Desmopressin may counteract polyuria in lithium-induced nephrogenic diabetes insipidus

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.

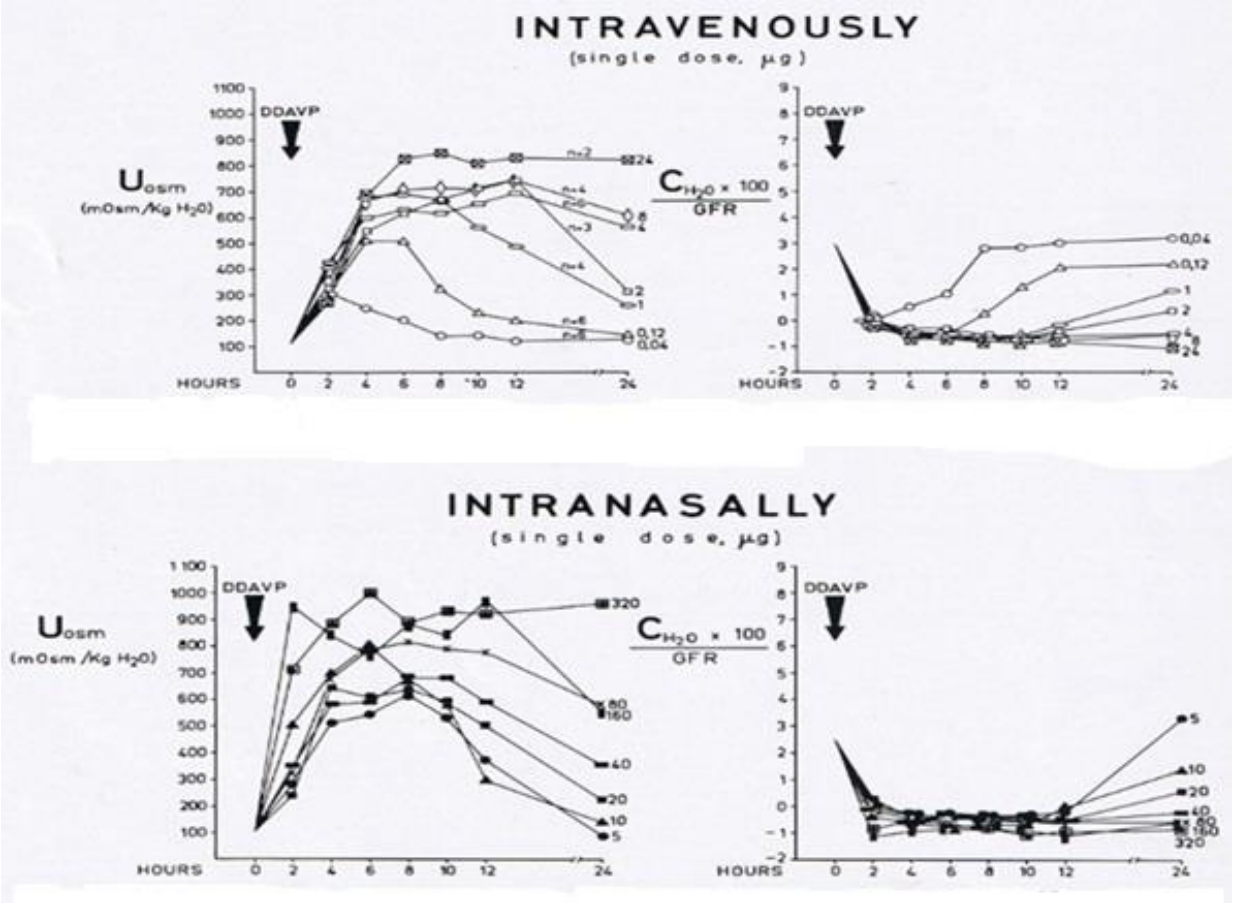
It should be noted that although certain hematological disorders caused by a lack of individual blood coagulation factors may improve dramatically in response to desmopressin normal blood coagulation is apparently less influenced by the peptide.

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.

