Controversies

July 18, 2019

Janos Radó: Desmopressin may counteract polyuria in lithium-induced nephrogenic diabetes insipidus

Review of the literature

Abstract

Lithium is a simple ion that remains the best, safest and least expensive treatment for the prevention of recurrent episodes of bipolar disorder. However, in many patients administration of lithium is associated with renal side effects. The most frequent side effect is a defect in urinary concentration which may lead to permanent lithium-induced nephrogenic diabetes insipidus. In the older literature this problem was treated with great attention; in the most recent publications, however, lithium-induced nephrogenic insipidus is hardly mentioned. Patients suffer from a disturbed night therefore it is an eminent goal to secure them some rest.

In our previous work administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis in lithium-induced nephrogenic insipidus enhanced by indomethacine (Radó and Zdravkova 1991; Radó 2018a,b; Radó 2019). The purpose of the present paper is to review the literature concerning the use of desmopressin in lithium-induced nephrogenic diabetes insipidus.

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). This concept is supported by many reports, among them those of Ban (2017); Gupta, Kripafani, Khastgir and Reilly (2013); Rybakowski (2017); and Severus, Taylor, Sauer et al. (2014). *However, its use has gradually declined and many less-established drugs are preferred.* It is underused because of its low therapeutic index, the need for regular blood tests and perceptions about its adverse effects, including renal problems (Gupta, Kripafani, Khastgir, Reilly 2013)

The most frequent renal problem encountered is the disturbance in water metabolism due to lithium-induced insufficiency in renal concentrating operation resulting in polyuria and polydipsia. Daily urine volume increases, in many cases more than 3-5 liters a day (Johnson 2018; Warnes 2019), but we have seen a patient, in whom in a stage of her long history it was

more than 10 liters. Patients suffer from a disturbed night. Therefore, it is an eminent goal to secure some rest for them. In the older literature this problem seemed to be very important (Johnson, Glenn, Hunt et al. 1984; Johnson 1998; Radó and Zdravkova 1991) and was treated with great attention. In the most recent publications, however, lithium-induced nephrogenic insipidus is hardly mentioned (Gupta and Khastgear 2017; Davis, Desmond and Berk 2018). The recommended drugs are mostly a thiazide diuretic (Mizuno, Fujimoto, Sugiyama et al. 2003), indomethacine (Weinstock and Moses 1990) and amiloride (Croft, Bedford, Leader and Walker 2018).

A Short Pharmacology of Desmopressin

Structural alterations of the vasopressin molecule resulted in 1-deamino-8-D-arginine vasopressin (DDAVP) or desmopressin, with increased antidiuretic potency, longer duration of action and lacking a 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, Marosi, Fischer et al. 1975a; Radó, Marosi, Szende et al.1976c). Robertson and his coworkers (Oiso, Robertson, Norgard and Juul 2013) wrote about our early investigations that "in patients with neurohypophyseal diabetes insipidus rapid infusion of 1 micgr desmopressin 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 micgr to 46 hours after 8 micgr."

Our further studies revealed large interindividual variability in the magnitude and duration of the antidiuretic response of desmopressin, which was contributed - at least in part - to the interindividual differences in renal concentrating power (Radó, Marosi, Borbely and Tako 1976a). The long duration of action of desmopressin is attributed mainly to its slow metabolic (enzymatic) degradation and both shortened duration of action (Radó, Marosi and Fischer 1976b) and lengthened duration of action (Radó and Marosi 1975b) were reported under varying pharmacological circumstances.

The effect of desmopressin was inhibited by glyburide, an antidiabetic compound, probably by competitive antagonism (Radó, Szende and Marosi 1974a; Radó, Szende, Marosi et al. 1974b) A similar antagonism by calcitonine was discovered later (Radó 2018ab). Comparison of the antidiuretic effects of single intravenous and intranasal doses of desmopressin in diabetes insipidus was also an important part of our investigations (Radó, Marosi and Fischer 1977). Intranasal administration of desmopressin was at that time a

comfortable way of administration and proved to be reliable and today desmopressin therapy can be carried out by ingesting dissolving tablets (Walle, Stockner, Raes and Nørgaard 2007).

