János P. Radó's Collection
Collated by Mateo Kreiker

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Biographic sketch by János P. Radó

Family History

My full name is János Péter Radó. I was born in Budapest, Hungary, May 25, 1930. My parents were living in the same flat, where I have spent my entire life since age 10. They were printers and owners of a printing office, which was located on the ground floor of a building (Hajós street 25, Budapest), on the first floor of which is our present home. The press was confiscated twice: for the first time in 1944, when Hungary was invaded by the Nazi army and the second time, in 1949 by the Soviet-backed Communist regime. This last time, the presses were destroyed. After the 1956 revolution, my parents left Hungary for Canada. They lived in Toronto for more than 25 years until they died there.

Degrees

I attended (1948-1954) and graduated from the Medical School of Budapest and became a specialist in Internal Medicine (1958), Endocrinology (1980) and Nephrology (1984). I successfully passed the examination of a course for Nuclear Medicine in 1966. (At that time, Nuclear Medicine was not yet a Specialty, not even a Subspecialty, in Hungary).

Employment

My clinical work began in 1954, in the Second Medical Department of the János Hospital, Budapest. I worked in this hospital for the next 26 and half years. From 1958 to 1980, I worked in the Isotopic Department and Metabolic Unit. This included four years in the Outpatient Clinic for Diabetic Patients (1958-1962) and a two-year absence on leave in The Netherlands (1976-1978). My clinical work was continued after the János Hospital years (1954-1980) in the Department of Hypertension and Nephrology in the Uzsoki Hospital (1980-1997). Here, as the leader of the department, I founded the Dialysis Unit of the Uzsoki Hospital and a Nephrological Laboratory for clinical and investigational purposes. After retiring from hospital clinical work in 1997, I became and am still a consultant in internal medicine, nephrology and endocrinology in a private medical institute, Virányos Outpatient Clinic.

Invention of Furosemide (Diuretic) Renography

A "by-product" of our Hungarian nuclear renal clearance studies with Hippuran 131 and 125 was the invention of the so-called "frusemide renography" which was first published in December 1967 in The Lancet and after then the extended studies, in 1968 in Nuclear Medicine.

Visiting Employment History

I was invited by Professor Evert Dorhout Mees as a visiting scientist to the Clinic of Hypertension and Nephrology of the Medical University of Utrecht, The Netherlands. The purpose of this invitation was to introduce in Utrecht those renal clearance studies for measuring glomerular filtration rate, as well as renal plasma flow, which was used by us in Budapest. I was paid by the Nierstichting Netherland. The Hypertension and Nephrology Clinic was working on nuclear methodologies in a very good cooperation with the Nuclear Department of Utrecht. The leader of this department, at that time, was Prof. Ephraim and his staff assistant was Dr. Oei HJ, a physician of Indonesian Chinese background, trained in Vienna. During our 2-year stay in The Netherlands, we became good friends with Dr. Oei and his family; we (my wife accompanied me to Holland) met several times in our homes. Although the scope of our nuclear studies in Utrecht was strictly confined on the renal isotopic clearances, I also discussed several times with Dr. Oei my favorite topic of furosemide (diuretic) renography. I gave reprints to Dr. Oei dedicated to him concerning furosemide (diuretic) renography, appearing in the aforementioned Lancet and Nuclear Medicine papers. I was glad to learn several years later, when I had already left The Netherlands to Hungary that my friend Dr. Oei, working in collaboration with Prof. EJ Dorhout Mees and Geyskes GG discovered the "captopril renography". "Captopril renography" was another example of a drug-induced distortion of the normal renogram used for the diagnosis for renovascular hypertension as was "diuretic renography" used in obstructive ureteral disorders, as well as other nephrological conditions.

Editorial Activity

I was Chief Editor of the *Hungarian Journal of Hypertension and Nephrology* from 1999 to 2012.

PhD, habilitation, Private Docent, Doctor of Science

For my scientific and clinical research work, I was awarded a PhD, in 1980, habilitation, in 1995 in the Semmelweis University, Budapest, the title of "private docent," in 1998, in the Semmelweis University Budapest, and Doctor of Science, in 1999, in the Hungarian Scientific Academy.

Titles of my dissertations

PhD: Clinicopharmacological Studies of Renal Pharmacons, Antidiuretics and Diuretics. Endocrine and Renal Pharmacology (1980). *Habilitation*: Renal Tubular Acidosis and its Complication of Nephrogenic Diabetes Insipidus (1995). *Doctor of Science*: Interaction of Medicines and Diseases in the Regulation of Serum Potassium. Hyperkalemias (1999).

Awards

In Hungary, for my scientific and clinical research work I was awarded the Semmelweiss Prize (1972), Markusovszky Prize (Hungarian Medical Weekly, 1989), Batthány Strattman László Prize (Governmental Award, 1996), Korányi Sándor Prize (Award of The Hungarian Nephrological Society, 2004), Life Achievement Award (award of the Medical University of Debrecen, 2005), Paul Gömöri Prize (award of The Hungarian Hypertension Foundation, 2005), Life Achievement Award of the Hungarian Foundation of Nephrology (2007), Török Eszter Prize (award of The Hungarian Hypertension Society, 2012,). I was selected for the Album of Portraits of the Pioneers, European Nephrological Archives, published by the EDTA-ERA at the Congress of the EDTA-ERA, on 24th May 2012, Paris, France.

Memberships

European Renal Association (ERA-EDTA), European Society of Hypertension (past), New York Scientific Academy (past), Hungarian Nephrological Society, Hungarian Hypertension Society, Hungarian Society of Internal Medicine, Hungarian Society of Radiology, Hungarian Society of Diabetes. President of the Committee for History of The Hungarian Nephrological Society.

Scientometria. Number of publications (405), Book and book chapters, Hirsch factor (30), citedness, (1929) impact factor

Number of publications: 355 printed articles on Hungarian, English and German from 1954 to 2013. Since then:2; altogether 357 (Compiled on the basis of the Library of the Hungarian Scientific Academie). Can be found in the INHN webpage, "Profiles").

Book

Haris Ágnes, Radó János: *A víz- és elektrolitháztartás zavarai: Differenciáldiagnosztika és terápia.* Budapest: Medicina Könyvkiadó, 2008. 395 pages

*Book chapters (*17*) in 3 Manuals.*

Thirteen book chapters In: Kakuk György (szerk.) Klinikai nephrologia: a vese belgyógyászati betegségeinek kézikönyve . 1201 p. Budapest: Medicina Könyvkiadó, 2004. One book chapter In: Rosivall L , Kiss I (eds.) Nephrologia. Elmélet és klinikum, dialysis, transplantatio . Budapest: Medintel Kiadó, 2003. p. 373. Three book chapters In: Kornya László (szerk.) Betegség enciklopédia I-II . 2564 p. Budapest: Springer Tudományos Kiadó, 2002. p. 691

Impact factor: exact sum of cumulative impact factor: 75,849 (collected in the years after 1974); estimated sum of the total cumulative impact factor: (estimated from the years from 1954 to 1974 on the basis of the 1998 impact factor values): 182,385

Titles of my 10 most important articles.

Radó JP, Banos C, Tako J
Frusemide renography.
LANCET 2: pp. 1419-1420. (1967)

Radó JP, Banos C, Tako J
Radioisotope renography during furosemide (lasix) diuresis.
Nuklearmedizin-Nuclear Medicine 7: pp. 212-221. (1968)

Herman E , Radó J

Fatal hyperkalemic paralysis associated with spironalactone. Observation on a patient with severe renal disease and refractory edema.

Archives of Neurology (Chicago) 15: pp. 74-77. (1966)

Radó JP

Water intoxication during carbamazepine treatment

British Medical Journal (BMJ) 3: p. 479. (1973)

Radó JP

Falsely high fluorescence in cortisol determinations due to the carbamazepine.

Hormone and Metabolic Research 5: p. 63.. (1973)

Radó JP , Borbely L

Enhancement of polyuria by glibenclamide in diabetes insipidus.

Lancet 2: p. 216.. (1971)

Radó JP

Combination of carbamazepine and chlorpropamide in the treatment of "hyporesponder" pituitary diabetes insipidus.

Journal of Clinical Endocrinology and Metabolism 38: pp. 1-7. (1974)

Radó JP , Szende L , Marosi J

Influence of glyburide on the antidiuretic response induced by 1-deamino-8-D-arginine vasopressin (DDAVP) in patients with pituitary diabetes insipidus.

Metabolism-Clinical and Experimental 23: pp. 1057-1063. (1974)

Radó JP , Tako J , Geder L , Jeney E

Herpes Zoster House Epidemic in Steroid-Treated Patients. A Clinical and Viral Study.

Archives of Internal Medicine (Chicago) 116: pp. 329-335. (1965)

Radó JP

Response to vasopressin analogues in diabetes insipidus

New England Journal of Medicine 295: p. 393. (1976)

March 17, 2016

János Radó: My 64-year (1954-2018) life product
Supplement to My Biographic Sketch

(Number in brackets below: publication list numbers

Underlined: indicates connection with neuropsychopharmacology)

Most important achievement:

Invention of "Furosemide renography" (41, 58,73,299,300,343,356)

1.Renal pharmacology

Hyperkalemic paralysis associated with spironolactone therapy (34, 60, 240)

Increase of sodium reabsorption in the distal tubule in response to furosemide (67)

Furosemide induced antidiuresis in diabetes insipidus (47)

Chlorpropamide antidiuresis in diabetes insipidus (69, 84, 93, 94)

Paradoxical increase of the renal concentrating operation in response to furosemide during infusion of hypertonic salt in man; description of the technic of two-minute clearance periods (74)

The effect of diazoxide and chlorpropamide on renal functions in man (114)

Dose-effect relationships in SIADH induced by clofibrate and carbamazepine (135)

Opposite effects of antikaluretic and antiprostaglandine compounds in Bartter syndrome (168)

Pharmacological investigation of dDAVP in diabetes insipidus: description of three different peak effects, relationships between the dose and duration of action, interindividual differences, and change in the metabolism of dDAVP in response to the prolonged treatment itself as well as coadministration of medicines having enzyminducer capabilities. (138, 139, 147, 148, 150, 155, 163, 166,167)

Decrease in the venous blood pressure and venomotor tone in response to a mercurial diuretic in cardiac insufficiency (5,13)

Effect of aldosterone and spironolactone on the renal tubules in Cushing syndrome associated with polyuria (29)

Site of effect of furosemide in man (43,45,47,48,57,65,67,72,74,81,83,85,96)

Mechanism of thiazide antidiuresis (31)

Mechanism of the chlorothiazide antidiuresis in diabetes insipidus and psychogenic polydipsia (36)

Patterns of potassium wasting in response to stepwise combinations of diuretics (286, 291)

Diuretic and antidiuretic effects of furosemide before and after Pitresssin (89)

Furosemide and thiazide potentiation because of differing site of effects (72)

Use of furosemide for the evaluation of the concentrating mechanism (61, 64)

Extreme antidiuresis in response to the combination of chlorpropamide with angiotensine (70,77, 90)

Effects of Ethacrynic acid on the specific renal functions (85,86)

Drug-induced antidiuresis in partial nephrogenic diabetes insipidus (249,INHN list, 2.)

Comparison of the diuretic effect of Azosemide and Furosemide (191,192)

Renal effects of angiotensine in man (296,304)

TTKG (transtubular potassium gradient) (293,294)

2.Nephrology-

Hipertonology Combined administration of Furosemide wash-out pyelography and furosemide radioisotope renography for the diagnosis of renovascular hypertension (101)

Furosemide-bicarbonate therapy in hyperkalemia and coma associated with renal tubular acidosis in refractory edema (104,106)

Acute effects of high dose furosemide in chronic renal insuffiency (115)

Change of the antikaluretic response in response to potassium sparing diuretics (91, 142, 144, 146, 149)

Hyperkalemia unresponsive to massive doses of aldosterone in chronic interstitial nephritis (153, 154)

Free water excretion in hypoaldosteronemic renal insufficiency (196)

"Exaggerated natriuresis" during intravenous infusion of hypertonic sodium chloride in hypertonics and healthy people (178)

"Outpatient hyperkalaemia" syndrome in hypertonic and renal patients (174)

Extreme juxtaglomerular hyperplasia in renovascular hypertension associated with "renal aldosteronism" (25)

Salt loading "in renal aldosteronism" before and after nephrectomy (71)

Effect of alpha-methyldopa, guanethidine and bethanidine on isotope-renography (68)

Different effects of frusemide administered during hypertonic saline infusion in healthy subjects and hypertensive patients (83)

Cephamandol induced acute renal insufficiency (232,233)

Anticonvulsive osteomalacia in sclerosis tuberosa associated with renal tubular acidosis (258)

3.Endocrinology-clinical chemistry

Falsely high fluorescence in cortisol determinations due to the carbamazepine (116)

Use of a simple fluorometric 11-hydroxycorticosteroids assay in the assessment of spironolactone-metabolite level in plasma and urine (120)

Use of a simple fluorometric 11-hydroxycorticosteroids assay for the investigation of interference induced by psychotropic drugs,triamtere, bencyclane, beta blocking agents (121, 122, 141, 152, 164)

Effect of dDAVP on plasma cortisol level (145)

Increase of plasma potassium level in response tot he upright posture: "upright hyperkalemia" (160, 161)

Glucose induced paradoxical hyperkalemia (183,185, 186,187,206,209-214, 219, 220, 225,227-231)

Dose-effect relationship of the ACTH-like effect of the peptide extracted from the tumorous tissue of a patient suffering from ectopic Cushing syndrome(175)

Cushing's Syndrome Associated With Chromophobe Adenoma Of The Hypophysis (30)

Effect of adrenocortical hormones on thromboplastin generation in hemophilia B (38)

Successful extraction of complicated cataract during steroid treatment in a patient suffering from haemophilia B. (24,26)

Adrenocortical insufficiency in spite of high corticosteroid excretion in a patient with thyrotoxicosis (63)

dDAVP Concentrating Test (166)

Diuretic effect of glibenclamide (95, 102)

Water intoxication induced by carbamazepine (117, INHN 1)

Combination of chlorpropamide and carbamazepine in the treatment of "hyporesponder" diabetes insipidus (127)

Interaction (antagonism) between dDAVP and glibenclamide (129)

Herpes zoster "house epidemic" developing in patients treated with corticosteroids; A clinical and Viral Study (28, 32,363)

Use of modern antidiuretic agents in the treatment of permanent lithium induced nephrogenic diabetes insipidus (Administration of excessive doses ofdesmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine) (INHN 2.)

