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Determinants of Urine Volume in ADPKD Patients Using the Vasopressin V2 Receptor Antagonist Tolvaptan

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Rationale & Objective: The vasopressin V2 receptor antagonist (V2RA) tolvaptan is the first drug that has been shown to slow the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD). However, V2RAs also cause polyuria, with urine output that averages 6 L/d. We assessed determinants of urine volume in patients with ADPKD using V2RAs because such information may help develop strategies to improve V2RA tolerability.

Study Design: Clinical trial of patients with ADPKD studied at baseline, after 3 weeks of V2RA treatment (tolvaptan, 90/30 mg, in the last week), and after a 3-week washout period.

Setting & Participants: The trial included patients with ADPKD with a wide range of kidney function (measured glomerular filtration rates [mGFRs]; range, 18-148 mL/min/1.73 m^2).

Intervention: Tolvaptan treatment for 3 weeks.

Outcomes: 24-hour urine volume.

Analytical Approach: Multivariable regression analysis with stepwise backward elimination was performed both during and without V2RA treatment to evaluate the influence of 24-hour osmolar excretion, mGFR, and total kidney volume on associations between tolvaptan and urine volume.

Results: Included were 27 patients (48% men, aged 46 ± 9.8 years with mGFRs of 61 ± 35 mL/min/1.73 m^2). V2RA treatment caused a median increase in urine volume of 128% (interquartile range, 75%-202%), to 5,930 ± 1,790 mL. 24-hour osmolar excretion was strongly associated with 24-hour urine volume (standardized $\beta = 0.73$; $P < 0.001$). During V2RA use, no independent associations were detected between 24-hour urine volume and mGFR, total kidney volume, or V2RA concentration.

Limitations: Limited sample size, no standardized diets.

Conclusions: Osmolar excretion is the major determinant of urine volume in patients taking V2RAs as a consequence of the inability to concentrate urine. Restriction of osmolar intake may therefore limit V2RA-induced polyuria, giving patients more control over the aquaretic side effects and improving the tolerability of these drugs.

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation of numerous cysts in both kidneys and progressive kidney function decline leading to a need for renal replacement therapy in 70% of affected patients.[1,2] It is the most common hereditary kidney disease.[3] ADPKD accounts for 10% of all patients who are currently dependent on renal replacement therapy.[4]

The vasopressin V2 receptor antagonist (V2RA) tolvaptan is the first treatment that has been shown to slow the rate of kidney function decline in patients with ADPKD. Recently it was approved for clinical use in Japan, Canada, the European Union, and the United States. In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, which included patients with ADPKD with earlier-stage disease, tolvaptan decreased the rate of kidney function decline by 26%, from −3.70 to −2.72 mL/min/1.73 m^2 per year, when compared to placebo.[5] Subsequently, the REPRISE trial showed in later-stage disease that tolvaptan slowed kidney function decline from −3.61 to −2.34 mL/min/1.73 m^2 per year, a difference of 35%.[6]

As most common side effects, V2RAs cause polyuria and consequently thirst, nocturia, and polydipsia in more than half the treated patients.[5,7,8] As reported here, polyuria amounts to urine output of 6.0 ± 1.8 L per day, which affects daily life and was the main reason for dose reduction and drug discontinuation in the TEMPO 3:4 trial.[5]

Most studies have focused on the efficacy and/or safety of V2RAs, whereas few have addressed tolerability. We aimed to assess determinants of polyuria in patients with ADPKD using V2RAs because such determinants may be of help to develop strategies that limit urine volume and consequently improve tolerability. To meet this aim, we analyzed a study that included patients with ADPKD with chronic kidney disease stages 1 to 4 who received 120 mg of the V2RA tolvaptan per day and collected 24-hour urine in 3 separate portions (during the day, evening, and night).

Methods

Study Population

We studied data from a prospective study of the short-term renal hemodynamic effects of the V2RA tolvaptan that was carried out in 27 patients with ADPKD. Details of the study have been described previously.[9] This study was conducted between 2011 and 2013. Patients were eligible

for inclusion if they were 18 to 70 years old and had ADPKD according to the modified Ravine criteria.[10] Inclusion was stratified according to screening estimated glomerular filtration rate (eGFR; calculated using the CKD-EPI creatinine equation) to ensure inclusion of patients over a wide range of kidney function, with 9 participants per eGFR stratum (eGFR > 60, 30-60, and <30 mL/min/1.73 m^2). The main exclusion criteria were diuretic use, diabetes mellitus, critical electrolyte imbalances, disorders in thirst recognition, kidney disease other than ADPKD, contraindications to magnetic resonance imaging, previous exposure to a V2RA, and uncontrolled hypertension. The study was approved by the Ethics Board of the University Medical Center Groningen and conducted in adherence to the International Conference on Harmonization-Good Clinical Practice. Written informed consent was obtained from all participants.

