

Janos Radó's final comment

on Barry Blackwell: The lithium controversy. A historical autopsy. Collated by Olaf Fjetland

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” [Rybakowsky 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 – vasopressine, dDAVP). This vasopressin derivative molecule has an extremely strong antidiuretic capability combined with a uniquely long duration of action (Radó 1975 a,b, 1976 a,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 than 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.

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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

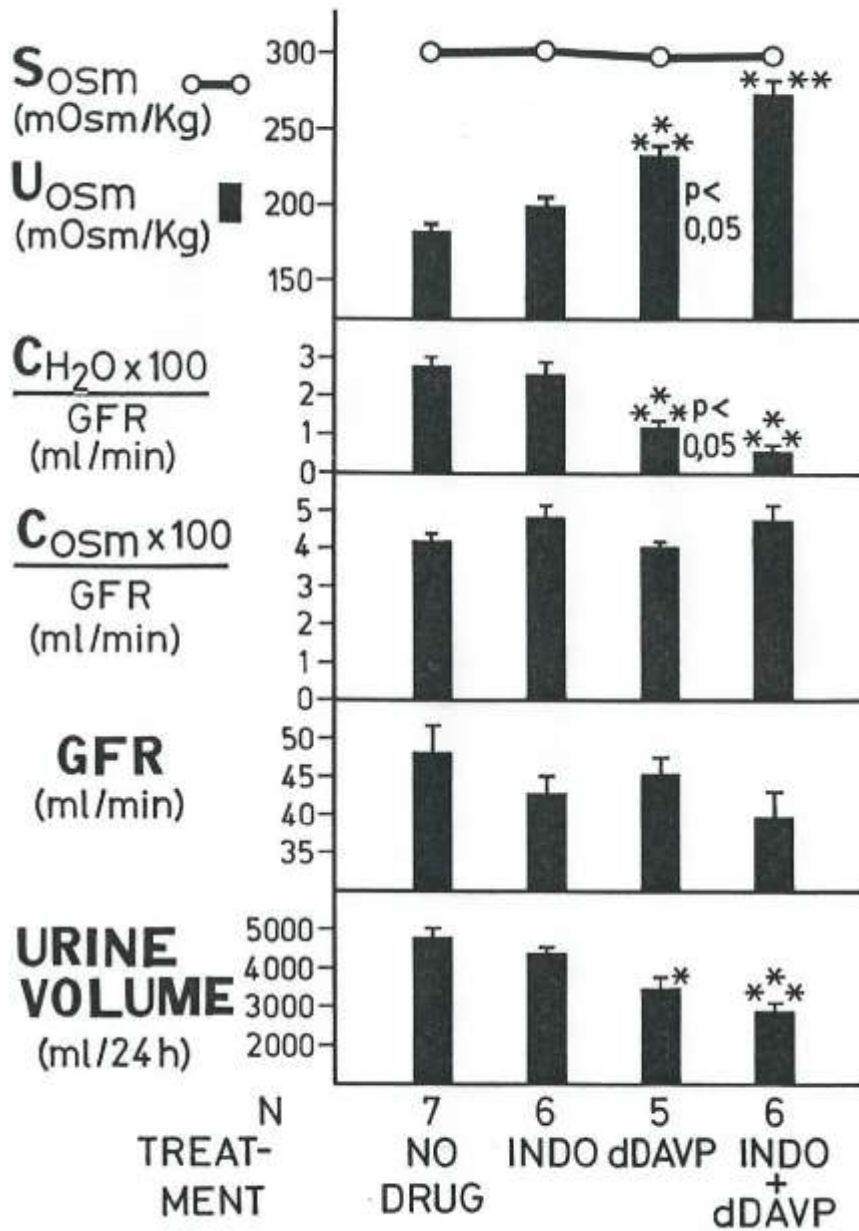
We can see in Figure 1 that *indomethacine* (administered alone) as compared to “no drug” did not cause significant change in urine volume and osmolality.

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 ($\text{CH}_2\text{Ox}100/\text{GFR}$) 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 ($p<0.001$) decreased while urine osmolality increased ($p<0.001$).

