János Radó: Renal Toxicity of Lithium in Historical Perspective with Special Reference To Nephrogenic Diabetes Insipidus and its Treatment

Abstract

Renal toxicity of lithium is a highly important subject which may jeopardize the use of an agent needed by millions suffering from recurrent episodes of bipolar disorder. Lithium may cause profound changes in the previously normal kidney functions and structure leading to end stage kidney disease. The recent use of *lower serum lithium levels,* however, almost eliminated the risk of lithium-induced renal failure.

In the present report we deal with disturbances of the normal concentrating operation of the kidney; lithium-induced concentrating defect and nephrogenic diabetes insipidus (NDI); and treatment of the lithium-induced disorders.

Treatment of the lithium-induced NDI consists of the thiazides, indomethacine and other non-steroid anti-inflammatory compounds as well as the administration of large doses of desmopressin, amiloride and combinations thereof. Administration of very high doses of desmopressin has resulted in clinically relevant antidiuresis, enhanced by indomethacine. Amiloride is a very special antikaluretic diuretic drug which can abolish several lithium-induced abnormalities. In such an important form of psychiatric treatment as lithium, a serious disturbance of water metabolism can be alleviated by the clever use of modern antidiuretic interventions.

Introduction

"Lithium is a simple ion that remains the best, safest and least expensive treatment for the prevention of recurrent episodes of bipolar disorder" (Blackwell 2018). However, long term administration of lithium has been associated with nephrotoxic effects, altering the structure or/and function of the kidney. Although chronic lithium therapy can cause advanced renal disease, most cases of nephrotoxicity are limited only to narrowed renal concentrating operation. Even in cases with the lithium-induced most severe disturbance of water metabolism, i.e., NDI, there are some therapeutic measures which can alleviate, to some extent, the patient's

suffering. Decreasing the polyuria may secure some rest for the patients during the night. Treatment options for the lithium-induced NDI were not fully considered in a recent review of lithium nephrotoxicity (Davis, Desmond and Berk 2018). More extensive analysis of these options is the purpose of the present article, with special reference to historical points of views.

Lithium Induced Nephropathy

General toxicity was a concern even for John Cade, the discoverer of the lithium therapy in 1947 (Cade 1949). The strongest propagator of this treatment, Morgens Schou, was also frightened of the side effects, considering that his loved brother's health was at stake (Schou 1958). Gordon Johnson investigated the influence of lithium treatment on the endogenous creatinine clearance and found that "overall, glomerular filtration rate fell within the established normal range" (Johnson 1984). However, Hestbech, Hansen and Amdisen (1977); Bendz (1983); Bendz, Aurell, Balldin et al. 1994; Bendz, Schön, Attman and Aurell (2010); and Boton, Gauiria and Battle (1987) found chronic renal lesions following long-term treatment with lithium. Chronic lithium therapy produces progressive interstitial fibrosis, hyperplastic changes in the medullary collecting ducts, distal tubule dilatation and microcyst formation (Croft, Bedford, Leader and Walker 2018). Renal failure occurs in chronic lithium treatment but is uncommon (Bendz Schön, Attman and Aurell 2010; Johnson 1998). Davis, Desmond and Berk (2018) developed a search strategy using the most valuable electronic databases to identify the most pertinent questions of lithium- induced nephropathy. They confirmed that there was no correlation between the duration of therapy and decreases in eGFR. At least 20 years or more is necessary for the development of lithium-induced end stage kidney disease. Nevertheless the incidence of the latter is not more than 0,2-0,7 % (according to Shine, McKnight, Leaver and Geddes [2015], 0,5-1%). Not only duration of therapy but other factors may also be relevant to the development lithium-induced nephropathy, such as age, female gender, other diseases favoring nephropathy (diabetes mellitus and hypertension), use of nephrotoxic drugs, prior episodes of acute lithium toxicity, etc. (Davis, Desmond and Berk 2018; Johnson 2018). However, Aiff, Attman P, Aurell et al. (2014) stress that the recent use of *lower serum lithium levels* almost eliminated the risk of lithium-induced renal failure.