Study Design

During the baseline visit, total kidney volume (TKV) and kidney function were measured. Venous blood samples were drawn and urine samples were collected. The following day, tolvaptan treatment was initiated in a split-dose regimen with 45 mg in the morning and 15 mg approximately 8 hours later. When tolerated, the dose was uptitrated to 60/30 mg after 1 week and to 90/30 mg after the second week. On the final day of this 3-week period and again after a 3-week washout period, the same measurements were repeated as performed during the baseline visit.

Measurements and Calculations

The 24-hour urine samples were collected on the day before the visit at baseline while using the V2RA and after the 3-week washout period. Urine was collected in 3 portions, one for the day (07:00-17:00), one for the evening (17:00-23:00), and one for the night period (23:00-07:00). Actual collection times could vary slightly; in case urine collections were not started at these precise time points, the exact time was noted and calculations were adjusted. Urine volume and concentrations of analytes were measured for each part of the day separately. Thereafter, the 3 separate portions were added and volume, concentrations, and excretions were calculated for the total 24-hour sample. Free-water clearance was measured as urine volume minus osmolar clearance. Osmolar clearance was calculated as (urine osmolality × urine volume)/plasma osmolality. Osmolality was measured using the freezing point depression method, sodium and potassium, using ion-specific electrodes, and urea, using an enzyme kinetic essay.

Plasma samples for tolvaptan measurement were collected during the treatment visit. Samples were taken at 6 time points, one before the 90-mg dose was administered (trough) and 5 in the 5 hours thereafter. Tolvaptan concentration was measured using a reverse-phase high-performance liquid chromatography system with tandem mass spectrophotometric detection.[11]

Fasting plasma copeptin levels were measured using a sandwich immunoassay (Thermo Fisher Scientific BRAHMS).[12] Kidney function measurements were performed in the 1- to 5-hour post–morning dose period using the continuous infusion method with ^{125}I-iothalamate and ^{131}I-hippuran.[13,14] Measured GFR (mGFR) was normalized to body surface area using the equation by Du Bois and Du Bois.[15] TKV was measured using a standardized magnetic resonance imaging protocol without the use of intravenous contrast.[8] Alice software (Perceptive Informatics) was used to measure TKV by calculating the volume of serial kidney outlines that were verified by independent radiologists familiar with ADPKD.

Statistical Analyses

Analyses were performed using SPSS, version 23 (SPSS Inc). Normally distributed variables are presented as mean ± standard deviation; others, as median with interquartile range (IQR). Categorical variables are presented as number and percentage of the entire study population. For all analyses, 2-sided $P < 0.05$ was considered statistically significant.

Urine volume, osmolality, free-water clearance, and osmolar excretions were compared between baseline, V2RA treatment, and washout using repeated-measurements analysis of variance or Friedman test in the case of non-normal distribution. Comparisons between day, evening, and night values were made using a paired-samples t test or Wilcoxon signed rank test in the case of non-normal distribution.

For univariable regression analyses, the independent variables were age, sex, mGFR, TKV, markers of osmolar intake (24-hour osmole, sodium, potassium, and urea excretions), variables that are associated with vasopressin secretion (plasma sodium and plasma osmolality), plasma copeptin, and pharmacokinetic variables (maximum concentration and area under the curve of plasma tolvaptan). Multivariable linear regression analyses were performed to find independent associations with 24-hour urine volume. All variables with $P < 0.1$ in univariable analyses were included. Variables were subsequently excluded from this model using stepwise backward multivariable linear regression analyses, creating a final model that only contains variables that are significantly associated with urine volume. Analyses were performed separately for the situation with and without V2RA use. Non-normally distributed variables were logarithmically transformed to fulfill the requirement of normal distribution of residuals.