We have elaborated a diagnostic procedure for the differentiation of the various concentrating defects by intranasal administration of desmopressin, the "desmopressin concentrating test" (Radó 1978). When we started our studies with desmopressin a "supramaximal" dose was 300 microgr given intranasally. In these early human pharmacology investigations 320 mcg was given as a quasi "single dose" during one hour to patients with neurohypophyseal (central) diabetes insipidus (Radó and Marosi 1975b). When we used desmopressin for nephrogenic diabetes insipidus 300 microgr was given during 24 hrs. (Radó and Zdravkova 1991). In the meantime, however, it became known desmopressin may also be effective in hematologic disorders; for these disorders, in certain cases, desmopressin was given in very extreme doses. The industry produced desmopressin preparations containing very high concentrations of desmopressin intended to act on the blood clotting mechanism for bleeding disorders. By using such a preparation (Octim Nasal Spray Ferring Pharmaceuticals Ltd) administration of 300 micrgr (150 micrgr into both nostrils) as a single dose is easily feasible. To the best of my knowledge this preparation has not been tried, up to now, in the therapy of the lithium-induced permanent nephrogenic diabetes insipidus.

Desmopressin Administered Alone in Nephrogenic Diabetes Insipidus

Although nephrogenic diabetes insipidus is said to be "vasopressin resistant," on the basis of ours and others' previous investigations we did not exclude the use of certain vasopressin derivatives in this condition because vasopressin resistance in many cases is not absolute (Canfield, Tamarappoo, Moses et al. 1997; Fujiwara and Bichet 2005; Khanna 2006; Oiso, Robertson, Norgard and Juul 2013; Moses, Scheinman and Oppenheim 1984). Large doses of desmopressin were successfully given to patients with congenital nephrogenic diabetes insipidus for antidiuretic purposes (Boccalandro, De Mattia, Guo et al. 2004; Canfield, Tamarappoo, Moses et al. 1997; Khanna 2006; Oiso, Robertson, Norgard and Juul 2013; Moses, Scheinman and Oppenheim 1984). The effectiveness of relatively large doses of vasopressin (and also excessive doses of desmopressin) can be significantly different even within one family with congenital nephrogenic diabetes insipidus (Radó and Szende 1995; Radó 2019). Probably the degree of resistance to vasopressin (desmopressin) may differ among the family members: one family member was treated successfully with desmopressin *for decades* and the case was published because the (congenital nephrogenic) *diabetes* insipidus was later associated with *diabetes* mellitus (Radó 2011). In our previous work we found that

in a patient with lithium-induced permanent nephrogenic diabetes insipidus in response to excessive *desmopressin* doses free water excretion (expressed in the percentage of glomerular filtration rate (CH_2Ox100/GFR)) significantly decreased and urine osmolality significantly increased (Radó 2018a).

A very special observation

Müller, Marr, Ankermann et al. (2002) investigated two unrelated families in which two children had inherited primary nocturnal enuresis *and* nephrogenic diabetes insipidus; they had mutations in the aquaporin-2 gene. The mutant proteins were inactive, suggesting that administration of desmopressin could not concentrate the urine in these patients. *However, treatment with desmopressin resolved primary nocturnal enuresis completely.*

Combination of Desmopressin with Other Antidiuretic Agents in Nephrogenic Diabetes Insipidus

Mizuno, Fujimoto, Sugiyama et al. (2003) treated a seven-year-old boy suffering from congenital nephrogenic diabetes insipidus who had demonstrated a partial response to desmopressin. Neither a low salt diet and a thiazide nor a large dose of desmopressin was effective in reduction of daily urine volume. *However combination of thiazide and a large dose of desmopressin resulted in a decrease in urine volume and disappearance of nocturia*.

Indomethacine and desmopressin was used for the first time in lithium induced nephrogenic diabetes insipidus in 1990 by Weinstock and Moses. They found in their two patients that indomethacine alone was practically ineffective, but *in combination with large doses of desmopressin urine volume decreased by 47% and 63% respectively, while urine osmolalities increased by200% and 227% respectively.*

Stasior, Kikeri, Duel and Seifter (1991) reported a patient with lithium-induced nephrogenic diabetes insipidus who was responsive to desmopressin in the presence of indomethacine, but not to desmopressin or indomethacine alone. A single dose of 6 micgr desmopressin subcutaneously (not a too large dose!) without indomethacine caused an increase in urine osmolality from 187 mOsm/Kg to 270 mOsm/Kg (44%). However, in response to the same dose of desmopressin *in the presence of indomethacine* urine osmolality increased from106 mOsm/Kg to 384 mOsm/Kg *(262%)*.