Disturbances in the Renal Concentrating Operation

In healthy people urine concentration can exceed that of plasma which is ca 290 mOsm/Kg. The osmolal concentration of the urine can be as high as 1200 mOsm/Kg during prolonged thirst. During water conservation the renal medullary interstitial tissue is hypertonic, due to the accumulated sodium and urea in consequence of the active sodium reabsorption in the ascending limb of the loop of Henle transporting the sodium into the medullary interstitium. *Its osmolality is as high as that of the concentrated urine.* The presence of vasopressin-induced increase of collecting tubular permeability allows diffusion of water back into the medullary interstitium down the established medullary osmotic gradient resulting in maximally concentrated urine. *Lithium* diminishes the osmotic gradient in the renal medulla reflected in a marked reduction in both osmolyte and urea content. Decrease in the renal medullary interstitial hypertonicity results in lower urinary concentration, polyuria and polydipsia. *Amiloride,* by increase in medullary osmolytes, restores the renal medullary interstitial hypertonicity, resulting in normalization of the renal concentrating mechanism and less and more concentrated urine. (Bedford, Leader, Jing et al. 2008b)

During ad libitum fluid as *intake* in healthy people the average urine osmolality is ca 600 mOsm/Kg. *During water diuresis* however, the urinary osmolality is ca 100 mOsm/Kg or less. The lowest value I observed in my human pharmacology studies was 40 mOm/Kg after water loading. In prolonged polyuria the osmotic concentration in the renal medulla decreases due to the "washout" effect with the consequence of reduced concentrating power.

In some patients with *neurohypophyseal (central) diabetes insipidus* the value of urine osmolality can be as high as 300 mOsm/Kg or more, though in most cases it is as in water diuresis. The osmolal concentration of the urine increases at least 9 % in response to vasopressin (Miller Moses test), so differentiation from the NDI - at least in the full cases - is simple. *In congenital NDI the urine osmolality figures are the same as in central DI, but are not responding to the antidiuretic hormone (ADH, vasopressin).*

The diagnosis may be difficult in patients *with the partial form* of the diseases. Fortunately, sophisticated molecular genetic studies provide exact methods for successful differentiation. The identification, characterization and mutational analysis of the two different genes, the arginine vasopressin receptor 2 gene (AVPR2) and the vasopressin-sensitive water channel gene (aquaporin 2 [AQP2]), provide the basis for understanding the two hereditary forms of renal diabetes insipidus: the X-linked NDI (relatively frequent) and the non x-linked