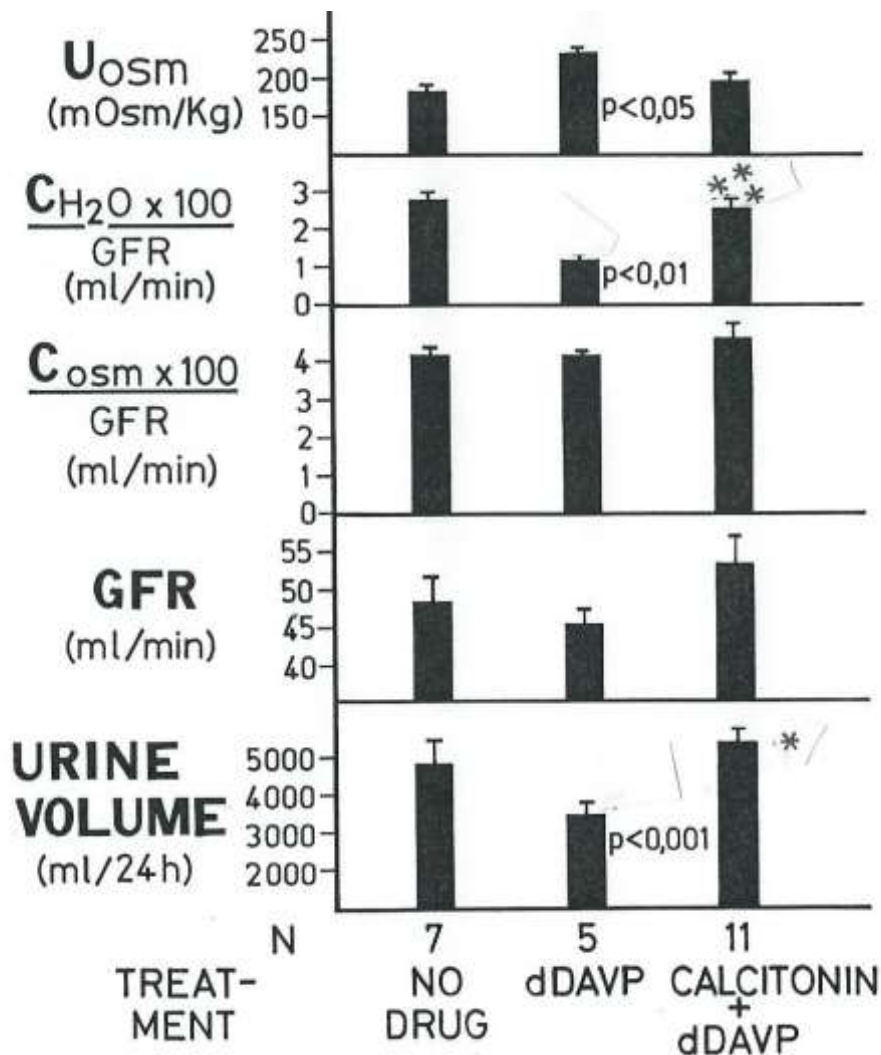
Figure 1



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).

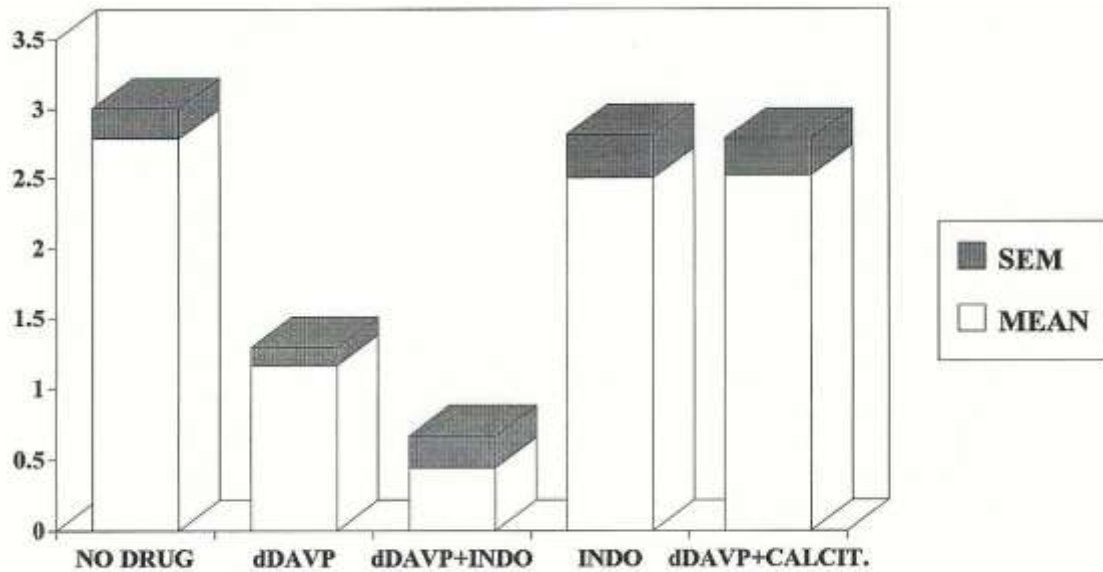
Figure 2



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 Calcitonine 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 Calcitonine) 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