Clinical use of "additive antidiuresis" with the various combinations of vasopressine, lysin-vasopressine, desmopressine, carbamazepine, clofibrate andchlorpropamide (98, 103, 111, 112, 118,119,123,127,135)

Antidiuresis induced by vasopressine, lysin-vasopressine, desmopressine, carbamazepine, clofibrate and chlorpropamide can be abolished by theadministration of glibenclamide (124, 125, 126,128, 129,132, 136)

Decrease of the antidiuresis during long-term treatment with carbamazepine due to enzyme induction (143, 147,157)

Simultaneous occurrence of diabetes insipidus and ascites due to liver cirrhosis (246)

Hann-syndrome (234)

Simultaneous occurrence of hyperkalemia due to aldosterone suppression and hyperfunctioning parathyroid adenoma (197)

Hypophosphatemic metabolic osteomalacia (261, 278, 284,285,295)

Clinical and laboratory effects of cloprednol (169)

Effect of dDAVP on the plazma renin activity in man (171)

Effect of dDAVP and indomethacine in Bartter-syndrome (167)

Effect of the humane and standard ACTH on the urinary excretion of cortisol (180)

Calcitonine abolishes the effect of desmopressine (INHN 2)

4.Diabetology

Paradoxical increase of peripheral glucose utilization in a patient with insulinoma treated with prednisolone (35)

Paradoxical effects of prednisone on glucose metabolism in cirrhosis of the liver (44)

Effect of chlopropamide in diabetes insipidus associated with diabetes mellitus (93, 94)

Congenital familiar nephrogenic diabetes insipidus associated with diabetes mellitus (352)

Glucose induced paradoxical hyperkalemia (183,185, 186,187,206,209-214, 219, 220, 225,227-231)

5. Hematology

Polycythemia vera turning into myelofibrosis in an individual with Pelger-Huet anomaly of the leukocytes; lack of decreased tolerance of the PH leukocytes toward radiotherapy. (16)

Mononucleosis infectiosa (One hundred and twenty eight cases from three department of hematology between 1930 and 1952) (1)

6.Cardiology

Interventricular perforation of the septum in myocardial infarction (the first two case in Hungary) (12)

Congenital septal defect associated with myocardial infarction in old age (8)

Radó, János (Nephro-endokrin pharmak)

1954

1. Devenyi P, Radó J
   Mononucleosis infectiosa
   Orvosi Hetilap95: pp. 464-469. (1954)

1955

2. Fodor I, Kincsesy A, Radó J
   [Diagnosis and pathology of perforated interventricular septum; intravital observation of two cases.]
   Orvosi Hetilap96: pp. 1293-1300. (1955)

3. Radó J
   [A case of Waterhouse-Friedrichsen syndrome of pneumococcal origin in old age.]
   Orvosi Hetilap96: pp. 1284-1287. (1955)

1956

4. Fodor I, Blumenfeld G, Radó J

   [ACTH therapy and its theoretical bases in novurit-refractor cardiac edema.]

   Orvosi Hetilap97: pp. 349-353. (1956)

5. Gonda E, Radó J

   [Venomotor tonus in circulatory diseases.]

   Orvosi Hetilap97: pp. 205-210. (1956)

6. Hammer S, Radó J

   [Pelger-Huet anomaly of leukocytes.]

   Orvosi Hetilap97: pp. 298-301. (1956)

1957

7. Radó J, Blumenfeld G, Barath F, Szirom I

   [ACTH therapy in cardiac edema refractory to novurit. II. Role of tubular factors in hypochloruria and mercury resistance.]

   Orvosi Hetilap98: pp. 408-413. (1957)

8. Radó J, Abraham K, Eszeki J

   [Combination of congenital interventricular septal defect and of a cardiac infarct in old age.]

   Zeitschrift für die Gesamte Innere Medizin und ihrE Grenzgebiete 12: pp. 1120-1123. (1957)

9. Radó J, Abraham K, Eszeki J

   [Simultaneous occurrence of congenital septal defect and cardiac infarct in old age.]

   Orvosi Hetilap98: pp. 1079-1081. (1957)

10. Radó J, Frank M, Fenyes I

    [Kidney function in diabetic coma.]

    Orvosi Hetilap98: pp. 650-653. (1957)

1958

11. Radó J, Blumenfeld G

    ACTH treatment for novurit-resistant cardiac edema; the role of tubular factors in hypochloruria and mercury-resistance.

ACTA Medica Scandinavica 160: pp. 15-23. (1958)

12. Radó J, Kincsessy A, Fodor I

[Clinical and pathological problems of the intraventricular septum perforation in the light of the literature and our own cases.]

Zeitschrift für die Gesamte Innere MEdizin und ihre Grenzgebiete 13: pp. 227-235. (1958)

13. Radó JP, Gonda E, Kovacs E

The role of venous constriction in circulatory disorders.

British Heart Journal 20: pp. 389-396. (1958)

1959

14. Radó J, Blumenfeld G, Hammer S

[Prednisone therapy of novurite-induced refractory cardiac edema. III. Significance of tubular mechanisms in the reversal of mercurial sensitivity.]

Magyar Belorvosi Archivum 12: pp. 183-188. (1959)

15. Radó JP, Blumenfeld G, Hammer S

The effect of prednisone and 6-methylprednisolone on mercurial diuresis in patients with refractory cardiac edema.

American Journal of the Medical Sciences 238: pp. 542-551. (1959)

16. Radó JP, Hammer S

Polycythemia vera turning into myelofibrosis in an individual with Pelger-Huet anomaly of the leukocytes. Blood 14: pp. 1143-1150. (1959)

1961

17. Radó J, Hamvas J, Bikich G

[Role of various factors in the pathogenesis of skin hemorrhage (steroid ecchymosis) due to new glucocorticoids.]

Magyar Belorvosi Archivum 14: pp. 107-118. (1961)

1962

18. Radó J, Hammer S, Szilagyi L

[Effect of new synthetic glucocorticoids (dexamethasone and medrol) on mercurial diuresis in liver cirrhosis. IV. Experimental studies on the renal and

extrarenal effect of steroids with special reference to the concentrating capacity of the kidney.]

Magyar Belorvosi Archivum 15: pp. 16-29. (1962)

1964

19. Radó J, Tako J, Geder L, Jeney E

    [Group Occurrance of Herpes Zoster in Patients Treated with Corticosteroids.]

    Orvosi Hetilap105: pp. 1266-1270. (1964)

20. Radó J, Hammer S, Szilágyi L

    Ujabb chlorothiazidszármazékok gyüjtőtubuláris hatása és annak jelentősége decompensált májcirrhosisban: a chlorothiazid és Aldacton eltérő hatása a distális nephronra

    Magyar Belorvosi Archivum 17: p. 298. (1964)

21. Radó J, Blumenfeld Gy

    Pleuropneumoniával szövődött generalizált herpes zoster

    Magyar Belorvosi Archivum 17: pp. 160-163. (1964)

22. Radó J, Takó J, Liszka Gy, Bodrogi Gy, Mihoczy L, Sárközy Gy, Világi Gy

    Tüdőtumort utánzó arteria pulmonális aneurysma Lutembacher syndromában és felnőttkori pitvari septumdefektusban

    Magyar Belorvosi Archivum 6: p. 317. (1964)

23. Tako J, Radó J

    [Generalized Herpes Zoster Complicated by Meningitis in a Patient Treated with Corticosteroids.]

    Orvosi Hetilap105: pp. 1271-1273. (1964)

1965

24. de Grosz I, Borbely L, Szabados D, Radó JP

    Successful extraction of complicated cataract in a patient suffering from haemophilia

    B. ACTA Ophthalmologica (1923-1994) 43: pp. 574-578. (1965)

25. Gomba Sz, Endes P, Radó J

    Verhalten des juxtaglomerularen Apparates bei renovascularer Hypertonie

    Zentralblatt für Allgemeine Pathologie und Pathologische Anatomie 111: p. 531. (1965)

26. Grosz I, Borbély L, Szabados D, Radó J

Sikeres hályogkivonás B-tipusu haemophiliában szenvedő betegen

Szemészet 102: pp. 76-80. (1965)

27. Radó J, Tako J, Miklos G

[Chromophobe Pituitary Adenoma Associated with Cushing's Syndrome.]

Orvosi Hetilap106: pp. 223-226. (1965)

28. Radó JP, Tako J, Geder L, Jeney

E Herpes Zoster House Epidemic in Steroid-Treated Patients. A Clinical and Viral Study.

Archives of Internal Medicine 116: pp. 329-335. (1965)

29. Radó JP, Tako J, Hammer C, Szilagyi L

[On the effect of aldosterone and aldactone A on various segments of kidney tubules in Cushing's syndrome with polyuria]

Zeitschrift für die Gesamte Innere Medizin und ihre Grenzgebiete 20: pp. 521-527. (1965)

30. Radó JP, Tako J, Miklos G

Cushing's Syndrome Associated with Chromophobe Adenoma of the Hypophysis.

ACTA Medica Scandinavica 177: pp. 667-672. (1965)

31. Radó JP

Mechanism of "thiazide" antidiuresis

Lancet *:(2) p. 1015. (1965)

32. Tako J, Radó JP

Zoster Meningoencephalitis in a Steroid-Treated Patient.

Archives of Neurology 12: pp. 610-612. (1965)

33. Tako J, Radó J

[Changes in the "functional reserve capacity" of the pituitary gland and the adrenal cortex under the effect of antithyroid therapy]

Orvosi Hetilap106: pp. 1646-1650. (1965)

1966

34. Herman E, Radó J

Fatal hyperkalemic paralysis associated with spironalactone. Observation on a patient with severe renal disease and refractory edema.

Archives of Neurology 15: pp. 74-77. (1966)

35. Radó JP, Tako J, Salamon F, Loczka B, Major E

Paradoxical increase of peripheral glucose utilization in a patient with insulinoma treated with prednisolone.

Endokrinologie 50: pp. 266-275. (1966)

36. Radó JP, Tako J, Szilagyi L, Hammer C

[Studies on the mechanism of chlorothiazide antidiuresis in diabetes insipidus and psychogenic polydipsia]

Zeitschrift für die Gesamte Innere Medizin und ihre Grenzgebiete 21: pp. 425-431. (1966)

1967

37. Banos CS, Tako J, Radó JP, Krasznai I, Goschl I

Diagnostic value of the 131I-labelled triiodothyronine red blood cell uptake test.

Nuklearmedizin-Nuclear Medicine 6: pp. 124-139. (1967)

38. Borbely L, Radó JP, Tako J, Farkas G, Szabados D

[Studies on the effect of adrenal cortex hormones on hemophilia]

Folia Haematologica 87: pp. 358-372. (1967)

39. Herman E, Radó J

[Fulminant pyelonephritis associated with Conn's syndrome]

Orvosi Hetilap108: pp. 1518-1520. (1967)

40. Radó J, Bános CS, Takó J, Szende L

Egyoldali nephrogen diabetes insipidus antibiotikus kezelés után

Magyar Belorvosi Archivum 20: pp. 241-253. (1967)

41. Radó JP, Banos C, Tako J

Frusemide renography.

Lancet 2: pp. 1419-1420. (1967)

42. Radó JP, Herman E

Conn's syndrome complicated by fulminant pyelonephritis in an old patient.

Journal of the American Geriatrics Society 15: pp. 448-454. (1967)

43. Radó JP, Tako J, Szabo T

Site of action of furosemide.

Journal of Clinical Pharmacology and the Journal of New Drugs 7: pp. 142-149. (1967)

44. Radó JP, Somogyi B, Takó J, Bikich Gy

Paradoxical effects of prednisone on glucose metabolism in cirrhosis of the liver

Zeitschrift für Vitamin Hormon und Fermentforschung 15:(4) pp. 343-355. (1967)

45. Radó JP, Borbely L, Tako J, Banos C

Effects of furosemide uring antidiuresis and antinatriuresis induced by angiotensin.

Medicina et Pharmacologia Experimentalis - International Journal of Experimental Medicine 17: pp. 373-377. (1967)

46. Radó JP, Tako J, Szanto Z

Aldosterone and cortisone requirement and metabolism in Addison's disease complicated by thyrotoxicosis.