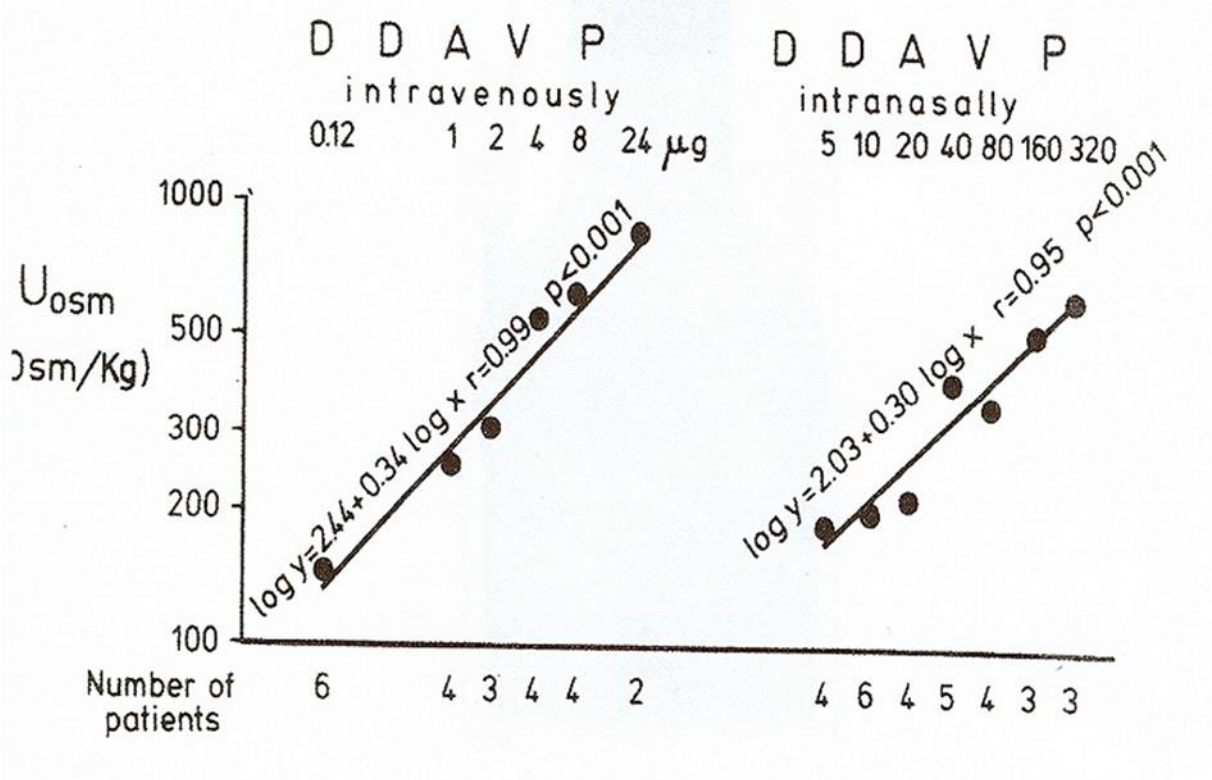
As shown in Figure 1 the relationship between time and free water clearance, expressed in the percentage of glomerular filtration (left part of the panel), and urine osmolality (right part of the panel), respectively, after *intravenous* (upper panel) and *intranasal* (lower panel) administration of 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

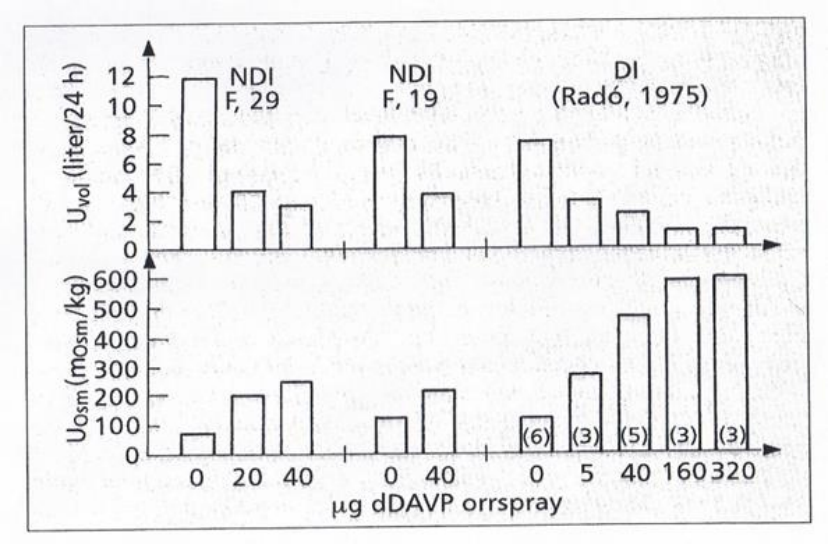


These basic clinicopharmacological observations were obtained in the mid-70s, 15 years earlier than the renal effects of lithium treatment were studied (Radó and Zdravkova 1991).

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

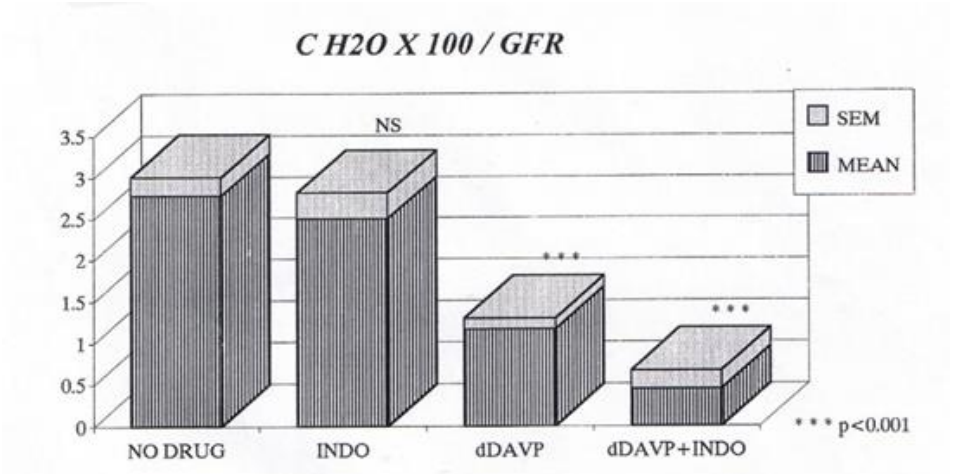
the Radó cases it was given in 0-320 ug once a day. The antidiuretic effect of desmopressin was followed by urine volume (liter/day, upper panel) and urine osmolality (mOsm/Kg, lower panel). In the two congenital cases of Moses, Scheinman and Oppenheim (1984), NDI responded to large doses of desmopressin. 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.

References:

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