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NEPHROLOGY ROUNDS

Paradoxical Hyponatremia on High-Dose Tolvaptan in ADPKD

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Received 4 February 2026; revised 16 April 2026; accepted 20 April 2026; published online 29 April 2026

Kidney Int Rep (2026) **11,** 106571; https://doi.org/10.1016/j.ekir.2026.106571

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in PKD1 or PKD2, is the most common hereditary kidney disorder and the fourth leading cause of end-stage kidney disease globally; vasopressin-driven cyclic adenosine monophosphate accumulation in collecting duct cells is the primary mechanism of cystogenesis.[1] Tolvaptan, a selective vasopressin2 (V2)-receptor antagonist, reduces cyclic adenosine monophosphate-mediated cystogenesis, and the landmark TEMPO 3:4 and REPRISE trials demonstrated significant slowing of kidney volume growth and estimated glomerular filtration rate decline, leading to regulatory approval for patients at risk of rapid progression.[2,3] Current guidelines recommend dose escalation to the maximum tolerated dose (120 mg/day), with polyuria, polydipsia, and nocturia recognized as expected pharmacological consequences of V2 receptor blockade rather than true adverse effects.[4] However, paradoxical severe hyponatremia has recently emerged as an under-recognized complication specifically linked to prolonged therapy at maximum doses, warranting reappraisal of current dosing strategies.[4,5]

Key teaching points of this case are presented in Table 1.[6,7]

Table 1. Teaching points

#	Key teaching points
1	Severe hyponatremia (< 125 mmol/l) can occur paradoxically in patients with ADPKD receiving tolvaptan, despite effective V2 receptor blockade confirmed by suppressed urine osmolality (Uosm; 85–145 mOsm/kg) and specific gravity (≤ 1.005).
2	This complication appears specifically linked to prolonged therapy (≥ 3 yrs) at maximum doses (120 mg/d) in patients with advanced CKD (stages G3b–G4). A consistent 5% overall incidence was reported independently by both Italian and Japanese centers; a 22% incidence was observed in the Italian high-risk subgroup (advanced CKD + max dose ≥ 3 yrs), a stratification not reported by the Japanese cohort.
3	Behavioral habituation to excessive fluid intake and concomitant low-sodium diets are key modifiable risk factors; downward sodium trends should be monitored prospectively as early warning signs, even when individual values remain within normal limits.
4	Urine osmolality and specific gravity (target < 250 mOsm/kg, SG ≤ 1.005) may serve as practical biomarkers to guide individualized tolvaptan dosing; prospective data indicate that up to 87.5% of patients achieve adequate V2 blockade at submaximal doses.[6]
5	Based on hypothesis-generating observations, dose optimization guided by Uosm/SG monitoring may improve outcomes in advanced patients with CKD on maximum doses; prospective validation is required before routine adoption.[7]

CASE PRESENTATION

As a leading Italian referral center for ADPKD management, our institution (IRCCS San Raffaele, Milan) has followed approximately 1000 patients with ADPKD over the past 15 years through a comprehensive multidisciplinary approach involving nephrologists, cardiologists, dietitians, and clinical psychologists.[8] Among 80 patients currently on chronic tolvaptan therapy, we identified 4 cases of severe hyponatremia (serum sodium < 125 mmol/l), representing 5% of the cohort. To provide context for this figure, all 4 cases occurred exclusively among patients with advanced chronic kidney disease (CKD; stages G3b–G4) receiving the maximum dose (120 mg/day) for at least 3 years. Of 18 patients meeting these specific high-risk criteria,

4 developed severe hyponatremia, corresponding to an incidence of 22% in this subgroup (Supplementary Table S1). These 2 denominators, 5% of all 80 tolvaptan-treated patients and 22% of the 18 high-risk patients, convey different and complementary messages about overall burden and concentrated risk, respectively. No cases of severe hyponatremia were observed at lower doses or during the initial years of therapy.

Brief clinical profiles of the 4 cases are summarized in Supplementary Table S1; key features are highlighted here. The most severe case involved a 52-year-old woman treated for over 5 years who presented with serum sodium of 118 mmol/l, manifesting progressive fatigue, nausea, headache, confusion, and psychomotor slowing. She had been maintaining fluid intake of approximately 6 liters daily while adhering to a low-sodium diet for blood pressure control. The remaining 3 patients presented with serum sodium of 119, 122, and 124 mmol/l, with symptoms ranging from fatigue and nausea to confusion and gait instability.

In all 4 cases, alternative causes of hyponatremia were systematically evaluated. Serum osmolality confirmed hypotonic hyponatremia; clinical and biochemical assessment indicated euvolemic status in all patients. Endocrine causes were excluded by normal thyroid-stimulating hormone and morning cortisol levels. Concomitant medications were reviewed and no recognized hyponatremia-inducing drugs were identified.

Importantly, all patients demonstrated profoundly suppressed urine osmolality (Uosm; 85–145 mOsm/kg) and specific gravity ($\leq$ 1.005), confirming effective V2 receptor blockade despite the paradoxical electrolyte disturbance. This apparent paradox underscores that hyponatremia in this context does not result from treatment failure but from excessive treatment success combined with maladaptive fluid intake behavior. The profound aquaretic effect at maximum doses, though pharmacologically effective, creates a situation where the kidney's enhanced capacity for free water excretion cannot compensate for habitual fluid intake that exceeds physiological needs. Contributing factors included excessive fluid intake in all patients and concomitant low-sodium diets ($<$ 2 g/day) in half of the cases, which reduce osmolar load and limit obligatory water excretion despite effective aquaresis. A gradual downward sodium trend was observed at quarterly monitoring visits preceding the acute episodes, even when individual values remained within normal limits, underscoring the importance of recognizing these trends as early warning signs. All patients recovered without sequelae; 3 successfully resumed therapy at reduced doses (Supplementary Table S1). Interestingly, no cases of hypernatremia were observed, suggesting that patients effectively compensate for aquaresis through increased fluid intake, a protective behavior that may, however, become maladaptive in advanced CKD.

