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Collated 14

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

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Janos Radó: Use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus

(Administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine)

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 d*rug" 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

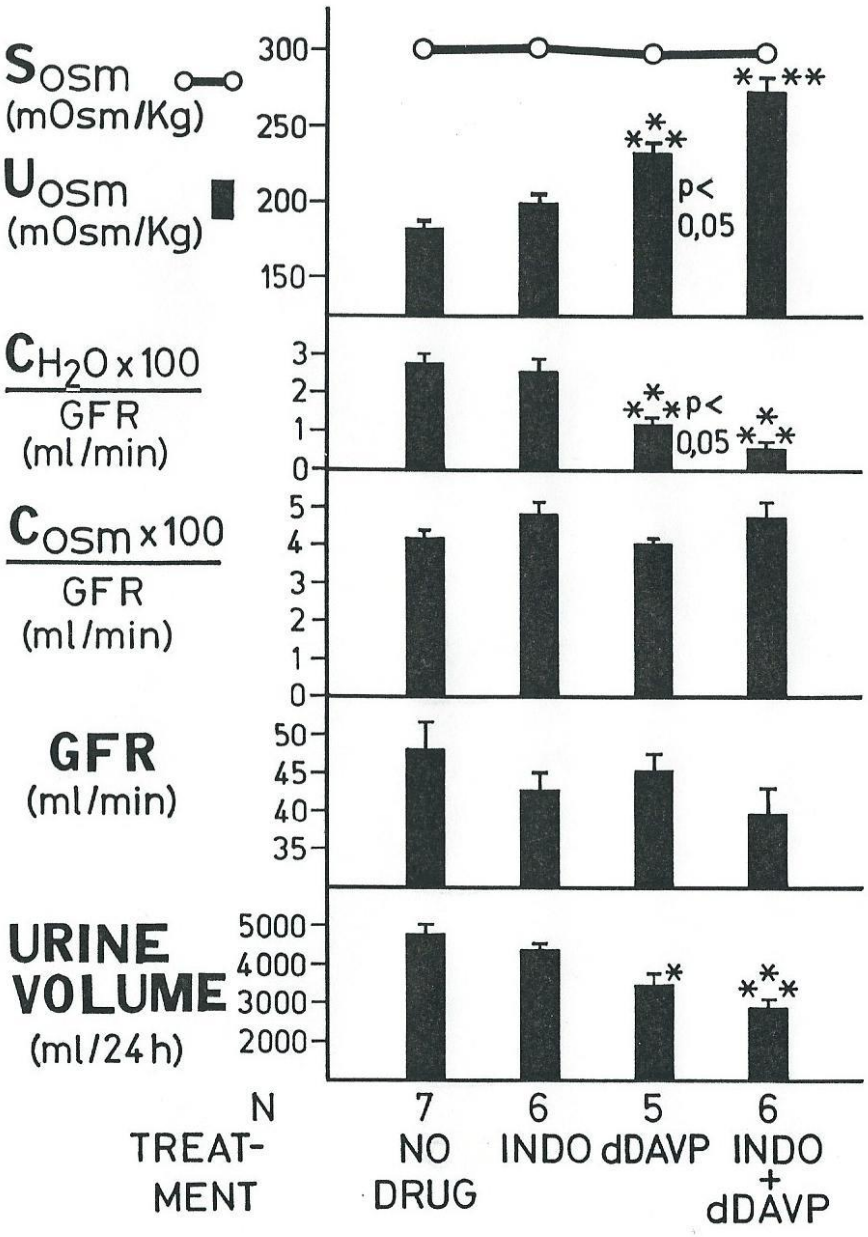
We can see in Figure 1 that *indomethacine* (administered alone) as compared to *"no drug"* did not cause significant change in urine volume and osmolality.

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 (CH_2Ox100/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 ($p<0.001$).