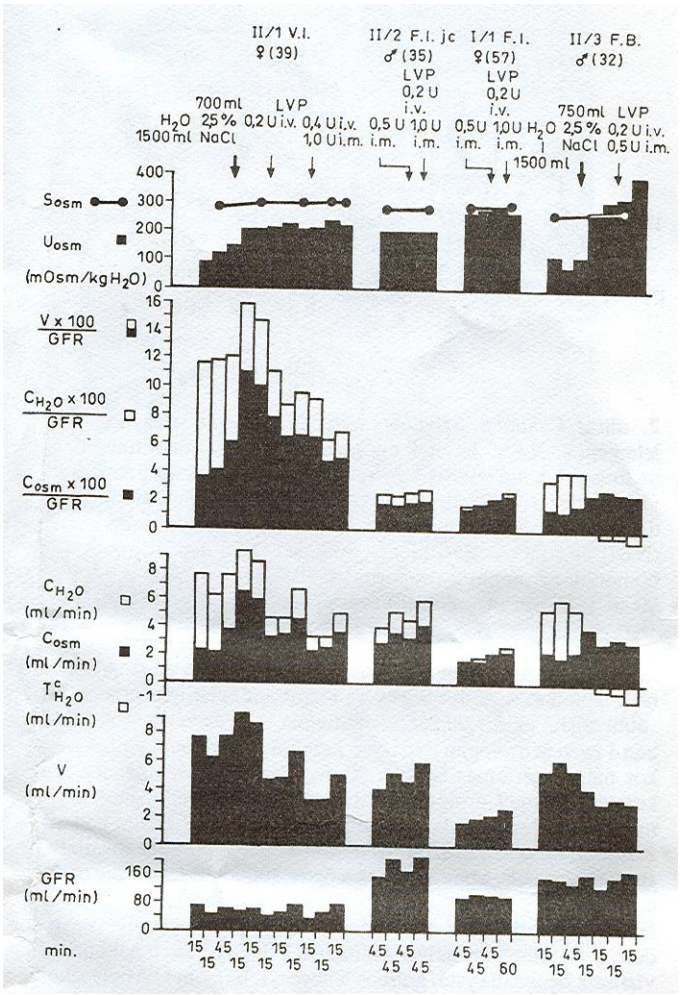
NDI (very rare) (Fujiwara and Bichet 2005). The two types of NDI result from mutation in the structure either of the V2 receptor or AQP2 which causes impaired arginine-vasopressin induced signal transduction (Canfield, Tamarappoo, Moses et al. 1997). "All families with hereditary diabetes insipidus (the X-linked NDI and the non x-linked NDI) should have their molecular defect identified" (Fujiwara and Bichet 2005).

The concentrating process normally starts with the binding of arginine-vasopressin to the V2 receptors on the *basolateral surface* of the principal cells in the collecting duct. It stimulates adenyl cyclase and influences the content of the intracellular vesicles, the AQP2 protein which is the "water channel" to be inserted in the *apical membrane* in the luminal site of the principal cell in the collecting duct. Vasopressin stimulation results in the 20-fold increase in water permeability of responsive principle cells.

Although the mechanisms of the development of inherited and acquired forms of diabetes insipidus are entirely different, *therapy of the two types is surprisingly similar*. In the patients with the full (complete) form of the inherited disease the vasopressin resistance may be absolute. However, many patients with congenital NDI suffer only in a partial form of the disease (Boccalandro, De Mattia, Guo et al. 2004). In such patients administration of large doses of DDAVP can alleviate somewhat the suffering. It is interesting that within one family huge interindividual variations can be observed in the degree of vasopressin resistance. On this basis the effectiveness of large doses of DDAVP can be significantly different within one family. Figure 1 shows our personal observations in such a family.

In a five- member congenital NDI family who were investigated during thirst and administration of lysin-vasopressin urine, osmolality values were 207 mOsm/Kg, 236 mOsm/Kg, 296 mOsm/Kg, 322 mOsm/Kg, and 405 mOsm/Kg. (Radó, Szende 1995). In Figure 1 only data of four members are depicted.

Figure 1



Investigational data of the *congenital* NDI family (Mother /I/1 F.I./ and three siblings). The effect of thirst and administration of lysine-vasopressin (doses are indicated above the figure) without or with infusion of hypertonic saline. It can be seen that in the first two members urine osmolality remains definitely *lower* than that of plasma. In the third member urine osmolality *reaches* that of plasma, while in the fourth member *surpasses* it.

Free water clearance (C_{H2O}) *increases* during hypertonic sodium chloride infusions while in response to administration of lysine-vasopressin it *decreases*. *Only in the fourth family member is free water clearance turned into free water reabsorption (Tc_{H2O}).* Changes are similar in the free water clearance expressed in the percentage of glomerular filtration rate ($C_{H2Ox100}$/ GFR). Osmolal clearance (Cosm) as well as Cosmx100/GFR markedly increased during hypertonic sodium chloride infusion in the first member of the family. Parallel changes were seen in urine flow (V)) and free water clearance.