Endokrinologie 52: pp. 12-21. (1967)

47. Radó JP, Banos CS, Marosi J, Tako J, Szilagyi L

Frusemide antidiuresis

Lancet *:(2) p. 569. (1967)

48. Radó JP, Borbely L, Banos CS, Tako J, Kovacs I

Actions of frusemide and a thiazide

Lancet *:(2) p. 465. (1967)

1968

49. Radó J, Tako J, Toth T, Endes P, Szabo T, Szanto E

[The effect of bethanide on aldosterone secretion in patients with renovascular hypertension]

Orvosi Hetilap109: pp. 628-632. (1968)

50. Radó J, Marosi J, Tako J, Devenyi I

[Aldacton causing intermittent hyperkalemic muscle paralysis]

Orvosi Hetilap109: pp. 452-455. (1968)

51. Radó J, Banos C, Tako J

[Radioisotope renography during furosemide(Lasix)-induced diuresis]

Orvosi Hetilap109: pp. 401-405. (1968)

52. Radó J, Marosi J, Tako J

[Incidence of hyperkalemia caused by Aldactone therapy and its significance in decompensated liver cirrhosis]

Orvosi Hetilap109: pp. 1911-1914. (1968)

53. Radó J, Szende L

A káliumkiválasztás paradox fokozódása spironolacton kezelés alatt májcirrhosisban

Magyar Belorvosi Archivum 21: p. 305. (1968)

54. Radó J

A hypertonia gyógyszeres kezeléséről: Symposium a Magyar Akadémián 1968 01 25

Magyar Belorvosi Archivum 5: p. 119. (1968)

55. Radó J, Borbély L, Takó J, Bános Cs

Diabetes mellitus és nephrogen diabetes insipidus együttes előfordulása: A pyelonephritissel járó concentrálási zavar mechanizmusának vizsgálata

Magyar Belorvosi Archivum 21: p. 97. (1968)

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July 26, 2018

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28   articles

I. Carbamazepine: Antidiuretic action: 20 articles

II. Carbamazepine: Water intoxication: 5 articles

III. Carbamazepine: Interaction with cortisol determination: 1 article

IV. Interference of psychotropic drugs with cortisol determination: 2 articles

I. CARBAMAZEPINE: ANTIDIURETIC ACTION (20 articles)

1. Radó J: Az endokrinologiai kutatások története az Uzsoki utcai kórházban és annak előzményei In: Rácz Károly , Tóth Miklós (szerk.)

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September 8, 2016

János Radó: The use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus

János Radó	January 25, 2018	Essay (Final comment on Barry Blackwell's The Lithium controversy, a historical autopsy)
Barry Blackwell	May 10, 2018	Comment
János Radó	January 8, 2020	Reply to Blackwell's comment
Gordon Johnson	July 5, 2018	Comment
János Radó	July 11, 2019	Reply to Johnson's comments
János Radó	September 13, 2018	Additional information: Calcitonin in Lithium-induced nephrogenic diabetes insipidus Calcitonin
Hector Warnes	January 17, 2019	Comment on additional information
János Radó	August 15, 2019	Reply to Warnes' comments

Abstract

Recent views about lithium therapy ("Lithium has been firmly established as the first-choice drug for preventing mood episodes in bipolar disorders, meeting all requirements of the Evidence-Based Medicine" [Rybakowski 2017]) made it worthwhile to seek further solutions for the alleviation of the side effects resulting from this therapy, first of all in the disturbance of water metabolism, occurring almost in every case of the patient population during long-term therapy. These views prompted us to publish our data concerning the use of modern antidiuretic agents in the treatment of "vasopressin resistant" lithium induced polyuria (permanent nephrogenic diabetes insipidus). We found that the administration of very high doses of Desmopressin resulted in clinically relevant antidiuresis, enhanced by Indomethacine and abolished by Calcitonine. Piroxicam, another nonsteroidal anti-inflammatory compound, also seemed to be antidiuretic, though in a less extent than indomethacine. The message of our writing is:

in such an important form of psychiatric treatment as Lithium is, a serious disturbance of water metabolism can be alleviated by the clever use of modern antidiuretic interventions.

Introduction

Lithium was introduced into clinical medicine (again) by Cade in 1949, for the treatment of certain psychiatric disorders. This type of therapy spread worldwide, became the "gold standard" and then gave its place to other psychotropic, and later neuropsychopharmacologic compounds (Ban 2017). Differing from the fate of many other drugs, however, lithium did not disappear totally from the palette. From time to time it appears from the dark as a "gold standard in its time," and as a possibility to treat "refractory conditions." In addition, lithium was declared many times not only a remedy of acute conditions, but as a prophylactic measure for the prevention of acute episodes of the bipolar disorder. The writer of these opinions met several patients whose Lithium treatment was going to be stopped by his or her psychiatrist, but they all were very unsatisfied with this decision. I think that the fact that the lithium carbonate molecule was too "simple" as compared to the modern drugs with more complicated chemical structures, and that therapy with Lithium was burdened with the need to determine blood levels several times in each case, as well as the number of serious side effects, not mentioning the known "corporate corruptions" in the industry producing and promoting more modern medicines (Barry Blackwell 2017), all may have played a role in the decreasing use of Lithium.

Excellent experts of lithium therapy stress the significance of this treatment. "Although a number of drugs with mood-stabilizing properties already exist, none has so far surpassed lithium as far as prophylactic efficacy in bipolar illness is concerned, not even to mention a duration of such prophylaxis" (Rybakowsky 2017). "The evidence base for lithium in the long-term treatment of bipolar disorders has strengthened. With no other drug available having such ample and consistent evidence for its efficacy lithium remains the most valuable treatment option in this indication" (Severus 2014). Further opinions about Lithium therapy can be found in collated documents in the INHN webpages under the heading Lithium controversy (Blackwell 2014.) In any case, use of lithium proved to be a valuable way to treat certain psychiatric diseases, with the probable capability to prevent acute episodes. Therefore, further studies concerning both the effects and side effects of lithium are not useless efforts even in the "molecular genetic era" of neuropsychopharmacology (Ban 2017).

Our Studies Concerning the Effects of Modern Antidiuretic Agents

One of the side effects of lithium is a disorder in renal concentrating operation (Forrest 1974; Glick 1984). The disturbance in water metabolism is appearing almost in every patient treated with lithium on a long-term basis (Allen 1989). The abnormality is frequently mild, manifesting in increased urine volume and polydipsia of various degree because of the decreased water reabsorption in the distal nephron. (Boccalandro 2004; Cohen 2002; Haris and Radó 2008; Kazama 2007). Sometimes, however, marked polyuria, resembling "diabetes insipidus" can develop. As this polyuria is "vasopressin resistant" by definition it is named "nephrogenic diabetes insipidus" (Bedford 2008; Kalra 2016; Radó 1978, 1998; Thompson 1997). We have dealt with these abnormalities for several years and during our studies we found a 61-year-old women patient suffering from affective bipolar disorder in whom nephrogenic diabetes insipidus developed during lithium therapy lasting more than 10 years. Her serum calcium, potassium and glucose levels were normal, 10 ug dDAVP into both nostrils was ineffective and the water deprivation test was negative. Therefore, diabetes mellitus, central diabetes insipidus and psychic polyuria have been excluded from the polyuric disorders, as well as the calcium or potassium abnormality induced nephrogenic diabetes (Radó 1991, 1993). As the polyuria did not cease after discontinuation of lithium it was named "permanent lithium induced nephrogenic diabetes insipidus" (Guirguis 2000; Neithercut 1990; Simon 1977). Although nephrogenic diabetes insipidus is said to be "vasopressin resistant," on the basis of our and others' previous investigations (Boccalandro 2004; Moses 1984; Radó 1978/b, 1995, 2004, 2007, 2011; Stasior 1991; Weinstock and Moses 1990), we did not exclude the use of certain vasopressin derivatives in this condition.

In our above-mentioned patient, polyuria developed during Lithium treatment; the average 24hr urine volume was 5483 ml, while the 24hr glomerular filtration rate (endogenous creatinine clearance) was only 31.5 ml/min. Alleviating polyuria is a very important immediate task in such patients: having a less disturbed night's rest. As mentioned above, despite the theoretical vasopressin resistant condition we gave excessive supramaximal doses of a very powerful antidiuretic compound, desmopressin (1-deamino-8-d-arginine –vasopressin, dDAVP). This vasopressin derivative molecule has an extremely strong antiuretic capability combined with a uniquely long duration of action (Radó 1975a,b, 1976a,b,c,d, 1977, 1978a). dDAVP was also given in certain cases of congenital and acquired nephrogenic diabetes insipidus for antidiuretic purposes (Boccalandro 2004; Moses 1984; Radó 1995). The administered doses were generally less then given by us. Nonsteroidal anti-inflammatory compounds have also been successfully administered in some cases of similar

conditions. These drugs were administered also in Lithium induced polyuria (Allen 1989; Radó 1991, 1993, 1995; Weinstock and Moses 1990; Vierhapper 1990). However, in several cases of these disorders with excessive polyuria, administration of nonsteroidal drugs failed or the effect was not satisfactory as shown in our patient presented here. The combination of dDAVP and nonsteroidal drugs also have been tried (Weinstock and Moses 1990). In such cases we used a combination of nonsteroidal drugs with excessive - supramaximal doses of dDAVP. A way to administer these two drugs is reported here.

As our patient suffered too from very severe arthritic and osteogenic pains, Calcitonin was also given. During these studies we discovered that co-administration of Calcitonin with dDAVP can abolish the antidiuretic effect of the latter (Radó 1991,1993). Surprisingly, the original condition of the nephrogenic diabetes insipidus is restored when adding Calcitonin to the continued administration of dDAVP. One of our main purposes is to describe this interaction between dDAVP and Calcitonine.

Investigations Performed During Maintained Lithium Therapy

We studied our patient both during maintained lithium carbonate treatment and again several months after the discontinuation of lithium. During maintained lithium therapy the investigated parameters can be seen in Figures 1, 2 and 3. Standard methods were used in the laboratory determinations as well as in the statistics. The patient was allowed to drink water "ad libitum." Daily sodium intake was 100 mmol, potassium intake was 40 mmol. dDAVP was given 30-30 ug into both nostrils 5 times a day, at 8 am, 12 am, 4 pm, 8 pm, and 12 pm.

Urine was collected in 24hr clearance periods. After a 7-day "no drug" period, indomethacine (75 mg per day) was given for six days. After a wash-out period, dDAVP was administered for five consecutive days. After that, indomethacine and dDAVP were given in combination for a 6-day period. (Duration of investigational periods are indicated with "N" in the figures.) The combination of calcitonin and dDAVP was studied in a 11-day period (daily 100 IU calcitonin was given).

Results are Summarized in Figures 1-3 and in the Table

We can see in Figure 1 that indomethacine (administered alone) as compared to "no drug" did not cause significant change in urine volume and osmolality.

However, dDAVP (administered alone) as compared to "no drug" significantly decreased (p<0.05) free water excretion expressed in the percentage of glomerular filtration rate (CH2Ox100/GFR) and increased (p<0.05) urine osmolality.

In response to dDAVP (administered alone) as compared to indomethacine (administered alone), urine volume (1 asterisk= p<0.05) and free water excretion decreased (3 asterisks= p<0.001) while urine osmolality increased (p<0.001).

After administration of the combination of indomethacine and dDAVP as compared to dDAVP (administered alone), urine volume (p<0.001) and free water excretion (p<001) decreased while urine osmolality increased (p<0.001).
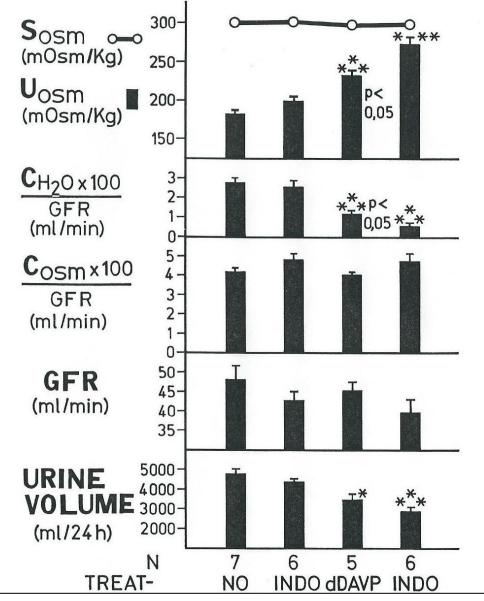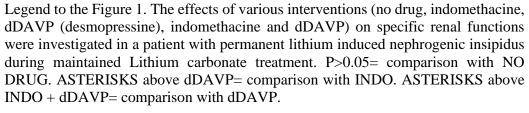
Figure 1

Legend to the Figure 1. The effects of various interventions (no drug, indomethacine, dDAVP (desmopressine), indomethacine and dDAVP) on specific renal functions were investigated in a patient with permanent lithium induced nephrogenic insipidus during maintained Lithium carbonate treatment. P>0.05= comparison with NO DRUG. ASTERISKS above dDAVP= comparison with INDO. ASTERISKS above INDO + dDAVP= comparison with dDAVP.

In Figure 2 we can see that dDAVP (administered alone) decreased urine volume ($p<0.001$) and free water excretion ($p<0,01$), while increased ($p<0.05$) urine osmolality as compared to "no drug" was seen. However, when calcitonin was combined with dDAVP urine volume ($p<0.05$) and free water excretion ($p<0.001$) increased and urine osmolality decreased (not significant) as compared to dDAVP (administered alone).
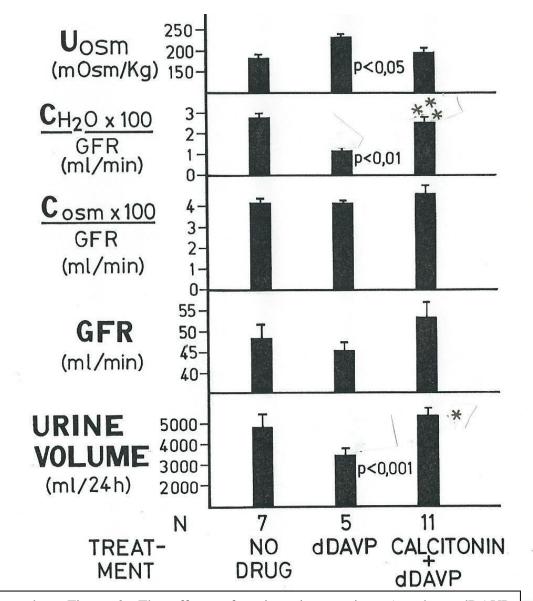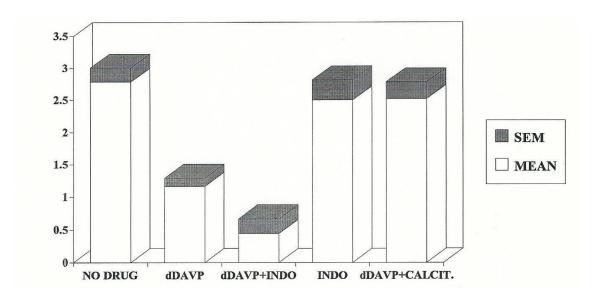
Figure 2

Legend to Figure 2. The effects of various interventions (no drug, dDAVP (desmopressine), Calcitonine and dDAVP) on specific renal functions were investigated in a patient with permanent Lithium induced nephrogenic insipidus during maintained lithium carbonate treatment. dDAVP induced a marked antidiuresis which has been abolished by Calcitonin despite further administration of dDAVP. ASTERISKS = comparison of CALCITONIN + dDAVP to dDAVP.