<i>DRUG</i>	<i>URINE VOLUME</i> (ml/min)	<i>Cosmx100/GFR</i> (ml/min)	<i>CH₂OX100/GFR</i> (ml/min)
NO	4778 \pm 335	4.17 \pm 0.21	2.78 \pm 0.22
INDO	4350 \pm 180	4.76 \pm 0.31	2.50 \pm 0.32
dDAVP'	3480 \pm 299 ^X	4.13 \pm 0.16	1.16 \pm 0.13 ^{XXX}
INDO+dDAVP	2875 \pm 161 ^{XXX}	4.71 \pm 0.40	0.44 \pm 0.22 ^{XXX Y}
CALCIT+dDAVP	5363 \pm 283	4.59 \pm 0.38	2.52 \pm 0.27 ^{YYY}

values are expressed as mean \pm SEM.

x=p<0.05; xxx = p< 0.001 as compared to "no drug" - Y= p< 0.05; YYY=p<0.001 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 Calcitonine.

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

Investigations Performed after Stopping Lithium Therapy

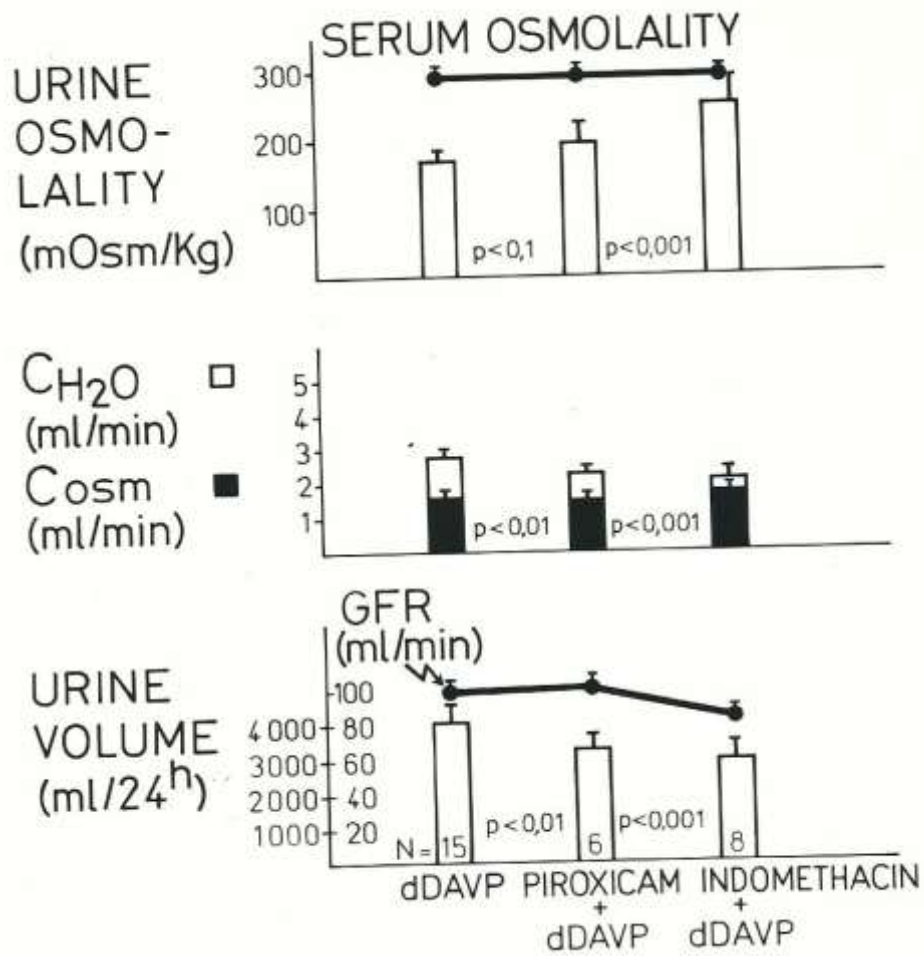
Polyuria remained and practically did not change during the next three years. Therefore, the diagnosis is: "permanent" lithium induced nephrogenic diabetes insipidus. Another interesting observation was that the glomerular filtration rate increased from the 31-47 ml/min value, found during lithium therapy, 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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