The values of the glomerular filtration rate (GFR) were normal in three members of the family.

The lowest numbers indicate the duration of the individual clearance periods.

Lithium – Induced Concentrating Defect

The lithium-induced disturbance in renal concentrating operation begins shortly after the introduction of the drug. Lithium entering the principal cells of the collecting duct through the sodium epithelial channel abolishes the formation of cyclic AMP and by that the vasopressin mediated insertion of the water channel protein aquaporin 2 into the apical membrane of the cells. Down regulation of AQP2 reduces water reabsorption because of decreasing water permeability of the tubules. Lithium therapy reduces also the organic osmolyte content of the renal medulla (Bedford, Leader, Jing et al. 2008b). Dissipation of the high solute content of the renal medulla, the decrease in renal medullary hypertonicity, is the other cause of the lithium polyuria. Amiloride restores renal medullary osmolytes and hypertonicity improving by that the renal concentrating operation (Bedford, Weggery, Ellis et al. 2008a; Bedford, Leader, Jing et al. 2008b).

The concentrating defect progressively increases during further administration of lithium. In Gordon Johnson's patient material (after 12 hr thirst and administration of pitressin) the average maximal urine concentration was of about 400 mOsm/kg in 11 patients treated two years with lithium, while it was only 200 mOsm/kg in three patients treated 10-20 years (Johnson 1984).

The concentrating defect can be demonstrated at least in 50% of all patients. It is questionable whether in any patient the renal concentrating operation can remain intact during administration of lithium for several decades. Also a difficult question where is the limit between "narrowed" concentration and NDI. NDI can be only "functional" or in all cases lithium induced morphological structural alterations are present. On the basis of modern studies we may account perhaps in all patients lithium-induced "remodeling" of cells in the cortical and medullary renal tubules. "The cellular effects of lithium treatment are broad and complex" (Nielsen, Hoffert, Knepper et al. 2008).

Lithium-induced NDI

Nephrogenic diabetes insipidus is a clinical condition characterized with vasopressin-resistant polyuria and polydipsia. One of the most frequent causes of acquired NDI is chronic administration of lithium; it develops after 10 years of treatment with lithium in more than 10% of the patients. Disturbance of water metabolism is the most characteristic alteration in lithium-induced NDI; *increased sodium excretion and hyperchloremic metabolic acidosis is also*

present. Decreased abundances of vasopressin governed aquaporin 2 and 3 water channels in the collecting duct is responsible for the insufficient tubular water reabsorption. Increased sodium excretion is caused by the reduced expression of the epithelial sodium channel in the cortical and outer medullary collecting duct. Lithium-induced increased expression of H^+ATPase in the collecting duct is associated with the impaired excretion of acid. (There are other mechanisms too, also leading to renal tubular acidosis.) Nielsen, Hoffert, Knepper et al. (2008) performed *"proteomic analysis"* of lithium-induced NDI and found previously unknown mechanisms for aquaporin down regulation as well as cellular proliferation. *Their model system was the inner medullary collecting duct isolated from lithium treated rats*. Their most important finding was that lithium treatment affected proteins involved in cell death, apoptosis and cell proliferation. Several *signaling pathways* were activated by lithium treatment, as well as the increased intracellular accumulation of beta-catenin and phosphorylated glycogen synthase kinase type 3beta. The authors remark that similar targets may have lithium in the brain. *It should be stressed again that the author's conclusion is "that the cellular effects of lithium treatment are broad and complex, and as such a single pathway leading to reduced AQP2 expression and subsequent polyuria is unlikely."*

Treatment of Lithium-induced NDI

Before the era of Modern Pharmacology congenital NDI could be treated only by providing water. "Adjuvant" therapy was the restriction of sodium and protein in the patient's diet, thus decreasing the excreted osmols and water