Results

Baseline characteristics of the 27 individuals included in the study are listed in Table 1. Participants had a mean age of 46 years with a wide range of kidney function. Mean

Table 1. Baseline Characteristics

Characteristic	Value
Age, y	46 ± 9.8
Male sex	13 (48%)
Weight, kg	83 ± 19
BMI, kg/m^2	26 ± 4.1
Systolic blood pressure, mm Hg	131 ± 11
Diastolic blood pressure, mm Hg	81 ± 8
Antihypertensive drug use	24 (89%)
ACEi/ARB use	23 (85%)
mGFR, mL/min/1.73 m^2	61 ± 35
TKV, mL	2,147 [1,100-2,767]
Plasma creatinine, μmol/L	154 [77-263]
Plasma osmolality, mOsm/kg	286 [281-293]
Plasma sodium, mmol/L	141 ± 1.7
Plasma potassium, mmol/L	4.2 [3.9-4.4]
Plasma urea, mmol/L	8.2 [5.6-15.4]
Plasma copeptin, pmol/L	9.6 [4.8-25.5]

Note: Continuous variables are presented as mean ± standard deviation (or median [interquartile range] when non-normally distributed); categorical variables, as number (percentage).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; mGFR, measured glomerular filtration rate; TKV, total kidney volume.

mGFR was 61 ± 35 (range, 18-148) mL/min/1.73 m^2. Median TKV was 2,147 (IQR, 1,100-2,767) mL. Twenty-six patients were able to tolerate tolvaptan 90/30 mg in the final week of treatment; 1 patient received 60/30 mg.

Results of 24-hour urine collections are shown in Table 2. Values are shown at baseline, after 3 weeks of treatment with the V2RA, and after a 3-week washout period. The median increase in 24-hour urine volume during V2RA treatment was 128% (IQR, 75%-202%; $P < 0.001$), from urine volume of 2,584 ± 839 mL at baseline to 5,930 ± 1,790 mL during V2RA treatment (Fig 1). Median increases over baseline during the 3 urine collection periods were 106% (IQR, 40%-185%) during the day, 177% (IQR, 129%-300%) during the evening, and 87% (IQR, 44%-192%) during the night. Higher baseline mGFR was strongly associated with a higher percentage and absolute increase in 24-hour urine volume during V2RA treatment (standardized β [St β] of 0.82 [$P < 0.001$ and 0.6 [$P < 0.001$]). Urine volume per hour while using the V2RA was higher during the evening (333 ± 139 mL/h) compared to the day (236 ± 99 mL/h; $P = 0.001$) and night (205 ± 65 mL/h; $P < 0.001$). Free-water clearance was −491 ± 952 mL/24 h at baseline. During V2RA treatment, it increased to 2,991 ± 1,328 mL/24 h. After the washout period, free-water clearance returned to baseline values, at a mean of −616 ± 943 mL/24 h. Osmolar water clearance was unchanged between study periods. V2RA treatment led to a small but statistically significant increase in plasma sodium and plasma osmolality (Table S1).

Median 24-hour urine osmolality decreased by 60% after V2RA treatment initiation, to 139 (IQR, 126-173) mOsm/kg ($P < 0.001$; Fig 1). Baseline mGFR was not associated with urine osmolality while using the V2RA (St β = −0.02; $P = 0.9$). Urine osmolality during the day and evening were similar (146 [IQR, 118-171] and 136 [IQR, 110-150] mOsm/kg, respectively; $P = 0.3$). However, during the night, urine osmolality was significantly higher (154 [IQR, 134-188] mOsm/kg [$P = 0.01$ and $P < 0.001$ vs day and evening, respectively]).

At baseline and during V2RA treatment, 24-hour urine excretions of osmoles, sodium, and urea were similar, with only potassium excretion being higher while using the V2RA ($P = 0.03$). At baseline, during V2RA treatment, and after wash-out, 24-hour osmolar excretions were highly correlated, the same holding true for 24-hour excretions of the individual osmolar components sodium, potassium, and urea (Table S2). On V2RA treatment, osmolar excretion during the day was 33.1 ± 11.3 mmol/h. In the evening, osmolar excretion was significantly higher at 44.1 ± 17.4 mmol/h ($P = 0.002$), and during the night, it was similar to the day (33.4 ± 10.5 mmol/h; $P = 0.9$).

As mentioned, hourly urine volume differed between day, evening, and night. Figure 2 investigates whether these differences were a consequence of different osmolar excretion (reflecting osmolar intake) or differences in urine osmolality (reflecting the level of V2 receptor antagonism). Because urine volume is osmolar excretion divided by urine osmolality, hourly urine volume can be depicted as a third "diagonal axis." Evening urine volume was 41% higher compared to the day. As shown in Figure 2, this was mostly due to higher osmolar intake. Urine volume was lower during the night, mostly due to increased urine osmolality.