In Figure 3 changes of free water excretion (expressed in the percentage of glomerular filtration rate) can be seen. dDAVP (administered alone) caused a decrease, while co-administration of indomethacine and dDAVP potentiated this effect. Indomethacine (administered alone) was practically without any effect. Calcitonin abolished the effect of dDAVP.

Figure 3

Legend to Figure 3. The effect of various interventions (no drug, dDAVP /desmopressine/, dDAVP and indomethacine, indomethacine, dDAVP and Calcitonin) on free water excretion expressed in the percentage of glomerular filtration was investigated in a patient with permanent lithium induced nephrogenic insipidus during maintained Lithium carbonate treatment. CH2Ox100/GFR ml/min mean values and standard error of the mean are given.

TABLE

DRUG	URINE VOLUME	$Cosmx100/GFR$	CH_2OX100/GFR
	(ml/min)	(ml/min)	(ml/min)
NO	4778 ± 335	4.17 ± 0.21	2.78 ± 0.22
INDO	4350 ± 180	4.76 ± 0.31	2.50 ± 0.32
dDAVP'	3480 ± 299^{X}	4.13 ± 0.16	1.16 ± 0.13^{XXX}
INDO+dDAVP	2875 ± 161^{xxx}	4.71 ± 0.40	$0.44\pm0.22^{xxx\ Y|}$
CALCIT+dDAVP	5363 ± 283	4.59 ± 0.38	2.52 ± 0.27^{yyy}

Values are expressed as mean±SEM. x=p<O.O5; xxx = p< 0.001 as compared to "no drug" - Y= p< 0.05; YYY=p<O.OOl as compared to the single drug.

Abbreviations:

dDAVP=1-deamino-8D-arginine   vasopressin=desmopressin.
INDO=indomethacine. CALCIT= calcitonine.
C_{osm} =osmolal clearance; $C_{H_2}O$=- free water clearance; GFR=glomerular filtration rate.

As shown in the table above, changes in urine volume, osmolal clearance and free water excretion (expressed in the percentage of glomerular filtration) can be seen numerically. Indomethacine (administered alone) was practically without any effect, while desmopressine (administered alone) caused significant decrease both in urine volume and free water excretion, enhanced markedly by the co-administration of indomethacine. (In osmolal clearance no significant change occurred.).

We can summarize the results of the first part of our present studies by reporting that administration of excessive doses of Desmopressin resulted in clinically relevant antidiuresis, enhanced by Indomethacine and abolished by Calcitonin.

After performing these investigations, administration of lithium carbonate was discontinued.

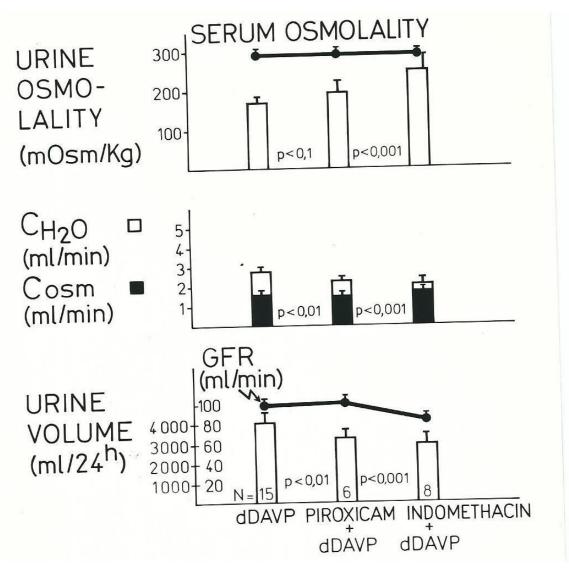## *Investigations Performed after Stopping Lithium Therapy*

Polyuria remained and practically did not change during the next three years. Therefore, the diagnosis is: "permanent" lithium induced nephrogenic diabetes insipidus. Another interesting observation was that the glomerular filtration rate increased from the 31-47 ml/min value, found during lithium therapy, to 130 ml/min two months after the discontinuation of lithium and permanently remained at this level. The increase of glomerular filtration apparently did not enhance the polyuria. Polyuria was, however, partially sensitive to Desmopressin.

After stopping lithium therapy, two months later the patient was studied again. This time the effect of dDAVP (administered alone) – "as baseline" – was compared with that of the combinations of dDAVP and indomethacine, as well as dDAVP and piroxicam. (To have an ideal baseline, discontinuation of dDAVP was not possible because it would have been unethical and the patient definitely opposed it.) Urine volume, free water excretion, osmolal clearance, urine and serum osmolality, as well as glomerular filtration rate were determined.

It can be seen in Figure 4 that indomethacine plus dDAVP as compared to dDAVP (administered alone) was antidiuretic (urine volume [p<0.001] and free water excretion

[p<0.001] decreased and urine osmolality [p<0.001] increased) without any consistent change in osmolal clearance, glomerular filtration rate and serum osmolality. Piroxicam plus dDAVP as compared to dDAVP (administered alone) was also antidiuretic (urine volume [p<0.01] and free water excretion [p<0.01] decreased and urine osmolality [p<0.1] 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 ca 20-30 %. It should be mentioned, that another nonsteroidal drug (aspirin) had no antidiuretic capability (Vierhapper 1990).

Figure 4

Legend to Figure 4. Two months after discontinuation of lithium carbonate treatment the effects of various interventions (dDAVP /desmopressine/, piroxicam and dDAVP, indomethacine and dDAVP) on specific renal functions were investigated in a patient with permanent lithium induced nephrogenic insipidus.

Conclusion

The message of our present writing is that in such an important form of psychiatric treatment as lithium is, a serious side effect, the disturbance of water metabolism, can be alleviated by clever use of modern antidiuretic interventions.

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January 25, 2018

Barry Blackwell's comment

I want to thank János Radó for his thoughtful final contribution to the collated lithium file. This is a fairy tale ending to a long saga which provides a detailed and inventive management of a serious side effect that may make a significant contribution to the safe use of a simple ion that remains the best, safest and least expensive treatment for the prevention of recurrent episodes of bipolar disorder. Schou and Cade would have been pleased.

May 10, 2018

János Radó's reply to Barry Blackwell's comment

I am delighted by the nice words of Barry Blackwell. This honor presented to me is extraordinary indeed, considering that it comes from one of the greatest persons in the field of treatment of bipolar disorder with lithium.

There could not be a higher praise for me than "Schou and Cade would have been pleased."

I felt that my merit is much lower than the one contributed to me by Barry Blackwell; that is the reason for which I was unable to reply to his comments for a long time.

January 8, 2020

Gordon Johnson's comment

Uncertainty concerning lithium's effects on renal function are widespread and may adversely affect clinical management. As Radó notes lithium is the drug of first choice in long term prophylactic treatment in bipolar disorder requiring clinical and laboratory monitoring.

Thirst and increase of urine volume (polyuria) are two of the most frequently reported side effects. These changes are attributed to decreased responsiveness of the renal tubules to the antidiuretic hormone. This impairment of urinary concentrating ability is considered a reversible pharmacological-effect. Polyuria has been reported in up to 50% of patients; with polyuria greater than 3 litres per 24 hours in 20% of patients on long term lithium therapy (Boton, Gauiria and Battle 1987). Such increased urine volume carries a potential risk of toxicity to the patients because of sodium depletion, excessive fluid loss or reduced fluid intake. Progressive impairment may occur in some patients leading to a diabetes insipidus syndrome.

In 5 to 10 % of patients the impairment of concentrating ability may be irreversible or only partly reversible upon lithium discontinuation (Bendz 1983).

In contrast glomerular function remains relatively unscathed (Johnson, Glenn, Hunt et al 1984). There is an inverse correlation between maintenance plasma lithium levels and urinary concentrating ability and plasma levels should be kept at the lowest level consistent with adequate therapeutic effect. As renal tubular concentrations of lithium may be 10-20 times that in plasma what are moderate differences in plasma level will be considerably amplified at the tubular level.

Radó reports a case study in a patient with irreversible diabetes insipidus associated with lithium maintenance treated in a cross over study with high dose pitressin analogue alone and in combination with indomethacin or calcitonin. Excessive doses of desmopressin alone had an antidiuretic effect with decreased urine volume and increased osmolality The nonsteroidal drug indomethacin enhanced the effect while calcitonin abolished it.

The mechanisms involved remain unexplained. No adverse effects were noted. The diabetes insipidus persisted following lithium discontinuation and remained unchanged over three years. A small improvement in glomerular filtration was noted. This also remained unchanged over the three years.

This is an interesting report of effective treatment paradigm in severe lithium induced diabetes insipidus and warrant s further investigation.

Risk factors associated with impaired renal function in patients on lithium are

1. Current or previous episodes of lithium intoxication
2. Lithium dose and plasma levels
3. Concomitant psychotropic medication
4. Cardiovascular disease
5. Age decline in GFR

There is no consistent evidence that differences in lithium preparations or dosage regimens effect renal function differentially. The clinical benefits obtained in the majority of patients far outweigh the identifiable risks of renal impairment.

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July 5, 2018

János Radó's reply to Gordon Johnson's comment

I would like to thank Gordon Johnson for his comments on my final comment on the collated document of Barry Blackwell's Lithium controversy project. I am especially grateful for his comments because it was from his reports that we learned the natural history of renal function changes in patients under lithium therapy (Johnson, Glenn, Hunt et al. 1984; Johnson 1998).

In some patients treated for 10-20 years urinary concentrating ability studied during administration of vasopressin decreased below plasma osmolality (300mosm/Kg). This observation was confirmed later by many investigators. Thus, the development of nephrogenic diabetes insipidus as a consequence of long-term lithium treatment is no longer a rarity. In some cases withdrawal of lithium resulted in improved renal function, while in others lithium-induced nephrogenic diabetes insipidus remained irreversible, e.g., "permanent" (Radó and Zdravkova 1991,1993). Even in these cases therapy is not absolutely hopeless. Several therapeutic options are available, by which the patient's rest during night can be somewhat secured by decreasing the polyuria with thiazide diuretics, indomethacine, amiloride, desmopressin and, most importantly, combinations of them (Croft, Bedford, Leader and Walker 2018; Mizuno, Fujimoto, Sugiyama et al. 2003; Radó 2018, 2019; Stasior, Kikeri, Duel and Seifter 1991; Weinstock and Moses 1990).

Although lithium-induced permanent nephrogenic diabetes insipidus is "by definition" a vasopressin-resistant condition, vasopressin resistance in many cases is not absolute (Canfield, Tamarappoo, Moses et al.1997; Moses, Scheinman and Oppenheim 1984). When we started our studies with desmopressin a "supramaximal" dose was 300 mcg 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 1975). When we used desmopressin for nephrogenic diabetes insipidus 300 mcg was given during 24 hrs (Radó and Zdravkova 1991,1993). In the meantime, however, it became known that desmopressin may be effective also in hematologic disorders. In these disorders, in certain cases, desmopressin was given in very extreme doses

The industry produced desmopressin preparations containing very high concentrations of desmopressin which acted on the blood clotting mechanism for bleeding disorders. By using such a preparation (Octim Nasal Spray Ferring Pharmaceuticals Ltd) administration of 300 mcg (150 mcg into each nostril) as a single dose is easily feasible.

To the best of my knowledge this preparation has not been tried, up to now, in the combination therapy (with indomethacine or other compounds) of the lithium-induced permanent nephrogenic diabetes insipidus. Nevertheless, Gordon Johnson's statement, based on his studies, is valid also at present: "the results confirm the safety of lithium administration in the majority of patients." This wise sentence has been corroborated since many times (Aiff, Attman P, Aurell et al. 2014; Blackwell 2014; Bendz Schön, Attman and Aurell 2010; Croft, Bedford, Leader and Walker 2018; Radó 2018, 2019; Rybakowski 2017; Severus 2014; Shine, McKnight, Leaver and Geddes 2015).

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July 11, 2019

János Radó: Additional information

Calcitonin in lithium-induced nephrogenic diabetes insipidus

In our previous studies the favorable antidiuretic action of Desmopressin was counteracted by the concomitant administration of Calcitonin in Lithium-induced permanent

nephrogenic diabetes insipidus (Radó 2018). However, the exact mechanism of the abolishment of Desmopressin-induced antidiuresis by Calcitonin was not clear. As the opinions in the literature are rather divided concerning the basic water metabolic action of Calcitonine, further considerations may have significance.