C*hlorothiazide*, the first thiazide diuretic, was introduced into clinical medicine in 1958. Crawford, Kennedy and Hill discovered in 1960 that in patients with central diabetes insipidus the high urine volume can be halved by the administration of the new drug. In our several studies we could corroborate the original results of these authors and extended those with other classes of diuretics (Radó, Bános, Marosi et al. 1968). The thiazide diuretic acts by inhibiting sodium reabsorption in the distal convoluted tubule which interferes with urine dilution, on the one hand, and (indirectly) enhances sodium reabsorption in the proximal tubules on the other. This latter mechanism decreases the delivery of the filtrate to the distal nephron and enhances there the reabsorption of sodium and water reducing by that the excreted volume of urine (Earley and Orloff 1962; Oiso et al. 2013). Modern studies proved that the antidiuretic effect

of hydrochlorothiazide in lithium-induced NDI is associated with upregulation of the aquaporin 2, the Na-Cl cotransporter and the epithelial sodium channel (Kim, Lee, Oh et al. 2004). *In the paradoxical thiazide antidiuresis finally sodium reabsorption (and water reabsorption) is increasing both in the proximal and distal nephron.*

Thiazides can be combined with amiloride, indomethacine, DDAVP etc. Congenital NDI was treated successfully with a thiazide combined with large doses of DDAVP (Mizuno, Fujimoto, Sugiyama et al. 2003)

Indomethacine, a prostaglandin synthetase inhibitor was also found to have antidiuretic properties in NDI. The efficiency is dependent upon inhibition of prostaglandin synthesis. Prostaglandins antagonize the effect of vasopressin. Indomethacine therefore increases concentrating capacity. *According to Oiso et al. (2013) indomethacine probably acts by inhibiting the retrieval of acquaporin 2 water channels from the apical membrane of the principal cells.* Simon, Garber and Arieff used indomethacine in lithium-induced NDI in 1977; Libber**,** Harrison and Spector administered it in 1986; Allen, Jackson, Winchester et al. in 1989; Vierhapper in 1990; Radó and Zdravkova in 1991 and 1993; and Thompson, France and Baylis in 1997. We administered indomethacine together with desmopressin in a patient with Bartter syndrome, and found a dramatic antidiuretic effect (Radó, Simatupang, Boer et al.1978). In our recent study (Radó 2018) we found that indomethacine had a more pronounced antidiuretic effect than *piroxicam*, another non-steroid anti-inflammatory compound.

For *Desmopressin (1-Deamino-8-D-Arginine Vasopressin: DDAVP)*, structural alterations of the vasopressin molecule resulted in increased antidiuretic potency, longer duration of action and lacking pressor effect due to decreased vasoconstrictor activity. In our studies carried out over 40 years we have demonstrated a relationship between the dose and both the magnitude and the duration of the antidiuretic effect (Radó et al. 1975c, 1976c). Robertson and his coworkers (Oiso et al. 2013) wrote about our early investigations that "in patients with neurohypophyseal diabetes insipidus rapid infusion of 1 /ug DDAVP increased urine osmolality to a maximum of 700-800 mOm/Kg; further increases in dosage only prolonged the duration of action from an average of 26 hours after 1 /ug to 46 hours after 8 /ug." Our further studies revealed large interindividual variability in the magnitude and duration of the antidiuretic response of DDAVP, which was contributed -at least in part- to the interindividual differences in renal concentrating power (Radó et al. 1976a). The long duration of action of DDAVP is attributed mainly to its slow metabolic (enzymatic) degradation, and both shortened duration of action (Radó et al. 1976b) and lengthened duration of action (Radó

et al 1975b) were reported under varying pharmacological circumstances. . Comparison of the antidiuretic effects of single intravenous and intranasal doses of DDAVP in diabetes insipidus was also an important part of our investigations (Radó, Marosi and Fischer 1977). Intranasal administration of DDAVP was at that time a comfortable way of administration and proved to be reliable. *Today DDAVP therapy can be carried out by oral melting tablets.* We have elaborated a diagnostic procedure for the differentiation of the various concentrating defects by intranasal administration of DDAVP, the "DDAVP concentrating test" (Radó 1978).