In our patient urine volume and free water clearance significantly decreased while urine osmolality significantly increased after administration of the combination of

indomethacine and desmopressin as compared to desmopressin administered alone (Radó 2018a).

In our further studies piroxicam plus desmopressin, as compared to desmopressin (administered alone), was also antidiuretic: urine volume and free water excretion decreased while urine osmolality increased without any consistent change in osmolal clearance, glomerular filtration rate and serum osmolality. These results support the contention that indomethacine is not the only nonsteroidal anti-inflammatory compound which can be used in the antidiuretic therapy. However, piroxicam seemed to be less antidiuretic than indomethacine by 20-30%.

Antidiuretic properties have been demonstrated for chlorpropamide, carbamazepine and clofibrate which potentiate the effect of desmopressin (Radó 2019). From these compounds probably only carbamazepine may be useful in a limited extent in the treatment of the lithium-induced nephrogenic insipidus. Statins (Bonfrate, Procino, Wang et al. 2015; Milano, Carmoniso, Gerbino and Procino 2017); metformin (Efe, Klein, LaRocque et al. 2016); sildenafil and calcitonine (Milano, Carmoniso, Gerbino and Procino 2017); prasugrel (Zhang, Peti-Peterdi, Brandes et al. 2017); and clopidrogel (Zhang, Peti-Peterdi, Heiney et al. 2015) were also shown to have some antidiuretic capabilities. Only calcitonine was combined with desmopressin (Radó 2018 a,b). In our hands, however, it was not an antidiuretic factor.

Administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine (Radó 2018a). Calcitonine is a "tricky" hormone, having both diuretic and antidiuretic properties. Diuretic effect of calcitonine was an observation found mainly in the older literature and is in harmony with our published data on a water mobilizing action (Radó 1991, 1993, 2018a). On the other hand, water retaining action was found (Elalouf, Roinel and de Rouffignac 1986) in response to human calcitonine in rats during micropuncture studies simulating the changes induced by desmopressin. Calcitonin was recommended as a possible treatment for hereditary nephrogenic diabetes insipidus by Milano, Carmoniso, Gerbino and Procino (2017).

Combinations of hydrochlorothiazide with indomethacine, amiloride with thiazide diuretics have additive antidiuretic effects (Milano, Carmoniso, Gerbino and Procino 2017). *All could have been combined - at least theoretically - with desmopressin to have a really potentiated antidiuretic intervention for the treatment of lithium-induced nephrogenic diabetes insipidus.*

Conclusion

It is important to save lithium treatment for millions of people suffering from bipolar disorder and other psychiatric abnormalities in an age when its use has gradually declined and many less-established drugs are preferred (Gupta, Kripafani, Khastgir, Reilly 2013.) This can be done (at least partly) by demonstrating that treatment of lithium-induced permanent nephrogenic diabetes insipidus is not so hopeless as it appears from some recent articles dealing with lithium induced nephrotoxicity. Our therapeutic armamentarium include several drugs, thiazide diuretics, nonsteroid anti-inflammatory drugs, amiloride and desmopressin. In this article we dealt with desmopressin administered alone and in combination with other drugs in the treatment of congenital, as well as lithium-induced nephrogenic diabetes insipidus. On the basis of the available literature desmopressin alone and in combination with other antidiuretic drugs seemed to be an effective means in counteracting lithium-induced polyuria.

References:

Ban TA: Neuropsychopharmacology in Historical Perspective. Education in the Field in the Post-Neuropsychopharmacology Era. Prologue. inhn.org.education. September 18, 2017.

Blackwell B. Lithium Controversy. A historical autopsy. inhn.org.controversies. June 19, 2014.

Blackwell B. Final reply to Janos Rado's final comment. inhn.org.controversies. May 10, 2018.

Boccalandro C, De Mattia F, Guo DC, Xue L, Orlander P, King TM, Gupta P, Deen PM, Lavis VR, Milewicz DM. Characterization of an aquaporin-2 water channel gene mutation causing partial nephrogenic diabetes insipidus in a Mexican family: Evidence of increased frequency of the mutation in the town of origin. J Am Soc Nephrol 2004; 15:1223-31.

Bonfrate L, Procino G, Wang DQ-H, Svelto M, Portincasa P. A novel therapeutic effect of statins in nephrogenic diabetes insipidus. J Cell Mol Med 2015;19:265-82.