These findings remarkably mirror data from Yamazaki *et al.*,[5] who reported 3 of 55 patients (5.5%) developing moderate-to-severe hyponatremia at Juntendo University Hospital, Tokyo—again exclusively in patients on maximum doses after prolonged treatment. To our knowledge, these represent the only 2 published reports specifically addressing this complication, although the European Renal Association consensus statement has explicitly acknowledged the risk of hyponatremia with excessive fluid intake in patients with declining kidney function.[4]

DISCUSSION

The convergence of Italian and Japanese findings strongly suggests that paradoxical hyponatremia is not a random occurrence but a specific risk of long-term high-dose tolvaptan therapy with a pattern consistent across both cohorts that appears specifically linked to advanced CKD, though the Japanese cohort is not characterized in equivalent detail and cross-cohort comparisons should therefore be interpreted with caution (Table 2). The pathophysiology reflects a complex interplay between drug-induced aquaresis, behavioral adaptation, and the intrinsic limitations of renal water handling in advanced CKD (Supplementary Discussion). The following 2 distinct mechanisms predispose to hyponatremia at maximum doses: first, intense thirst drives fluid consumption beyond

Table 2. Comparison of hyponatremia incidence: San Raffaele Center (Italy) versus Juntendo University (Japan)

Parameter	San Raffaele (Italy)	Juntendo (Japan)
Total patients on tolvaptan, *n*	80	55
Severe hyponatremia ($<$ 125 mmol/l), *n* (%)	4 (5.0%)	3 (5.5%)
Lowest serum Na^+ recorded (mmol/l)	118	117
Tolvaptan dose at onset	120 mg (100%)	120 mg (100%)
Time on max dose before onset	$\geq$ 3 yrs	$>$ 5 yrs
CKD stage at hyponatremia	G3b–G4 (100%)	NR
Excessive fluid intake, *n* (%)	4 (100%)	3 (100%)
Concomitant low-sodium diet, *n* (%)	2 (50%)	NR
Uosm at hyponatremia (mOsm/kg)	85–145	NR
Urine SG at hyponatremia	$\leq$ 1.005	NR
Recovery without sequelae, *n* (%)	4 (100%)	3 (100%)
Tolvaptan resumed after recovery	3 (75%)	3 (100%)

CKD, chronic kidney disease; NR, not reported; SG, specific gravity; Uosm, urine osmolality;. Data represent clinical observations from 2 independent centers. Statistical comparison was not performed because of the descriptive nature of both reports and small sample sizes.

physiological needs, creating positive water balance compounded by urinary sodium losses; second, behavioral habituation over years perpetuates high-volume drinking even as thirst perception attenuates, producing a progressive dissociation between perceived need and actual requirement. Concomitant dietary sodium restriction, while appropriate for hypertension management, further narrows the safety margin by reducing osmolar load and limiting free water excretion (Supplementary Discussion). In advanced CKD, the substantially reduced nephron mass may lead to V2 receptor saturation at lower doses, whereas the attenuated diluting capacity makes these patients particularly vulnerable to even modest fluid excess, a risk factor explicitly recognized in the European Renal Association consensus statement.[4]

These observations raise a hypothesis-generating question that warrants prospective investigation— is mandatory escalation to maximum doses always necessary? Growing evidence suggests that urine osmolality suppression, rather than absolute dose, reflects therapeutic V2 blockade. *Post hoc* analyses of TEMPO 3:4 demonstrated that Uosm reduction independently predicts clinical outcomes regardless of dose.[9] In a prospective study, Roca Oporto *et al.*[6] showed that 87.5% of patients achieved target Uosm ($<$ 200 mOsm/kg) at the starting dose of 45/15 mg, with $>$ 50% reduction in estimated glomerular filtration rate decline, 5% discontinuation rate, and no hepatotoxicity, evidence that individualized dosing is feasible, though generated outside the present series. Our own previously published experience with urinary biomarker-guided dosing further supports this approach,[7] and we separately observed accelerated renal function decline in approximately 10% of our advanced patients with CKD on maximum doses, with improvement upon dose reduction (Supplementary Discussion); however, these observations were not prospectively tested in the current case series.

Based on these convergent but hypothesis-generating observations, we propose that Uosm and specific gravity monitoring may represent a rational framework for individualized dosing. Target suppression $<$ 250 mOsm/kg (specific gravity $\leq$ 1.005) could serve as a therapeutic end point rather than reflexive escalation to maximum doses in all patients; morning spot Uosm and specific gravity are simple, inexpensive tests suitable for routine use. Enhanced vigilance is warranted for patients on maximum doses beyond year 3, with any downward sodium trend prompting reassessment of fluid intake behavior, dietary sodium, and tolvaptan dose. Patient education should address behavioral habituation, ideally with psychological support. Importantly, these recommendations are based on retrospective, small-sample observations and require prospective validation in controlled studies before they can be adopted in routine clinical practice.

DISCLOSURE

All the authors declare no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

Discussion. Expanded Pathophysiological Considerations and Clinical Evidence.

Figure S1. Severe Hyponatremia in Long-Term Tolvaptan Therapy: Incidence and Risk Stratification.

Figure S2. Clinical Management of Tolvaptan-Treated ADPKD.

Table S1. Detailed Clinical Characteristics of Hyponatremia Cases.

Table S2. Urine Osmolality as a Guide for Dose Optimization: Summary of Evidence.

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