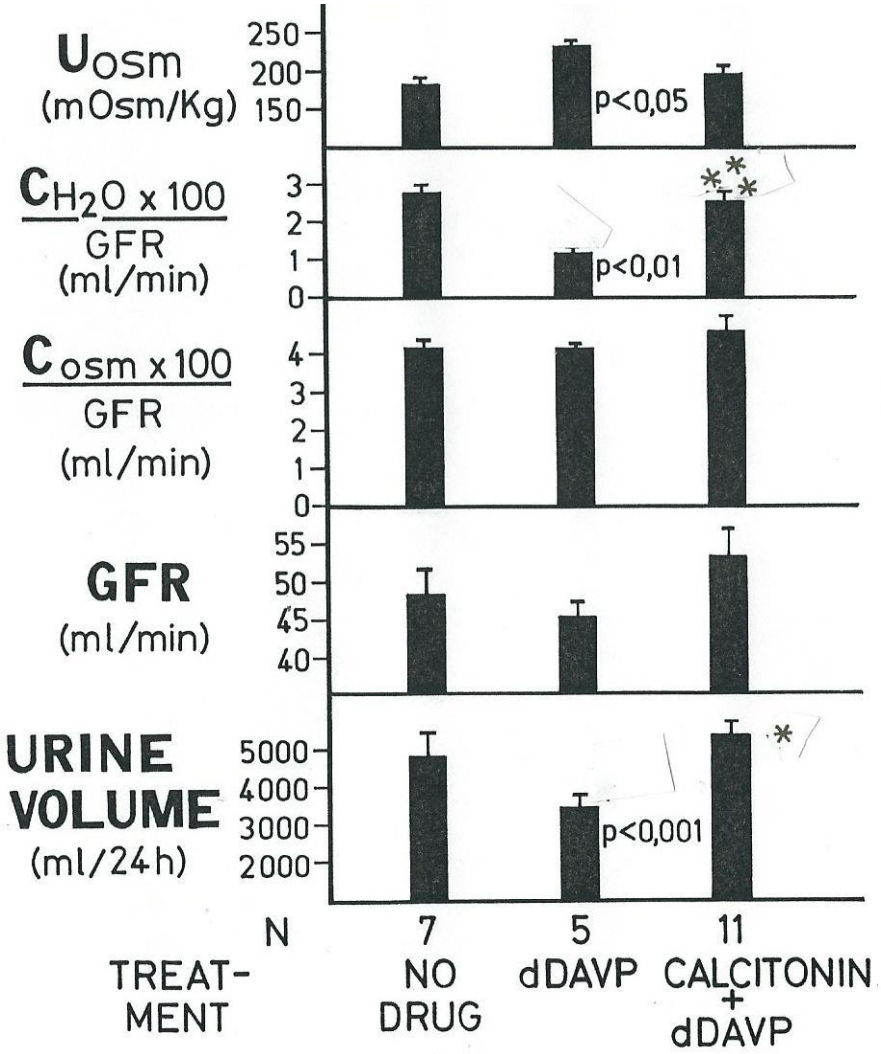
Figure 1



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).

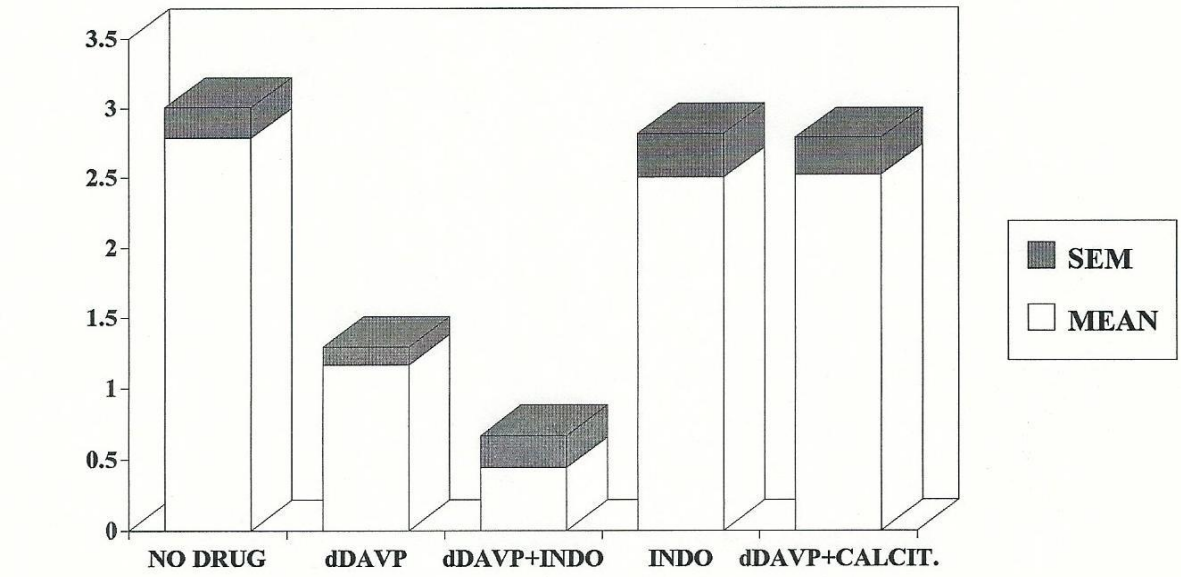
Figure 2



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. CH_2Ox100/GFR ml/min mean values and standard error of the mean are given.