Canfield MC, Tamarappoo BK, Moses AM, Verkman AS, Holtzman EJ. Identification and characterization of aquaporin-2 water channel mutations causing nephrogenic diabetes insipidus with partial vasopressin response. Human Molecular Genetics 1997; 6: 1865-171.

Croft PK, Bedford JJ, Leader JP, Walker RJ. Amiloride modifies the progression of lithium-induced renal interstitial fibrosis. Nephrology (Carlton). 2018 Jan;23(1):20-30.

Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. BMC Nephrology 2018; 19:305.

Efe O, Klein JD, LaRocque LM, Ren H, Sands JM. Metformin improves urine concentration in rodents with nephrogenic diabetes insipidus. JCI Insight. 2016 Jul 21;1(11).

Elalouf JM, Roinel N, de Rouffignac C. Effects of human calcitonin on water and electrolyte movements in rat juxtamedullary nephrons: inhibition of medullary K recycling. Pflugers Arch. 1986; 406:502-8.

Fujiwara TM, Bichet DG. Molecular Biology of hereditary diabetes insipidus. J Am Soc Nephrol 2005; 16:2836-46.

Gupta S, Kripafani M, Khastgir U, Reilly J. Management of the renal adverse effects of lithium. Advances in psychiatric treatment. 2013; 19, 457–66.

Gupta S, Khastgear U. Drug information update. Lithium and chronic kidney disease: debate and dilemmas. BJPsych Bulletin 2017;41:216-20.

Johnson G. Lithium early development, toxicity and renal function Neuropsychopharmacology 1998; 19:200-5

Johnson G, Glenn E, Hunt G, Duggin G, Horvath JS, Tiller DJ. Renal function and lithium treatment: initial and follow up tests in Manic-Depressive patients. J. Affective Disorders 1984; 6: 249-63.

Johnson G. Comment on Janos Rado's final comment. In: Blackwell B. The Lithium Controversy. A historical autopsy. inhn.org.collated. July 5, 2018.

Khanna A. Acquired nephrogenic diabetes insipidus. Semin Nephrol 2006;26: 244-8.

Milano S, Carmoniso M, Gerbino A, Procino G. Hereditary nephrogenic diabetes insipidus: Pathophysiology and possible treatment. An Update. Int J Mol Sci. 2017 Nov 10;18(11).

Mizuno H, Fujimoto S, Sugiyama Y, Kobayashi M, Ohro Y, Uchida S, Sasaki S, Togari H. Succesful treatment of partial nephrogenic diabetes insipidus with thiazide and desmopressin. Horm Res. 2003;59(6):297-300.

Moses AM, Scheinman SJ, Oppenheim A. Marked hypotonic polyuria resulting from nephrogenic diabetes insipidus with partial sensitivity to vasopressin. J Clin Endocrinol Meta.1984; 59:1044–9.

Müller D, Marr N, Ankermann T, Eggert P, Deen PMT. Desmopressin for nocturnal enuresis in nephrogenic diabetes insipidus. Lancet 2002;359 (9305) 495-7.

Oiso Y1, Robertson GL, Nørgaard JP, Juul KV. Clinical review: Treatment of neurohypophyseal diabetes insipidus. J Clin Endocrinol Metab. 2013 Oct;98(10):3958-67.

Radó JP. 1-desamino-8-D-arginine vasopressin (desmopressin) concentration test. Am J Med Sci 1978; 275: 43-52.

Radó J. Diabetes mellitus és (nephrogen) diabetes insipidus együttes előfordulása. Hypertonia és Nephrologia 2011;15:183-7.

Radó J. Final comment (Use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus. In Blackwell B: The lithium controversy. A historical autopsy inhn.org.controversies. inhn.org.collated. January 25, 2018a.

Radó J. Addition to final comment. Calcitonin in lithium-induced nephrogenic diabetes insipidus. In Blackwell B. The lithium controversy. A historical autopsy. inhn.org.collated Sept.13, 2018b.

Radó J. Renal Toxicity of Lithium in Historical Perspective with Special Reference To Nephrogenic Diabetes Insipidus and its Treatment. inhn.org.collated May 2, 2019.

Radó JP, Marosi J. Prolongation of duration of action of 1-deamino-8-D-arginine vaso(desmopressin) by ineffective doses of clofibrate in diabetes insipidus. Horm Metab Res 1975b; 7: 527-8.