Calcitonin is a "*tricky*" hormone, having both diuretic and antidiuretic properties. *Diuretic effect* of Calcitonin was an observation mainly in the older literature (Carney, and Thompson 1981; Keeler, Walker and Copp 1970) and is in harmony with our published data on a water mobilizing action (Radó 1991, 1993, 2018). On the other hand, *a water retaining action* was found by the de Rouffignac group (Elalouf, Roinel and de Rouffignac 1986) in response to *human* Calcitonine in rats during microculture studies *simulating* the changes induced by Desmopressin. The results of these investigations were later confirmed by elegant sophisticated methods (Bouley 2011) *indicating that Calcitonine has a vasopressin-like action, indeed*. Calcitonine was even recommended - though purely on theoretical basis - for the treatment of nephrogenic diabetes insipidus, i.e., in a vasopressin resistant condition (Bouley et al. 2011).

An alternative explanation to the complicated water effects of Calcitonin may be provided by supposing that both Desmopressin and have an effect on the same renal tubular site on the vasopressin (V2) receptor, but the effect of Calcitonin is weaker than that of Desmopressin. So, Calcitonine, by occupying the receptors, can have a competitive antagonism with the Desmopressin molecule. *Further studies are necessary to confirm or exclude the possible competitive antagonism between Desmopressin and Calcitonin.*

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September 13, 2018

Hector Warnes' comment on János Radó's additional information

About 10% of patients on long-term lithium prophylaxis (more than 10 years) may develop a "Lithium induced nephrogenic diabetes insipidus" (Khanna 2006). I had two cases in my clinical praxis of bipolar patients who had severe polydipsia and polyuria. They woke up four or five times at night to urinate large volumes (more than 3 L/24 hrs; less 300 osmolality). I consulted a nephrologist who wisely advised me to change the medication because of the abnormal creatinine clearance and the glomerular filtration rate. The condition is caused by complete or partial resistance of the kidneys to arginine vasopressin, the antidiuretic hormone. It is considered a serious adverse effect, because of the risk of developing dehydration (sodium may decrease to less than 170 mmol/L). It has also been observed during treatment with clozapine, in patients with hypokalemia and hypercalcemia, and it has been identified as a rare genetic cause of the disorder.

I am not sure that lithium is the first line of treatment in bipolar disorder even though there is a group of bipolar patients (approximately 40%) who are responsive to lithium prophylaxis.

I would not take it lightly if the patient developed nephrogenic diabetes insipidus because of the kidney risks involved unless lithium has been the only mood stabilizing drug that kept the patient symptom free for many years. We are also aware that an important percentage of patients suffering from medical, neurological or psychiatric disorders are not compliant with the instructions given by their doctors.

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January 17, 2019

János Radó's reply to Hector Warnes' comments

Many thanks to Hector Warnes for his recent very interesting comments on my additional final comment of September 13, 2018.

I absolutely agree with Hector Warnes that: "I would not take it lightly if the patient developed nephrogenic diabetes insipidus because of the kidney risks involved unless lithium has been the only mood stabilizing drug that kept the patient symptom free for many years."

In some patients treated more than10 years with lithium urinary concentrating ability decreases below plasma osmolality. Development of nephrogenic diabetes insipidus as a consequence of long-term lithium treatment is not a rarity anymore. In the two patients with severe disturbance in the renal concentrating operation of Hector Warnes it was a really wise decision to stop lithium therapy. In some cases withdrawal of lithium results in improvement in renal function, while in others lithium-induced nephrogenic diabetes insipidus remains irreversible (Radó and Zdravkova 1991,1993). Even in these cases of "lithium-induced permanent nephrogenic diabetes insipidus" therapy is not absolutely hopeless, there are several therapeutic options available, by which the rest of the patient during night can be somewhat secured by decreasing the polyuria. Thiazide diuretics, indomethacine, amiloride, desmopressin and most importantly combinations of them are our armamentarium in the alleviation of polyuria and polydipsia (Croft, Bedford, Leader and Walker 2018; Mizuno, Fujimoto, Sugiyama et al. 2003; Radó 2018; Radó 2019; Stasior, Kikeri, Duel and Seifter 1991; Weinstock and Moses 1990).

It was the conclusion of our previous work that in such an important form of psychiatric treatment as lithium is, a serious side effect, the disturbance of water metabolism, can be alleviated by clever use of modern antidiuretic interventions. (Radó 2018)

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August 15, 2019

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).
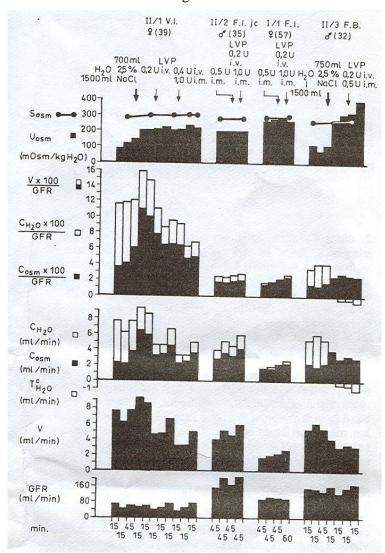
The diagnosis may be difficult in patients with the partial form of the diseases. Fortunately, sophisticated molecular genetic studies provide exact methods for successful differentiation. The identification, characterization and mutational analysis of the two different genes, the arginine vasopressin 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 ($CH2O$) 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 ($TcH2O$). Changes are similar in the free water clearance expressed in the percentage of glomerular filtration rate ($CH2Ox100/GFR$). 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

Chlorothiazide, 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: DDAV*P), 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 Radó's patients with central diabetes insipidus (Radó 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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May 2, 2019

Janusz Rybakowski's commentary

The paper written by János Radó provides a detailed description of one of the frequent renal side-effects of lithium: an impairment of renal concentrating ability which, in rare cases, can have its apogeum in lithium-induced nephrogenic diabetes insipidus. As to diabetes insipidus, the author discusses the available treatments of this condition pointing to the clever use of modern antidiuretic interventions. This may provide clinicians employing lithium in patients with mood disorders and encountering such a side effect, a variety of options for its management.

However, from nearly a half-century perspective of the practice of lithium treatment, I can voice an opinion that lithium-induced impairment of renal concentrating ability, leading infrequently to nephrogenic diabetes insipidus, may not be a major kidney problem connected with the long-term lithium therapy. This side-effect of lithium can be observed as early as after several weeks of lithium therapy and, in most cases, disappears completely after lithium discontinuation; it can also be effectively treated according to Dr. Radó's guidelines. During long-term lithium treatment, many patients present some degree of impairment of renal concentrating ability, however, in most cases it does not have significant clinical importance and does not lead to lithium discontinuation. The most important kidney side-effect is lithium nephropathy, developing mostly after 10 or more years of lithium treatment and, in some cases, can result in renal failure and make a real case for termination of lithium therapy. In good responders to long-term lithium, it may have a detrimental effect to the illness since a replacement of lithium with another mood stabilizer is usually not so effective.

My experience with lithium therapy dates back to 1970 when I started such treatment at the Department of Psychiatry, Medical Academy, Poznan, Poland. Two years later I described, first in Polish medical literature, a case of lithium-induced diabetes insipidus. This side effect occurred after several weeks of lithium therapy and disappeared following lithium discontinuation (Rybakowski and Daszynska 1972).

In recent years our group has performed a number of studies on kidney function in long-term lithium-treated patients. In the study published in 2012, 80 patients with a bipolar

mood disorder (26 male, 54 female), aged 60 ± 11 years, receiving lithium for 5-38 (16 ± 9) years, were investigated. Decreased estimated glomerular filtration rate (eGFR) values <60 ml/min/1.73/m² were found in 23% of patients, significantly more frequently in men that in women (38% vs. 16%). Specific gravity of the urine, equal to or below 1.005, was recorded in 21% of men and 14% of women (Rybakowski, Abramowicz, Drogowska et al. 2012).

Since the inhibition caused by lithium of the glucogen synthase kinase-3beta (GSK-3β) makes it the main mechanism of lithium action, we were interested whether the functional -50 C/T polymorphism of the GSK-3β gene could be associated with kidney function in 78 long-term lithium-treated bipolar patients. We found such an association with a lithium effect on urine concentrating capacity. Patients homozygous for C allele had significantly higher urine specific gravities (1.019 ± 0.008) compared to the remaining genotypes (1.013 ± 0.007) ($p = 0.035$), with no influence attributed to the duration of lithium treatment. Other parameters of kidney function (serum creatinine, eGFR, serum NGAL and urinary β2-MG levels) were not different between genotypes (Rybakowski, Abramowicz, Szczepankiewicz et al. 2013).

As previously mentioned, the main reasons for lithium discontinuation in long-term lithium-treated patients are the symptoms of lithium-induced nephropathy. However, such a discontinuation, especially in "excellent lithium responders" (ELR), is associated with a high risk of relapse and a treatment-resistant course. We assessed kidney function during a five-year follow-up in the ERL with the glomerular filtration rate (GFR)< 50 ml/min/1.73 m2. Three males and one female were included. At the beginning, their age was 61 ± 0.8 years and duration of lithium treatment was 27 ± 9 years. Kidney parameters (serum creatinine, GFR and urine specific gravity) were assessed at least three times during the five-year follow-up period. In three patients having the initial GRF between 47–48 ml/min/1.73 m2, the kidney parameters did not show significant changes and the patients continued lithium treatment. The patient with the lowest GFR (32 ml/min/1.73 m2) had a 14% decrease in GFR and a 10% increase in serum creatinine. However, urinary specific gravity increased during this time from 1.003 to 1.007. In this patient, the dose of lithium was decreased by one-third and he was placed under strict nephrological observation. Therefore, based on the results and in the ELR with the GFR not much lower than 50 ml/min/1.73 m2, we suggest continuing lithium with a yearly check on kidney parameters. In the ELR with a much lower GFR, a reduction of lithium dose and nephrological observation along with more frequent monitoring would be recommended (Abramowicz, Permoda-Osip, Nowak et al. 2017).

We also described five patients (two men and three women, aged 64-79 years) with ultra-long-term lithium treatment (40-45 years) and good response to such treatment. Their

serum lithium level was maintained within the range of 0.60-0.65 mmol/l, except for one male, having 0.7-0.8 mmol/l. One man had stage 3 chronic kidney disease and the other stage 2/3 chronic kidney disease. All three women had asymptomatic stage 2 chronic kidney disease. However, no progression has been observed within the last five years. The urine specific gravity in all patients was above 1.005. In all patients the cognition and professional activity were at the level of healthy subjects with comparable age and years of education. Their functioning in family and social roles was good. The beginning of lithium prophylaxis had usually been made within the first three years of the illness. Therefore, we could conclude that in patients with favorable response to lithium, such a longitudinal administration of the drug can produce satisfactory performance in vocational and psychosocial areas and the management of potential adverse effects can be adequate (Permoda-Osip, Abramowicz, Kraszewska et al. 2016).

In conclusion, from a long-term lithium administration perspective, the issue of lithium-induced diabetes insipidus is much less important than lithium-induced nephropathy. However, Dr. Radó should be congratulated for his excellent review of treatment possibilities for this lithium-induced side effect. In my opinion, the extensive therapeutic experience of Dr. Radó with lithium-induced diabetes insipidus deserves an updating publication in a regular bipolar disorder journal and I would encourage him to submit such a paper to the International Journal of Bipolar Disorders.

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June 20, 2019

János Radó's reply to Janusz Rybakowski's commentary

Many thanks to Professor Rybakowski for his comment, which is as comprehensive as a comment could be. We are grateful for the perfect evaluation of the clinical significances of the different lithium-induced renal abnormalities.

Professor Rybakowski stresses that the most important kidney side effect is lithium-nephropathy resulting in renal failure and makes a real case for termination of lithium therapy. It is sometimes a tragic event for the excellent responding long-term treated patient because of the high risk to relapse.

We have to congratulate the Rybakowski Group for their wise recommendations in lithium therapy (lowering plasma lithium levels, more intensive role of nephrologists, etc.) by which they are able to continue lithium treatment (in their excellent responding patients) even with lithium-induced nephropathy.

However, our field is lithium-induced permanent nephrogenic diabetes insipidus and other associated abnormalities. In such a patient with advanced lithium-induced renal tubular acidosis severe metabolic bone disease also developed (Radó 2018). Bone pain could not be easily eliminated. Calcitonin was administered with a surprising result. The antidiuretic action of desmopressin was abolished and the polyuria was restored. It is interesting that a basically (probably) antidiuretic molecule behaved as a "diuretic." We proposed the possibility of a competitive antagonism between desmopressin and calcitonin (Radó 2018)

By the way, I read recently with great enthusiasm Professor Rybakowski's excellent 2018 review article on Challenging the negative perception of lithium and optimizing its long term administration. The significance of this work is characterized by a remark of Domenico De Berardis at the end of the publication: "The underutilization of lithium is a plague and …malpractice. Your paper should be read by all psychiatrists and residents."

I appreciate very deeply Professor Rybakowski's commentary on my "Review of the literature" (Radó 2019).

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June 27, 2019

Janusz Rybakowski's response to János Radó's reply

I was greatly flattered by the appraisal of my comment by János Radó. It seems that the bottom line for both of us is to efficiently alleviate possible renal obstacles to long-term lithium treatment, be it nephrogenic diabetes insipidus or lithium-induced nephropathy. We concur with the notion that lithium should be used more frequently and, by doing so, it would be able to help the larger number of patients.

While lithium is the drug of choice for preventing recurrences in bipolar (and probably also unipolar) mood disorder, the fringe benefits of lithium therapy should also be emphasized. These are connected with anti-suicidal, antiviral and neuroprotective properties of this ion. Among all mood-stabilizing drugs, lithium is the most powerful for preventing suicidal behavior (Cipriani, Hawton, Stockton and Geddes 2013). The antiviral effect of lithium was demonstrated by showing a reduction of labial herpers frequency in long-term lithium-treated patients (Rybakowski and Amsterdam 1991). Finally, neuroprotective effects of lithium have been demonstrated such as increasing cerebral volume, decreasing risk of dementia as well as promising results in Alzheimer's disease (Rybakowski, Suwalska and Hajek 2018). Interestingly, the effect of lithium in dementia might be connected with its action against herpes viruses (Rybakowski 2019). A recent paper of Van Gestel, Franke, Petite et al. (2019) could also be recalled showing that lithium-treated bipolar patients show the features of decreased brain aging.