TABLE

DRUG	***URINE VOLUME***	***Cosmxl00/GFR***	***CH_2OXIOO/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±0.22$^{xxx\ Y}$
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.
Cosm =osmolal clearance; C_{H2} 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

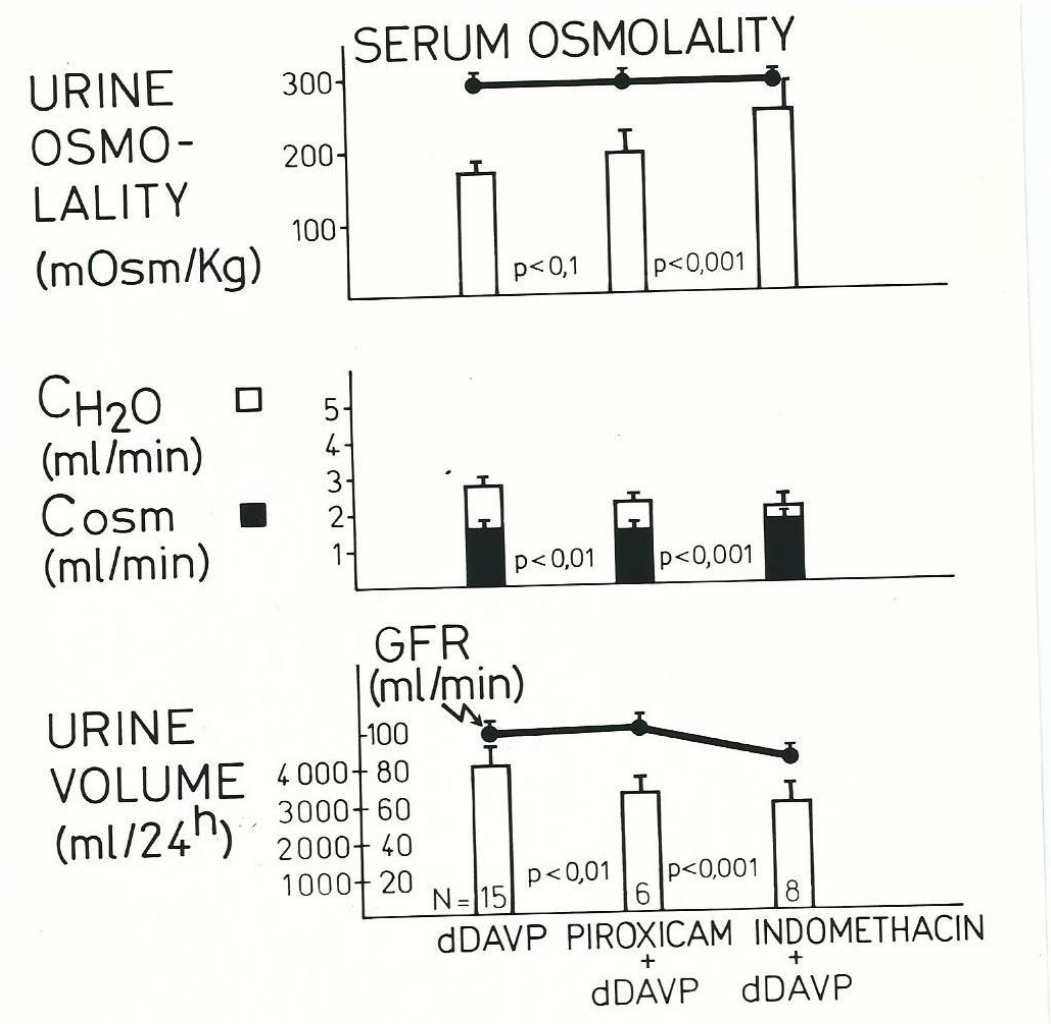
Polyuria remained and practically did not change during the next three years. Therefore, the diagnosis is: “permanent” lithium induced nephrogenic diabetes insipidus. Another interesting observation was that the glomerular filtration rate increased from the 31-47 ml/min value, found during lithium therapy, 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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Acknowledgment. The author expresses his sincere thanks to Dr. Zdravkova Sznyeska, nephrologist, for her contribution in collecting data and handling the statistical analysis.

January 25, 2018

Barry Blackwell's reply

I want to thank Janos 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

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

Janos 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

Barry Blackwell's final reply to Janos Radó's final comment

I want to thank Janos 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

Janos 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 Janos 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

Janos 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

January 2, 2020