilute and curing little more than thirst, at that time, few could have predicted the use of lithium as a highly effective mood stabilizer, much less, its significant renal toxicity.

Lithium influences multiple elements in the renal urinary concentrating mechanism, potentially leading to nephrogenic diabetes insipidus (NDI). The pathophysiology of this condition includes entry of lithium into principal cells in the collecting duct by substituting for sodium on the epithelial sodium channel and accumulation in these cells, which dysregulates various downstream signaling pathways. One such pathway may involve the inhibition of glycogen synthase kinase type 3 (GSK3), which, paradoxically, may be protective in acute kidney injury.[2] Moreover, lithium-treated patients are characterized by elevated urinary prostaglandin E2 levels, likely the result of increased activity of cyclooxygenase-2. These, and possibly other events, reduce plasma membrane abundance of aquaporin-2 in affected cells, leading to impaired water reabsorption. In the longer term, lithium also lowers the ratio of principal to intercalated cells, resulting in augmentation of this effect.[3]

Prolonged exposition to lithium also places the kidney at risk for permanent injury via poorly defined pathways, in which inhibition of GSK3 again appears to be a cornerstone.[4] Lesions associated with chronic use include interstitial fibrosis and proximal tubular atrophy, and at a later stage, glomerulosclerosis.[5] The majority of patients with clinically evident lithium-induced nephropathy display microcyst formation, which is characteristic of lithium toxicity.[6]

Despite a large swathe of publications over the past decades, studies providing estimates of renal risks in unselected, well-monitored patients are still poorly aligned. In this issue of the *Netherlands Journal of Medicine*, Doornebal et al. report on a first cross-sectional baseline analysis of 98 lithium-treated patients recruited from two Dutch mental health centres for an ongoing prospective study.[7] They gave eligible patients a 40 µg intranasal dose of a vasopressin analogue (dDAVP) to determine maximal urine osmolality. After an average of eight years on lithium, 51 percent had a moderately decreased urinary concentrating ability, while 16 percent were diagnosed with NDI. As expected, defects in urinary concentrating ability became more prevalent the longer patients had been on lithium, appearing in up to 78 percent of those who had used it for over 15 years. Interestingly, it appears that patient-reported symptoms such as thirst and nocturia, which are frequently reported by lithium-treated patients,[8,9] are poorly correlated with the presence of NDI. In addition, in this population and other published reports, defects in urinary concentrating ability, which may become partly irreversible, occurred before a decrease in the estimated glomerular filtration rate (eGFR).

Most chronic kidney disease (CKD) appears only after at least a decade of lithium use.[10] Of note, toxicity-related discontinuation of lithium may have led to significant underreporting of such outcomes in this and previous cross-sectional studies. Data on predictors of the development of CKD during lithium treatment, in particular the relationship between baseline urinary concentrating ability and delayed eGFR decline, are lacking. Indeed, future data from the prospective study of this cohort will answer the question of whether more dilute urine in dDAVP-challenged patients may indeed be viewed as a presage to imminent kidney function decline.

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