Radó JP, Marosi J, Borbely L, Tako J. Individual differences in the antidiuretic response induced by single doses of 1-deamino-8-D-arginine-vasopressin (desmopressin) in patients with pituitary diabetes insipidus. Int J Clin Pharmacol Biopharm 1976a; 14: 259-65.

Radó JP, Marosi J, Fischer J. Shortened duration of action of 1-deamino-8-D-arginine vasopressin (desmopressin) in patients with diabetes insipidus requiring high doses of peroral antidiuretic drugs. J Clin Pharmacol 1976b; 16: 518-24.

Radó JP, Marosi J, Fischer J. Comparison of the antidiuretic effects of single intravenous and intranasal doses of desmopressin in diabetes insipidus. Pharmacology 1977; 15: 40-5.

Radó JP, Marosi J, Fischer J, Tako J, Kiss N. Relationship between the dose of 1-deamino-8-d-arginine vasopressin (desmopressin) and the antidiuretic response in man. Endokrinologie 1975a; 66: 184-95.

Radó JP, Marosi J, Szende L, Borbely L, Tako J, Fischer J. The antidiuretic action of 1-deamino-8-D-arginine vasopressin (desmopressin) in man. Int J Clin Pharmacol Biopharm 1976c; 13: 199-209.

Radó JP, Szende L, Marosi J. Influence of glyburide on the antidiuretic response induced by 1-deamino-8-d-arginine vasopressin in patients with pituitary diabetes insipidus. Metabolism 1974a; 23:1057-63.

Radó JP, Simatupang T, Boer P, Dorhout Mees EJ. Pharmacologic studies in Bartter's syndrome: effect of desmopressin and indomethacin on renal concentrating operation. Part II. Int J Clin Pharmacol Biopharm 1978; 16:22-6.

Radó JP, Szende L. Simultaneous familial occurrence of distal renal tubular acidosis, polycystic kidney and nephrogenic diabetes insipidus. Orvosi Hetilap 1995; 136:995-1001.

Radó JP, Szende L, Marosi J, Juhos É, Sawinsky I, Takó J. Inhibition of the diuretic action of glibenclamide by clofibrate, carbamazepine and 1-deamino-8-D-arginin vasopressin (desmopressin) in patients with pituitary diabetes insipidus. Acta Diabetologia Latina 1974b;11:179-97.

Radó JP, Zdravkova S. Lithium-induced chronic water-metabolism disorder (nephrogenic diabetes insipidus). Orv Hetil. 1991;132, 1987-90.

Rybakowski J. Final comment: Half a Century of Inspiring Lithium Controversy. Barry Blackwell: The Lithium controversy: A historical autopsy. Collated by Olaf Fjetland. inhn.org. collated. September 30, 2017.

Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, Geddes JR. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. International Journal of Bipolar Disorders 2014; 2:15.

Stasior DS, Kikeri D, Duel B, Seifter JL. Nephrogenic diabetes insipidus responsive to indomethacine plus desmopressin. New Eng J Med 1991; 324: 850-1.

Vierhapper H. Indomethacine in the treatment of lithium-induced nephrogenic diabetes insipidus. Arch Int Med 1990; 150: 2419.

Walle JV, Stockner M, Raes A, Nørgaard JP. Desmopressin 30 years in clinical use: A safety review. Curr Drug Saf. 2007 2:232-8.

Warnes H. Comment on Janos Radó's additional final comment: Calcitonin in lithium-induced nephrogenic diabetes insipidus. In: Blackwell B: The lithium controversy. A historical autopsy. inhn.org.collated. January 16, 2019.

Weinstock RS, Moses AM. Desmopressin and indomethacine for nephrogenic diabetes insipidus in patients receiving lithium carbonate. South Med J 1990; 83: 1475-7.
ZhangY, Peti-Peterdi J, Brandes A, Riquier-Brison A, Carlson NG, Müller CE, Ecelbarger CM, Kishore BK. Prasugral suppresses development of lithium-induced nephrogenic diabetes insipidus in mice. Purinergic Signalling 2017; 13:239-48.

ZhangY, Peti-Peterdi J, Heiney KM, Riquier-Brison A, Carlson NG, Müller CE, Ecelbarger CM, Kishore BK. Clopidrogel attenuates lithium-induced alterations in renal water and sodium channels/transporters in mice. Purinergic Signalling 2015; 11:507-8.

inhn.org.

July 18, 2019