We also analyzed urine volume, urine osmolality, and osmolar excretion per eGFR stratum (Table S3). At baseline, urine osmolality was significantly lower in the lowest eGFR stratum and urine volume was higher. During V2RA treatment, patients with lower eGFRs had a smaller percentage decrease in urine osmolality and a smaller increase in urine volume. There were no significant differences in urine volume or urine osmolality while using the V2RA. At baseline, 24-hour osmolar excretion was the same in all strata and did not change.

Table 3 shows univariable correlations between preselected variables and, as the dependent variable, 24-hour urine volume with and without V2RA treatment. While using the V2RA, higher mGFR and higher 24-hour excretions of sodium, potassium, urea, and osmoles were associated with 24-hour urine volume (Fig 3). Tolvaptan plasma concentrations, which ranged from 149 to 1,570 ng/mL during kidney function testing, were not associated with urine volume. Without V2RA treatment, female sex, lower mGFR, higher TKV, higher 24-hour sodium excretion, higher 24-hour osmolar excretion, and higher plasma osmolality were associated with higher 24-hour urine volume.

Multivariable regression analysis using stepwise backward elimination was performed with 24-hour urine

Table 2. The 24-Hour Urine Volume and Urinary Excretion of Osmoles

	Baseline	Tolvaptan	Washout	*P*
Volume, mL/24 h	2,584 ± 839	5,930 ± 1,790	2,443 ± 791	<0.001
Day, mL/h	108 ± 41	236 ± 99	100 ± 40	
Evening, mL/h	112 ± 55	333 ± 139	121 ± 52	
Night, mL/h	106 ± 54	205 ± 65	92 ± 44	
Free-water clearance, mL/24 h	−491 ± 952	2,991 ± 1,328	−616 ± 943	<0.001
Day, mL/h	−26 ± 38	122 ± 70	−30 ± 39	
Evening, mL/h	−24 ± 58	182 ± 95	−30 ± 54	
Night, mL/h	−11 ± 41	90 ± 50	−17 ± 37	
Urine osmolality, mOsm/kg	359 [289-425]	139 [126-173]	351 [267-433]	<0.001
Day, mOsm/kg	363 [283-478]	146 [118-171]	367 [294-426]	
Evening, mOsm/kg	341 [273-532]	136 [110-150]	366 [283-425]	
Night, mOsm/kg	327 [273-381]	154 [134-188]	341 [276-470]	
Osmolar excretion, mOsm/24 h	881 ± 225	858 ± 231	879 ± 256	0.7
Day, mOsm/h	38.3 ± 12.5	33.1 ± 11.3	37.3 ± 13.1	
Evening, mOsm/h	38.9 ± 13.3	44.1 ± 17.4	43.6 ± 15.5	
Night, mOsm/h	33.1 ± 12.4	33.4 ± 10.5	31.4 ± 15.6	
Sodium excretion, mmol/24 h	159 ± 56	149 ± 53	152 ± 67	0.5
Day, mmol/h	6.8 ± 3.2	5.5 ± 2.1	6.5 ± 3.5	
Evening, mmol/h	7.2 ± 3.4	7.6 ± 4.1	7.4 ± 4.0	
Night, mmol/h	6.0 ± 2.7	6.1 ± 2.5	5.4 ± 3.2	
Potassium excretion, mmol/24 h	76 ± 22	89 ± 38	77 ± 26	0.03
Day, mmol/h	3.7 ± 1.1	3.8 ± 2.2	3.5 ± 1.2	
Evening, mmol/h	3.5 ± 1.3	4.8 ± 2.3	4.1 ± 1.8	
Night, mmol/h	2.2 ± 1.9	2.8 ± 1.1	2.2 ± 1.2	
Urea excretion, mmol/24 h	400 ± 117	378 ± 109	395 ± 120	0.3
Day, mmol/h	16.9 ± 5.7	14.3 ± 5.0	16.3 ± 5.8	
Evening, mmol/h	17.6 ± 6.1	19.4 ± 7.3	19.7 ± 7.7	
Night, mmol/h	15.8 ± 6.4	15.2 ± 5.2	14.8 ± 6.9	

Note: Variables are presented as mean ± standard deviation, or as median [interquartile range] when non-normally distributed. *P* values are given for repeated-measurements analysis of variance or Friedman test for non-normally distributed values.