"Vasopressin-like" antidiuretic action has been reported after administration of carbamazepine, even leading to water intoxication (Radó 1973). Clofibrate has also a similar effect. The development of a drug-induced inappropriate secretion of antidiuretic hormone syndrome has been described after combined administration of carbamazepine and clofibrate (Radó, Juhos and Sawinsky 1975a). Combination of carbamazepine and chlorpropamide was effective in the treatment of "hyporesponder" diabetes insipidus (Radó et al 1974a). Antidiuretic effect of small doses of DDAVP could be enhanced by the coadministration of carbamazepine or/and clofibrate and can be inhibited by glyburide (Radó 1974b,c).

Indomethacine and DDAVP was used for the first time in lithium induced NDI in 1990 by and Weinstock and Moses and in 1991 by Stasior, Kikeri, Duel and Seifter. We used successfully excessive doses of DDAVP combined with indomethacine or piroxicam for the alleviation of polyuria in lithium induced NDI (Radó and Zdravkova 1993; Radó 2018)

Amiloride is a potassium retaining (antikaluretic) diuretic. Polyuria and polydipsia due to lithium-induced NDI *decreases* during administration of amiloride. Amiloride improved responsiveness to arginine-vasopressin stimulated translocation of AQP 2 to the apical membrane of the principal cell and increased AQP2 excretion as well as maximal urinary osmolality (Bedford Leader, Jing et al. 2008b**).** Inhibiting the lithium- induced epithelial sodium channel in the collecting duct with amiloride reduces the lithium induced down-regulation of the acquaporin 2 expression. Amiloride reduces transcellular lithium transport, intracellular lithium concentration and lithium-induced inactivation of GSK-3-beta (Kalra, Zargar, Sunil et al. 2016). Amiloride therapy alleviated also the chronic lithium therapy produced progressive interstitial fibrosis and hyperplastic changes in the medullary collecting ducts (Croft, Bedford, Leader and Walker 2018).

A Vasopressin–analogue (DDAVP) in NDI a "Vasopressin-Resistant" Condition?

Yes, In Large Doses in NDI.

Per definition, NDI is a vasopressin-resistant condition. In two congenital cases of Moses, Scheinman and Oppenheim (1984), however, NDI responded to large doses of DDAVP. Though 25-50 times as resistant to DDAVP nasal spray as Rado's patients with central diabetes insipidus (Rado 1975c) these patients could be treated effectively with large doses of the nasal spray. Our dosage protocol is in total agreement with the calculation of Moses, Scheinman and Oppenheim. We gave 250-300 /ug DDAVP nasal spray to our lithium induced NDI patient, which is ca 25 times more than a normal 10 /ug dose (Radó 2018). In our patient with lithium-induced NDI (Radó 2018) 24 hr urine osmolality before treatment was 175 mOsm/Kg, while under treatment with excessive doses of DDAVP plus indomethacine it was 280 mOsm/Kg. Others have similar experiences (Oiso et al. 2013; Mizuno, Fujimoto, Sugiyama et al. 2003; Stasior, Kikeri, Duel and Seifter 1991; Weinstock and Moses 1990).

Conclusions

Lithium is important for the world's millions of patients with recurrent episodes of bipolar disorder -- based on the works of Ban 2017, Blackwell 2014 and 2018, Rybakowski 2017, Severus 2014 and others. Lithium remains a key treatment, although its use needs monitoring and a safety-conscious approach is needed (Shine, McKnight, Leaver and Geddes 2015). The burden of the not too uncommon side effect, the lithium-induced NDI can be alleviated somewhat by the clever use of modern antidiuretic agents (indomethacine combined with excessive doses of desmopressin), including also the use of amiloride, and thiazides.

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