It should be hoped that disseminating knowledge on the efficient managing of lithium-induced renal side effects could contribute to more common application of this therapeutic ion in mood disorders.

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November 14, 2019

János 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 (CH2Ox100/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.

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June 27, 2019

Robert H. Belmaker's comments

Thank you for asking me to comment on this learned and mechanistically sophisticated piece by János Radó. I certainly agree that we must find treatments for lithium side effects so that fewer patients feel that they have to stop lithium. However, Radó does not give a biochemical explanation of lithium-induced nephrogenic diabetes insipidus and whether it is so clear that it is related to genetic forms. His data is basically one case of desmopressin-treated lithium-induced diabetes insipidus. Radó points out that the older literature assumed a lower maximum dose for desmopressin; now desmopressin is given in much, much higher doses for its effect on clotting. However, therein exactly lies the rub: the molecule has effects on physiology other than on the kidney, especially at high doses. That is justified for a severe clotting disorder. But we really do not know whether these clotting effects and others not yet known of high dose desmopressin are justified if the high doses were to be given widely for lithium-induced nocturia.

November 21, 2019

János Radó's reply to Robert H. Belmaker's comments

I am grateful for Robert H. Belmaker's essay discussing the divergent physiologic effects of desmopressin on the kidney and blood.

Lithium polyuria covers a broad spectrum of renal concentrating defect. From a small increase of the daily urine volume (perhaps not perceived even by the patient taking lithium)

to high polyuria, 10-12 liter a day, or much more. Such magnitude of water intake leaves practically no rest during the night; the patient awakes every half an hour throughout the night to void. We know the natural history of the development of lithium-induced nephrogenic diabetes insipidus, it requires at least 10 years of drug consumption, so generally not the youngest patients suffer from this condition (Radó 2018).
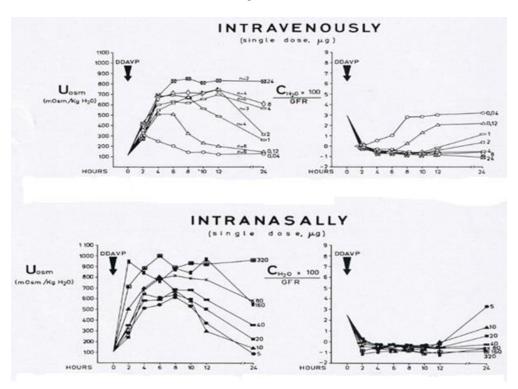
Young patients with lithium polyuria can adapt to the high water intake relative easily with increasing urinary bladder capacity. One of our young female patients voided in 800 ml portions; older patients are mostly not so "fortunate." Decrease in urinary bladder capacity occurring frequently in older patients to 200 ml or 100 ml or less combined with heavy polyuria induced by lithium is a severe curse, begging relief. I feel that in such a dramatic clinical situation administration of very high doses of desmopressin in combination with indomethacine is justified despite the potential influence on blood clotting mechanism.

It should be noted that although certain hematological disorders caused by a lack of individual blood coagulation factors may improve dramatically in response to desmopressin normal blood coagulation is apparently less influenced by the peptide.

Our experience with the administration of excessive doses of desmopressin began in years 1975-1977, before we began treating patients with lithium (1989-1996). We participated in the elaboration of the clinical pharmacology of desmopressin using extremely small and (at that time) "extremely high" doses of the peptide in patients with central diabetes insipidus, otherwise healthy persons.
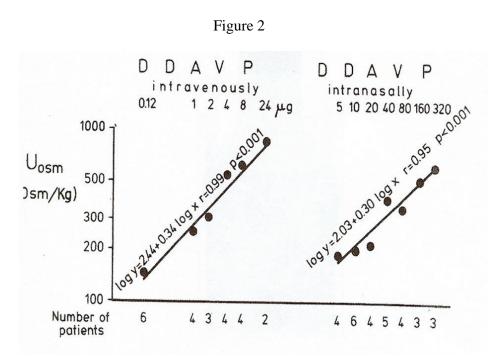
As shown in Figure 1 the relationship between time and free water clearance, expressed in the percentage of glomerular filtration (left part of the panel), and urine osmolality (right part of the panel), respectively, after intravenous (upper panel) and intranasal (lower panel) administration of desmopressin (DDAVP) in patients with central diabetes insipidus. Maximal intravenous dose was 24 ug desmopressin, while maximal intranasal dose was 320 ug (Radó, Marosi, Szende et al. 1976). A very special dose-response relationship is obvious: increasing the dose of desmopressin results in a progressive increase in the magnitude of the antidiuretic response (in free water clearance and urine osmolality) but only to a maximal limit; after that, only the duration of the antidiuretic response increases. These data stress the significance of the increase of the dose not only in the magnitude but also in the duration of the antidiuretic response.

Figure 1

The dose-response relationship of desmopressin is striking in Figure 2 using only changes in urine osmolalality (Radó, Marosi and Fischer 1977). By the equations presented in Figure 2 (below) one can estimate the expected urine osmolality value (antidiuretic response) after using a given intravenous or intranasal dose of desmopressin (DDAVP) within the first 24 hours after dosing.
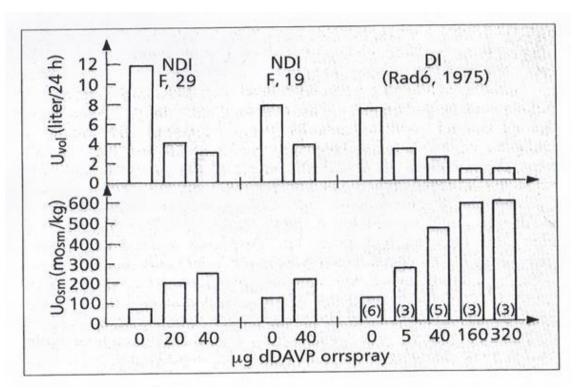
Figure 2

These basic clinicopharmacological observations were obtained in the mid-70s, 15 years earlier than the renal effects of lithium treatment were studied (Radó and Zdravkova 1991).
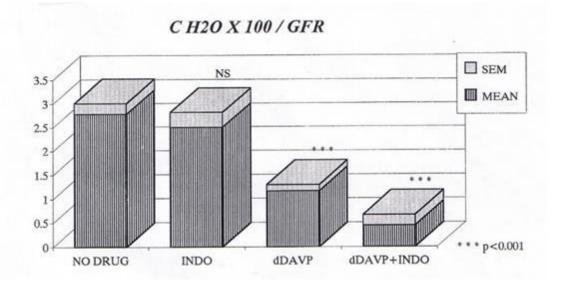
Using our above data including our dosage protocol obtained on the patients with central diabetes insipidus (practically "healthy subjects") Moses and his coworkers (1984) were able to calculate the degree of "vasopressin resistance" in their two patients with congenital nephrogenic diabetes insipidus (NDI). In Moses, Scheinman and Oppenheim's (1984) Figure 3, data of their two congenital NDI cases (in left side and center) were compared with that of Radó's 20 patients with central diabetes insipidus (in five columns on the right side DI). In the Moses group cases, desmopressin was given intranasally ("DDAVP orrspray") 6x20 ug and 6x40 ug, respectively, per day, while in the Radó cases it was given in 0-320 ug once a day. The antidiuretic effect of desmopressin was followed by urine volume (liter/day, upper panel) and urine osmolality (mOsm/Kg, lower panel). In the two congenital cases of Moses, Scheinman and Oppenheim (1984), NDI responded to large doses of desmopressin. Though 25-50 times as resistant to desmopressin nasal spray as Radó's patients with central diabetes insipidus (Radó, Marosi, Fischer et al. 1975), 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 about 25 times more than a normal 10 /ug dose.

Figure 3

We can see the dramatic antidiuretic effect of desmopressin administered alone and the potentiation of indomethacine in our case of lithium-induced permanent nephrogenic diabetes insipidus shown in Figure 4 (Radó 2018).

Figure 4

We administered high doses of desmopressin also in patients with congenital nephrogenic diabetes insipidus as well as in other type non lithium-induced acquired nephrogenic insipidus. So, we had ample clinical experiences using high doses of desmopressin in several individuals before treating lithium-induced permanent nephrogenic

diabetes insipidus. We have never had observed any significant side effect of administration of high doses vasopressin in the practically "healthy" patients and in the ones with congenital or acquired (but not lithium-induced) nephrogenic diabetes insipidus.

Further studies are necessary to evaluate the exact significance of the influence of desmopressin on the coagulation system as a risk factor in the treatment of lithium-induced severe concentrating defect.

We learned from Robert H. Belmaker's comments, however, that we should not use desmopressin, a drug with a potential effect on blood coagulation, widely in lithium-treated patients with slight impairment of renal concentrating operation.

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January 9, 2020

János Radó: Mechanism of Lithium Induced Polyuria in Historical Perspective

Abstract

The present therapy for lithium-induced nephrogenic diabetes insipidus in man is to counter anti-vasopressin action of lithium by administration of thiazide diuretics, antiprostaglandin compounds (indomethacine) combined with large doses of desmopressin. (Amiloride supplements the "present therapy" drug group). The "future" treatment seems to be (on the basis of recent animal experiments) to enhance the sensitivity of the kidney to vasopressin action by administering pharmacologic blockade of renal P2Y12 receptor. On theoretical basis it is conceivable that the present therapy of lithium-induced nephrogenic insipidus perhaps could be combined with the "future" pharmacologic blockade.

Introduction

In 1978 we found that in response to indomethacine administered to polyuric patient with familial Bartter syndrome, urine osmolality and free water reabsorption increased simultaneously with the decrease in the excretion of prostaglandin E2 (PGE2) (Radó, Simatupang, Boer and Mees 1978). In 2012 Zhang and his coworkers found that lithium-induced polyuria is due to resistance of the medullary collecting duct to the action of arginine vasopressin, apparently mediated by increased production of PGE2 (Zhang, Pop, Carlson and Kishore 2012). Therefore, PGE2 must be a key factor in the understanding and treatment of lithium polyuria. My early studies on indomethacine and desmopressin in Bartter polyuria, later studies on indomethacine and desmopressin in lithium-induced permanent nephrogenic diabetes insipidus and the results of the new studies of many investigators working in groups with Zhang and with Zhang and Peti-Peterdi ("Zhang and Peti-Peterdi group") are discussed together.

The purpose of this paper is to review the newer literature concerning the relationship between lithium polyuria and chemical (PGE2 and other), as well as genetic (P2Y12 receptor) factors.

Early Studies

In 1978 we investigated the effect of indomethacin and desmopressin on water excretion in a 32-year-old patient with familial Bartter's syndrome in whom urinary

concentration was impaired during ad libitum fluid intake without any decrease in maximal concentrating ability (Radó, Simatupang, Boer, Dorhout Mees 1978).

As shown in Figure1 and Table1, in response to indomethacin, urine osmolality and free water reabsorption increased simultaneously with the decrease in the excretion of prostaglandin E2. The indomethacin-induced improvement was, however, less than that obtained after desmopressin with or without indomethacin.

Desmopressin (Minirin) was administered in doses of 40 micrograms three times a day intranasally. After a control period (17 days) the effects of daily 200mcg indomethacine was studied during the last 12 days of a month treatment period. One week after discontinuation of indomethacine treatment desmopressin was given again in the same dose as previously.

We compared the urine osmolality findings obtained in healthy subjects and in a polyuric patient with Bartter syndrome without treatment ("no drug") and after administration of desmopressin (DDAVP) or indomethacine, as well as after combined administration of desmopressin and indomethacine during ad libitum fluid intake (Figure 1). Two determinations were done during administration of desmopressin after prolonged water restriction (quadrants).
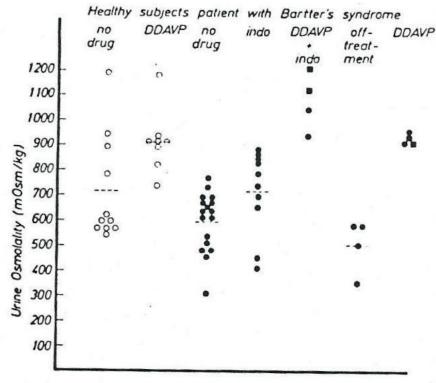

Figure 1. Urine osmolality (U_{osm}) was lower in the untreated patient than in the healthy subjects. After DDAVP this difference disappeared. Indomethacin induced a marked increase in U_{osm} in the patient.

As shown in Figure 1, in the patient with Bartter syndrome indomethacine potentiated the effect of desmopressin (DDAVP). During prolonged water restriction and desmopressin administration, urine osmolality was 924 mOsm/Kg, increasing to 1169 mOm/Kg in response to indomethacine (quadrant).

Table 1 shows the effects of indomethacine, desmopressin (DDAVP) and indomethacine plus desmopressin on specific renal function. Results of statistical analysis are

	Control	Indomethacin	Indomethacin + DDAVP	Off-treatment Control	DDAVP
n (days)	17	10	2	4	2
Urine osmolality (mOsm/Kg)	594ˣ ± 28	713ˣ ± 52	990' ± 22	504 ± 55	927' ± 28
Osmolal clearance (ml/min)	3.17 ± 0.16	2.94 ± 0.23	2.71 ± 0.45	2.91 ± 0.26	2.86 ± 0.22
Free water reabsorption (ml/min)	1.62 ± 0.14	1.70 ± 0.21	1.91 ± 0.25	1.16 ± 0.20	1.98 ± 0.17
Glomerular filtration rate (ml/min/1.73 M^2)	94.1 ± 3.5	92.6 ± 5.3	110.8 ± 12	96.2 ± 9.4	112.6 ± 8.5

x = p<0.05.   z = contracted: 958 ± 30   (p<0.001 as compared to control; p<0.005 as compared to indomethacin)
Osmolal clearance and free-water reabsorption is expressed in the percentage of glomerular filtration rate.