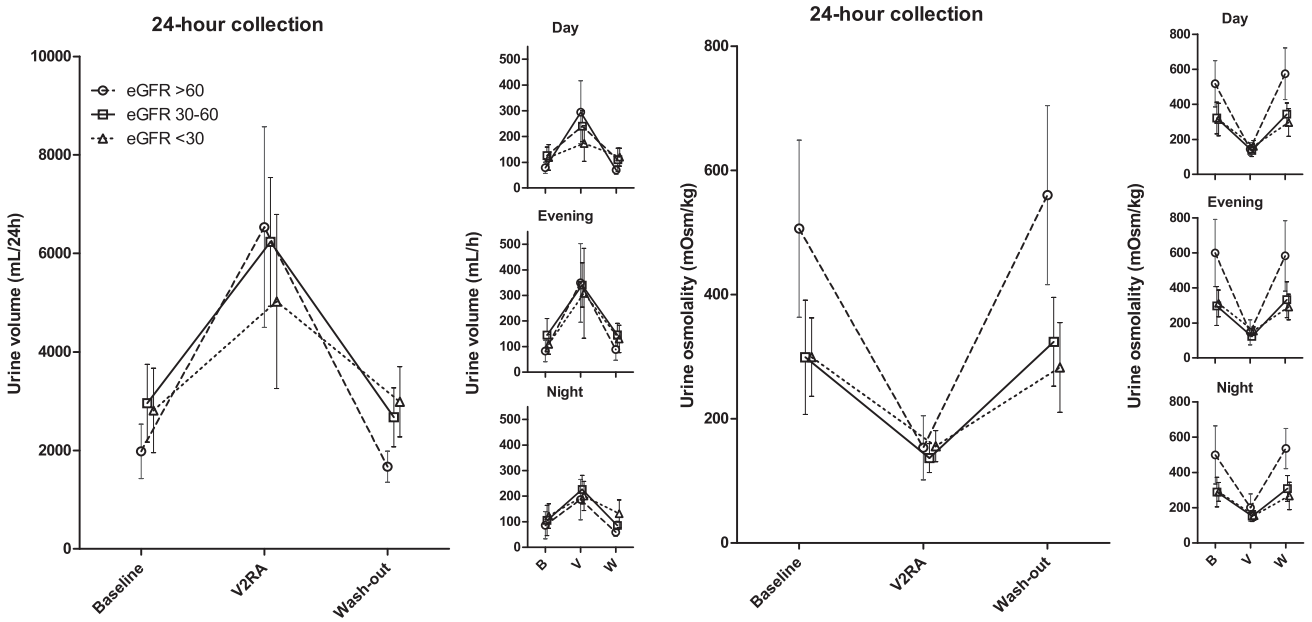

Figure 1. Urine volume and osmolality per estimated glomerular filtration rate (eGFR) stratum at baseline, after 3 weeks of vasopressin V2 receptor antagonist (V2RA) treatment, and after a 3-week washout period. Mean ± standard deviation are shown. In the 24-hour collection, urine volume was significantly different across eGFR strata at baseline and after the washout period, but not during V2RA use. Urine osmolality was significantly different at baseline and after the washout period, but not during V2RA use.

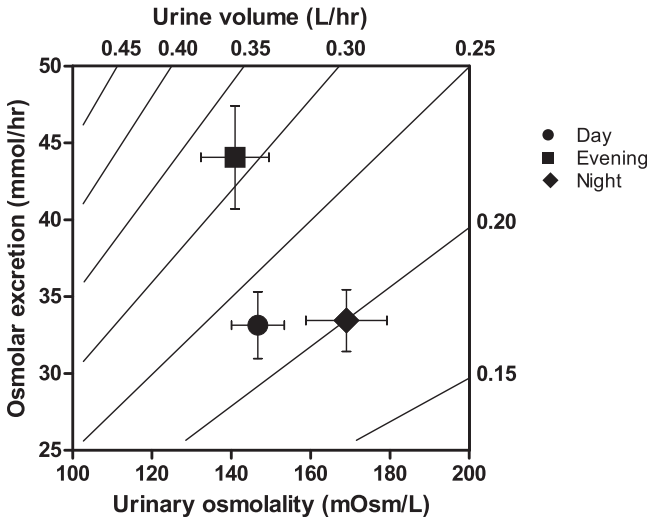

Figure 2. Relationship between osmolar excretion, urine osmolality, and urine volume during vasopressin V2 receptor antagonist use. Mean ± standard error values are shown for day, evening, and night. Urine volume is displayed by diagonal lines, with osmolar excretion (y-axis) divided by urine osmolality (x-axis) equaling urine volume.