Table 1. Effect of Indomethacin and DDAVP on renal concentrating operation during ad libitum fluid intake.

indicated.

Effect of indomethacine on prostaglandins

During indomethacin treatment, excretion of PGE2 was decreased from 138.3 ng/24 hrs to 55 ng/24 hrs (normal range: 9-12 ng/24 hrs). PGA decreased from 205 ng/24 hrs to 97 ng/24 hrs (normal range: 71-144 ng/24 hrs), PGB decreased "from 95 ng/24 hrs to 49 ng/24 hrs (normal range: 36-74 ng/24 hrs) and PGF decreased from 146 ng/24 hrs to 64' ng/24 hrs (normal range: 40-83 ng/24 hrs).

The blood level of PGE1 also decreased from 38.9 pg/ml to 23.2 pg/ml (normal: 5.5 ± 0.8 pg/rnl). PGA changed from 241 pg/ml to 269 pg/ml (normal: 94 ± f 5 pg/rnl), PGB from 129 pg/ml to 107 pg/ml (normal: 1 il9 ± 14 pg/nil) and PGF from 22 pg/ml to 9.4 pg/ml (normal: 17.2 ± 3.3 pg/ml).

(We are greatly indebted to Prof. Dr. A. Hornych, Hopital Broussais, Paris, who kindly performed the prostaglandin determinations).

Later Studies on Indomethacine and Desmopressin

In "use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus" (Radó 2018a) we found that administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine. A theory was proposed why the presumed antidiuretic drug calcitonine exerted a "diuretic" action by abolishing the effect of desmopressin (Radó, Zdravkova 1991, 1993; Radó 2018b). These results and thoughts were discussed by Gordon Johnson (2018) and Hector Warnes (2019). Renal toxicity of lithium was reviewed in a balanced manner, considering both the renal insufficiency and end-stage renal disease, as well as the prominant tubular abnormality of nephrogenic diabetes insipidus (Radó 2019b). In this review the role of the large doses of desmopressin was analyzed in counteracting polyuria in congenital as well as in lithium-induced nephrogenic diabetes insipidus during combined administration of many different drugs (thiazide diuretics, indomethacine, piroxicam, calcitonine, etc.). Other drugs also having antidiuretic properties but without coadministration with desmopressin were also mentioned (metformin, statins, sildenafil, clopidrogel, prasugral etc.). Finally, antidiuretic drugs which could have been combined with desmopressin, but not promising in the treatment in lithium-induced nephrogenic insipidus, i.e., chlorpropamide, clofibrate and carbamazepine, were also included. From these compounds carbamazepine is an exception: its weak antidiuretic effect, combined with desmopressin, may be advantageous when it is otherwise indicated from psychiatric point of view (Radó 2019a)

New Investigations of the Zhang and Peti-Peterdi Group

Zhang and his coworkers found that lithium-induced polyuria is due to resistance of the medullary collecting duct to the action of arginine vasopressin (AVP), apparently mediated by increased production of PGE2. Genetic deletion of the P2Y2 receptor offered significant resistance to development of lithium polyuria. This change was accompanied by alterations in PGE2 signaling mediated by a marked decrease in the prostanoid EP3 receptor protein abundance thus attenuating the decrease in cAMP, modulator of arginine vasopressin, in the renal medulla (Zhang, Pop, Carlson and Kishore 2012; Zhang, Hansson, Liu , Kishore 2019).

P2Y12 Receptor Localizes in the Renal Collecting Duct

P2Y12 receptor signaling reduces cellular cAMP levels, the central modulator of arginine vasopressin. It was hypothesized that if expressed in the renal collecting duct P2Y12 receptor

may play a role in renal handling of water in health and in nephrogenic diabetes insipidus. P2Y12 receptor mRNA expression in rat kidney, and immunolocalized its protein and aquaporin-2 in collecting duct principal cells was found (Zhang, Peti-Peterdi, Müller et al. 2015).

Short-Term Studies in the P2Y12 Receptor Knockout Mice

In the P2Y12 receptor knockout mice, enhanced vasopressin activity and increased renal sodium conservation was found. These animals were less sensitive not only to the diuresis enhancement induced by lithium, but also to the lithium-induced natriuresis and kaliuresis due to the attenuation of down regulation of the major natrium or kalium transporter/channel proteins in the collecting duct (Zhang, Li, Kohan et al. 2013).

Long-Term Studies in the P2Y12 Receptor Knockout Mice

Age matched wild type and P2Y12 receptor knockout mice were fed regular or lithium-added diet for five months. There was a steady increase in lithium-induced polyuria, nariuresis and kaliuresis in wild type mice, but increases in these parameters were very low in the knockout mice. Lithium-induced collecting duct proliferation was significantly lower in the knockout vs wild type mice. The results demonstrate that genetic deletion of P2Y12 receptor protects against the key structural and functional alterations in lithium-induced nephrogenic diabetes insipidus. Genetic deletion of P2Y12 receptor offers long-term (five months) protection against lithium-induced polyuria, natriuresis, kaliuresis and collecting duct remodeling and cell proliferation (Zhang, Riquier-Brison, Liu et al. 2018)

The most widely studied purinergic receptor in the kidney is ATP-activated P2Y12 receptor which is expressed in the collecting duct. Signaling mediated through P2Y12 receptor antagonizes the vasopressin action by enhancing the production of PGE2 (Kishore, Carlson, Ecelbarger et al. 2015).

The present therapy for lithium-induced nephrogenic diabetes insipidus in man is to counter anti-vasopressin action of lithium. The future treatment is to enhance the sensitivity of the kidney to vasopressin action (Kishore, Carlson, Ecelbarger et al. 2015).

Administration an Irreversible Inhibitor of the P2Y12 Receptor (clopidogrel)

Clopidogrel bisulfate significantly increased urine concentration and aquaporine protein in the kidneys of Sprague–Dawley rats but did not alter urine concentration in

Brattleboro rats that lack arginine-vasopressin. Clopidogrel administration also significantly ameliorated lithium-induced polyuria, improved urine concentrating ability and aquaporine protein abundance and reversed the lithium-induced increase in freewater excretion. Selective blockade of P2Y12 receptor by the reversible antagonist PSB-0739 in primary cultures of rat inner medullary collecting duct principal cells potentiated the expression of aquaporine and cAMP production induced by desmopressin (Zhang, Peti-Peterdi, Müller et al. 2015).

Clopidrogel alone increased renal aquaporin 2, Na-K-2Cl cotransporter, Na-Cl cotransporter and the subunits of the epithelial Na channel (ENaC) in renal medulla. When combined with lithium, clopidrogel prevented downregulation of aquaporin, Na-K-ATPase and Na-K-2Cl cotransporter but was less effective against downregulation of cortical sodium channel (α- or γ-ENaC). Thus, clopidrogel primarily attenuated lithium-induced downregulation of proteins involved in AVP-sensitive water conservation (Zhang, Peti-Peterdi, Heiney et al. 2015)

Clopidrogel is an antiplatelet drug of the thienopyridine group extensively used in cardiological clinical medicine. Another such drug is prasugral and both are ADP antagonists acting on the P2Y12 receptor. Administration of prasugral completely suppressed lithium-induced polyiuria and polydipsia in rats (Zhang, Peti-Peterdi, Brandes et al. 2017)

Pharmacologic Blockade of Renal P2Y12 Receptor

Pharmacologic blockade of renal P2Y12 receptor in rodents increases urinary concentrating ability by augmenting the effect of vasopressin on the kidney and ameliorates lithium-induced nephrogenic diabetes insipidus by potentiating the action of vasopressin on the renal collecting duct (Zhang Peti-Peterdi, Müller et al. 2015). This strategy may offer a novel and effective therapy for lithium-induced nephrogenic diabetes insipidus in man.

Conclusion

Pharmacologic blockade of renal P2Y12 receptor may be combined - at least theoretically - with anti-prostaglandin agents (non-steroidal anti-inflammatory compounds) and supplemented with large doses of desmopressin in the treatment of lithium-induced nephrogenic diabetes insipidus. Lithium-induced excessive prostaglandinuria (increased excretion of PGE2) can be prevented by pharmacologic blockade of the renal P2Y12 receptor and antagonized by the administration of indomethacine.

We are all definitely convinced by the enormous work of Ban (2017), Blackwell (2014), Rybakowski (2017), Severus, Taylor, Sauer et al. (2014) and others that millions

suffering from bipolar disorder need lithium treatment and making it safer by eliminating (at least partly) its most frequent side effect lithium polyuria, is a decent goal for both the investigators and physicians.

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July 4, 2019

Samuel Gershon's comments

Dr. Radó's report is a detailed outline of his studies on the lithium-induced side effect which had been a serious concern in these cases but also developed it. A number of treatments have been proposed over the years and some have had some beneficial effects (Coats, Trautner and Gershon 1957).

Lithium is a specific for manic-depressive disorder. Initially, it produces a clear effect on water and electrolyte balance, manifest by an increase in urine volume and thirst. These effects are also seen by its special effect in the manic phase of this disorder. It has been shown that on initial administration there is a retention of lithium in the body, until the mania abates, increased excretion occurs and then homeostasis is restored (Trautner, Morris, Noack and Gershon 1955). In overdose lithium can cause toxicity (Coats, Trautner and Gershon 1957).

One of the rarer effects is the manifestation of a diabetes insipidus-like syndrome. Dr. Radó's paper presents his studies on this particular side effect. It is a very good and thorough presentation, not only of the history of this issue, but a presentation of what now should be the best treatment method available.

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November 14, 2019

János Radó's reply to Samuel Gershon's comment

Thank you, Samuel Gershon, for your comments. In my opinion, you are one of the greatest experts on lithium. Your classic studies on the fate of lithium in the human body and its relationship with the different phases of manic-depressive disorder is worth remembering and learning.

I am delighted by the honor presented to me by your reading and evaluating my work on lithium nephrotoxicity and available treatment methods.

January 23, 2020

Edward Shorter: The Q-T interval and the Mellaril story: a cautionary tale

Is a lengthening of the Q–T interval in the ECG benign or pathological in drug action? This produced a small controversy in the 1960s that had a major impact on patient care. In 2000, the Novartis Company cautioned physicians about further use of the antipsychotic drug Mellaril (thioridazine). The company announced that the drug can entail dangerous cardiac complications. This information was already known in the mid-1960s, and not only did Sandoz (one of the predecessor companies of Novartis) ignore it, they attempted to discount it at scientific meetings and disregarded the warnings of several clinical scientists. Moreover, in various ad campaigns Sandoz showed elderly "patients" in the artwork, emphasizing that the drug was suitable for geriatric cases, precisely the population most at risk of such complications. The story is a textbook case of ignoring scientific warnings in favor of corporate interests.

It was known early on that Sandoz's new antipsychotic agent thioridazine (Mellaril), launched in the United States in 1959, lengthened the Q–T interval. But was this good or bad?

There was the benign repolarization school. In 1964, M.H. Wendkos, a cardiologist at the Veterans Administration Hospital in Coatsville, Pennsylvania, published a paper on pharmacologic studies in a hitherto unreported "benign repolarization disturbance among schizophrenics" (Wendkos 1964). Wendkos re-stated this position in his presentation at a psychopharmacology meeting in Quebec (see below), arguing that the recorded ECG changes "represent a benign repolarization disturbance rather than an adverse cardiac effect" (Wendkos 1965).

But events were in the saddle and galloped in a very different direction. Some background: It happens quite frequently that drugs are withdrawn or new warnings of their side-effects are circulated. Yet the story of Sandoz's antipsychotic medication Mellaril (thioridazine) represents an almost textbook case of a company marching into trouble by ignoring warnings.

On July 31, 2000, Novartis Pharmaceuticals sent a letter to all physicians and pharmacists in Canada, warning that the use of the drug Mellaril should be significantly curtailed. The preparation should henceforth be restricted only to those schizophrenic patients "who fail to show an acceptable response . . . to other antipsychotic drugs." The

reason? "Mellaril has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including Mellaril, have been associated with torsade de pointes-type arrhythmias and sudden death" (Novartis Pharmaceuticals Canada, 2000).

Simultaneously, the August 18 issue of the Psychiatric News cautioned its readers that thioridazine "will include a new boxed warning regarding potentially fatal cardiovascular effects and will be restricted to second-line use." The reason again was that "TdP (torsades de pointes) develops spontaneously, usually without warning, and requires immediate emergency intervention." The note stated that the risk of sudden death was "high" (Psychiatric News 2000).

These warnings came more than thirty years too late. Here is how the controversy unfolded:

In 1963, H.G. Kelly and coworkers in the Faculty of Medicine of Queen's University in Kingston, Ontario, reported 28 electrocardiograms that depicted a quinidine-like effect of thioridazine on ventricular repolarization (prolongation of the QT interval) in doses as low as 200 mg. a day. T-waves were flattened out and sometimes inverted, occasionally S–T segments became convex and new waves appeared. In that study, two fatal cases of arrhythmia occurred (Kelly et al., 1963).

By this time the Sandoz company, of course, knew of the Queen's University deaths, and their medical advisor, Roy Stewart, a Montreal cardiologist, brought this to the attention of Thomas Ban, chief of the clinical research service at Verdun Protestant Hospital, a psychiatric inpatient facility in the outskirts of Montreal. It was at Stewart's request that Ban designed a clinical study, conducted in collaboration with André St. Jean, Scientific Director at Hôpital des Laurentides in L'Annonciation, Quebec, comparing the effects of thioridazine, chlorpromazine, and trifluoperazine on the ECG. In 1964 the investigators reported that thioridazine "modifies the terminal portion (S–T segment, T and U waves) of the human ECG." They found that, whereas similar changes took place in only 1 of the 6 subjects taking trifluoperazine, and in 3 of 6 taking chlorpromazine, such changes were noted in all 6 of the 6 patients on thioridazine by the 8th day of drug administration, i.e., with 200 to 400 mg of thioridazine per day (Ban and St. Jean, 1964).

The study had been completed in 1963, but before it was published, the following incident occurred at Hôpital des Laurentides: A patient who had been receiving high (1500 mg per day) doses of thioridazine over a period of ten weeks, suddenly became unconscious and passed into a state of shock. It happened that there were two physicians in the room, one

of them a cardiologist. An ECG demonstrated ventricular tachycardia. It was noted that a prior ECG of the patient, six weeks after the initiation of thioridazine therapy, had shown bradycardia and prolongation of the QT (Desautels et al., 1964).

These findings led Ban and co-workers to conduct a survey to determine the incidence of cardiac conductance changes with thioridazine. It was clear that such complications existed, but what was the size of the problem? Ban presented the results later in 1964 at the fourth congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Birmingham, England. Of the 92 patients receiving drugs other than thioridazine, 12, or 13 percent, displayed an abnormal ECG. Seventeen, or 77.3 percent of all patients receiving thioridazine, manifested abnormal ECG's (Ban et al., 1965).

In 1964 or 1965 Ban travelled to Basel to report these findings to Sandoz and met with the president and head of pharmacology of the firm (Ban TA, personal communication to E Shorter, 11 Mar 2013).

On June 4, 1965, the Quebec Psychopharmacological Research Association organized a special symposium at the Hôpital des Laurentides on ECG changes with psychoactive drugs. Ban and coworkers reviewed the aforementioned studies as well as some findings based on a further series of four studies which indicated that "the lowest dose (of thioridazine) which brought about changes was 150 mg per day" (St Jean et al., 1965). At the same meeting Edward Kingstone, in his review of the literature on "neuroleptic drugs and the ECG," pointed out that in 1964 Graupner and Murphree also described ECG changes associated with the use of thioridazine (Kingstone, 1965). Of the 55 patients they studied, 44 percent developed abnormal electrocardiograms. Most of the changes were concerned with the T-wave. They appeared at all dose levels from 150 to 900 mg per day (Graupner and Murphree, 1964).

In organizing the symposium, Ban wanted to ensure that a fair picture of Mellaril was offered. He had mentioned the meeting to Sandoz, and the company paid the travel cost for Wendkos to attend (Ban, 2011).

Here is where events took over. Other investigators began learning of the cardiac dangers of thioridazine. In the mid-1960s, Louis Gottschalk, then at the Cincinnati General Hospital, warned Sandoz privately that Mellaril was dangerously increasing the QT interval. Gottschalk later said in an interview, "We got the idea to find out whether there are any differences in the psychoactive drug metabolites in people that get these cardiac irregularities. And lo and behold, we did discover that a metabolite that is not psychoactive, sulforidazine,

does have an adverse cardiovascular effect . . . and [we] tried to get the drug companies to provide further financial support so we could study the biochemical basis. . . . But they were doing so well marketing their drugs, that they would not fund it" (Gottschalk, 2011a). Gottschalk, who in the meantime had moved to the Irvine campus of the University of California, reported with co-workers the existence of this previously unknown metabolite of mesoridazine and thioridazine in 1974 (Dinovo et al., 1974); details of a GLC analysis followed in 1976 (Dinovo et al., 1976).

Did Sandoz then become interested? Not really. Gottschalk later said, "Everybody told me that the metabolite was not pharmacologically active. I asked the head of the organic chemistry department at UCI whether she could manufacture it for me because I wanted to test the effects of the metabolite on cardiovascular function in dog experiments. She could do it for a certain amount of money, but I never was able to obtain the necessary funds. In general, pharmaceutical companies are not very interested in trying to discover what triggers the adverse side effects of drugs" (Gottschalk, 2011b)..

Gottschalk was not the only researcher to be brushed off by Sandoz. In 1974 Donald Gallant and co-workers at Tulane University reported a double-blind ECG comparison of thioridazine and thiothixene (Dillenkoffer et al, 1974). "Only one of the 13 thiothixene patients had prolongation of the Q–T," said Gallant later in an interview, "but 13 out of 13 patients on 800 milligrams a day of thioridazine, and 7 of 13 on 400 milligrams a day had prolongation of the Q–T interval. We published that. In fact, my cardiology fellow that read the EKGs could identify thioridazine, blind. . . . After we published, somebody from Sandoz called and started yelling on the phone at me, criticizing me, saying I was unethical for publishing the data. This was 1972 [1974], and I was shocked that someone from a pharmaceutical firm would start telling me I'm unethical for publishing these findings. . . . It was solid, solid data and Sandoz Company never made any mention about it" (Gallant, 2011).

These early warnings did not prevent Sandoz from further marketing the preparation. Indeed, to go by the visual content of the company's advertisements for Mellaril, the drug was pitched to physicians as especially suitable for geriatric use, a population at risk of cardiac complications. And in 1978 George Simpson and co-workers at Rockland State Hospital found that it was precisely in the elderly that thioridazine prolonged QT intervals (Branchey et al, 1978). "I stopped using thioridazine at that time," Simpson later said in an interview (Simpson, 2011).

An analysis of images depicted in Mellaril advertisements in Diseases of the Nervous System (after 1989 the Journal of Clinical Psychiatry) showed that Sandoz launched four

major ad campaigns featuring elderly "patients." For example in three ads which appeared between May and July 1983, a clearly elderly woman was shown and the text stated that Mellaril "helps keep the disturbed geriatric at home" (Dis Nerv Syst, 1983). An ad featuring an older male golfer ("effective control of psychotic symptoms") ran 14 times (Dis Nerv Syst, 1979–80). Ban in his Psychopharmacology for the Aged, published in 1980, noted that "thioridazine has become one of the most extensively employed psychotropic drugs in the aged" (Ban, 1980).

While the Ban studies showed that cardiac conductance changes appeared at daily dosages above 150 mg., the above-mentioned ads indicated that dosages below 300 mg were relatively safe. ("Daily doses in excess of 300 mg should be used only in severe neuro-psychiatric conditions.") (Dis Nerv Syst, 1979–80).

For Sandoz – and its successor organization Novartis – it was irresponsible not to say reckless to have ignored such warnings for more than thirty years, putting the lives of many patients at risk. The entire story of shortsightedly placing corporate interests ahead of science could be found in an MBA curriculum on how not to market a pharmaceutical preparation.

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July 18, 2013

János Radó's Comment

I read with interest the Mellaril (thioridazone) Story. It is shocking (even now) how the pharmaceutical industry disregarded the thioridazine induced abnormal ECG changes. The dose-related lengthening of the Q-T interval occurring in a very high percentage of the thioridazine-treated patients "in a drug treated population which will be in the multiple tens of million patient" (Beasley 2015).

The insensitiveness of Sandoz in the thioridazine case resembles to me another phenomenon which had occurred in the case of another Swiss firm, CIBA.

In 1973, we reported in the British Medical Journal the first well-documented case of water intoxication induced by another psychotropic drug carbamazepine (Tegretol). After this first report of water-intoxication, a series of such carbamazepine-induced complication was published in the British Medical Journal and in other journals (Radó 1973). Large patient populations were studied and the hyponatremia associated with the use of carbamazepine was well documented. I, personally, published 19 articles on the use of carbamazepine (alone or in combination with chlorpropamide) in diabetes insipidus. In these articles, we described the changes observed in serum sodium levels. Despite this evidence, hyponatremia and water intoxication was not listed among the side effects in the advertisements of carbamazepine (Tegretol) for several years. CIBA was as insensitive in the case of hyponatremia and water intoxication induced by carbamazepine as was Sandoz in the case of thioridazine-induced ECG alterations.

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September 24, 2015

Photos of János Radó

(From left): Nadia Kuprina, Giorgina B.Piccoli, János Radó, Stanley Shaldon and Jacques Bernheim. Photo taken in Paris, France on May 24, 2012. Photo received from János Radó. (Individual Photos).

Vignette 1

János Radó Hungarian, nephrologist, endocrinologist and inventor of "diuretic renography," is pictured with Stanley Shaldon (Great Britain) and Jaques Bernheim (Israel), Pioneers of the Archives of European Nephrology, on the stage during the Opening Ceremony of the ERA-EDTA Congress held in Paris, France, May 24, 2012. Giorgina B. Piccoli, filmmaker, poet, artist, and nephrologist, along withopera-singer Nadia Kuprinaare also pictured. Piccoli conducted all of the 27 interviews seen in the film"Portraits of Pioneers" that was shown at the conference. It was based on an initiative of the Société de Néphrologie that wasinitially limited to French-speaking and Italian Pioneers of Nephrology and then extended to the whole of Europe. Photo taken by Maria Radó.

August 2, 2018

Vignette 2: History of the photo taken on May 24, 2012, in Paris

During the first days of Spring 2011 I was informed by László Rosivall, President of the Hungarian Kidney Foundation, that I had been chosen by Pierre Ronco, Professor of Nephrology, Hôpital Tenon (Hôpitaux Universitaires Est Parisien), Paris, for an in-depth interview. It was known at that time that Pierre Ronco had been selected for President of the Congress of Nephrology to be held in Paris in May 2012 and Laszló Rosivall was a member of the Scientific Comittee of that Congress. Professor Rosivall's decision was endorsed by a voting in the Steering Commitee of the Hungarian Society of Nephrology.

The interview was conducted by Dr. G.B. Piccoli on September 13, 2011, in Bruxelles, Belgium, in a cafe on the Grote Markt, and was filmed by Gilberto Richiero and his photographer, in the presence of Professors Ronco and Rosivall and my wife.

The interview was about patients and doctors; clinical medicine and nephrology; and personal history and views, including my life story and achievements.

Seven years later, on April, 2018, Piccoli wrote an article in BMC Nephrology entitled "On the shoulders of giants. The story behind the Pioneers of Nephrology project" (Piccoli, Jaar and Henderson 2018). In the article she declares: "…the interviews are not dealing with their achievements and their success: they try to pass on to future generations the idea of how they were, why they were passionate, what they loved, and, last where they found poetry in our profession."

My interview was one of 27 interviews of the "Pioneers of the Archives of European Nephrology," among them an interview with the "Master of the Masters," Gabriel Richet, at that time 97-years-old (Piccoli, Richiero and Jaar 2018). The interviewers wanted to listen to the stories of the Pioneers and compose from them a film to be presented on the evening of the Opening Ceremony of the XIIth congress of Nephrology held in Paris on May 24, 2012.

The spirit of the interview was very special indeed. I cannot describe it in simple words. It is well characterized, however, with Piccoli's own words in the quotation above. The interview was (also) about poetry, i.e., poetry in medicine. Piccoli has a sui generis gift (among several other talents) of making poetry even from nephrology. Piccoli is a nephrologist in Torino, Italy (nowadays also in Le Mans, France), and an internationally known poet.

Piccoli describes the story of her achievement in the Archives of the European Nephrology. The project began almost 30 years ago when, with her two friends (David and Paolo), they made a film about Shoah (the Holocaust). Her next film was about the Pioneers of Nephrology, with Giorgina's self-selected producer Pierre Ronco. Although David and Paolo did not take part in this film, concerning the interviews David suggested to Giorgina: "take the poetry out of them. It has to deal with poetry in the end" (Piccoli, Jaar and Henderson 2018). So, when I got the question about poetry in the course of the interview, I responded with a short story of my medical life.

I had observed the development of an interventricular septal defect (the first case in Hungary) in one of my cardiac patients when I was a young resident in 1954, in the János Hospital of Budapest. My chief, the great internist Fodor Imre, however, did not believe in this diagnosis. So, I went to the chief pathologist (Professor Antal Kálló) noting my diagnostic opinion. Everyone on the staff from the medical and pathological departments was present at the necropsy when my clinical diagnosis was confirmed. I was sure that I would be fired and there would be no job offer in any hospital in Hungary in the near future. After a sleepless night, next day I participated in the morning conference as usual, Imre Fodor declared that he was proud to publish with me this interesting, rare, extraordinary case (Fodor, Kincsesy and Radó 1955; Radó, Kincsessy and Fodor 1958). Later, in 1956. when he suffered from a deadly disease, Fodor invited me to join his treatment team, even though I was the youngest member in the department. What is this, if not poetry?

In the photograph taken on May 24, 2012, by my wife, G.B. Piccoli stands between Nadia Kuprina, opera singer, and me on the stage of the Big Auditorium of the Conference Center Paris. In the photo you can see two others, Stanley Sheldon, one of the founding fathers of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and a famous British-French nephrologist, and Jacques Bernheim, eminent nephrologist from Israel. (Unfortunately, both have since died). The other 24 famous nephrologists on the stage are not seen in this photo, among them Gabriel Richet, Stewart Cameron, Evert Dorhout Mees, Carl Eric Mogensen, Anita Aperia, Eberhard Ritz and Eliahou Ypersele.

The complete interview series of all Nephrology Pioneers can now be seen on videos on the ERA-EDTA website (era-edta.org). In the near future plans are underway for their edited text to be available in a remarkable new series of BMC Nephrology. The editor of this journal is none other than Giorgina Piccoli, shown in the photo between Nadia Kuprina and me.

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December 20, 2018

From left to right: János Radó and Thomas A. Ban. Photo taken on October 11, 2014, in Budapest, Hungary, on the occasion that they were receiving their diamond diploma, 60 years after graduation from medical school. Photo received from János Radó.

Individual photos September 3, 2015

September 10, 2020