volume as the dependent variable, both during and without V2RA treatment. Variables that were univariably associated with urine volume ($P < 0.1$) were entered into the models. Because 24-hour osmolar excretion consists of sodium, potassium, and urea, we chose to enter only osmolar excretion and not its components for the first analysis (Table 4). In the normal situation (without using a V2RA), mGFR and 24-hour osmolar excretion were independently associated with 24-hour urine volume (R^2 of the model = 0.50). While using the V2RA, only 24-hour osmolar excretion was independently associated with 24-hour urine volume ($R^2 = 0.54$).

We repeated the multivariable regression analysis with 24-hour urine volume with V2RA as the dependent variable and now entered the individual components of 24-hour osmolar excretion (sodium, potassium, and urea) instead of 24-hour osmolar excretion to the model as independent variables. Again, only variables that were univariably associated with urine volume ($P < 0.1$) were entered into the model. Significant associations with 24-hour urine volume were found for 24-hour sodium excretion (St β = 0.58, unstandardized β = 19.5; $P < 0.001$) and 24-hour potassium excretion (St β = 0.39, unstandardized β = 18.4; $P = 0.008$), whereas 24-hour urea was not independently associated with 24-hour urine volume (R^2 of the final model = 0.59).

Discussion

In this study in which 27 patients with ADPKD received the V2RA tolvaptan for 3 weeks, we investigated possible determinants of urine volume, both with and without V2RA treatment. In multivariable regression analysis, we found that lower mGFR and higher 24-hour osmolar excretion were independently associated with higher urine volume in patients with ADPKD without tolvaptan. After 3 weeks of V2RA treatment, the median increase in 24-hour urine volume was 128% (IQR, 75%-202%), reaching a mean 24-hour urine volume of 5,930 ± 1,790 mL (247 ± 75 mL/h). Urine volume per hour increased most during the evening period (median increase of 177% [IQR, 129%-300%]), to 333 ± 139 mL/h. In multivariable linear regression analysis, only 24-hour osmolar excretion was independently associated with 24-hour urine volume while using the V2RA. When the individual components of osmolar excretion (sodium, potassium, and urea) were entered into a multivariable model instead of total osmolar excretion, 24-hour sodium excretion and 24-hour potassium excretion were independently associated with 24-hour urine volume.

The increases in urine volume and free-water clearance are in line with the adverse events reported in the TEMPO 3:4 trial. In this trial, aquaresis-associated side effects such as polyuria, nocturia, thirst, and polydipsia were reported by more than half the patients. These side effects were the most common reason for discontinuing treatment (in 8.3% of patients).[5,16] Aquaretic side effects are a consequence of blocking the vasopressin V2 receptor, which limits water reabsorption in the collecting duct and lowers urine osmolality. Urine osmolality was lowest during the

Table 3. Univariable Associations Between Study Variables and 24-Hour Urine Volume Without and With V2RA

	Without V2RA		V2RA	
	St β	*P*	St β	*P*
Age, y	0.19	0.3	−0.18	0.4
Male sex	−0.36[a]	0.07[a]	0.002	0.9
mGFR, mL/min/1.73 m^2	−0.55[a]	0.003[a]	0.39[a]	0.05[a]
Ln(TKV)	0.41[a]	0.03[a]	0.20	0.3
Sodium excretion, mmol/24 h	0.49[a]	0.01[a]	0.67[a]	<0.001[a]
Potassium excretion, mmol/24 h	0.09	0.7	0.52[a]	0.005[a]
Urea excretion, mmol/24 h	0.25	0.2	0.60[a]	0.001[a]
Osmolar excretion, mmol/24 h	0.35[a]	0.07[a]	0.73[a]	<0.001[a]
Plasma sodium, mmol/L	0.09	0.7	0.28	0.9
Plasma osmolality, mOsm/kg	0.62[a]	0.001[a]	0.06	0.8
C_{max} tolvaptan	—	NA	0.06	0.8
$AUC_{0\text{-}5h}$ tolvaptan	—	NA	0.04	0.9
Ln(copeptin)	0.46[a]	0.02[a]	0.15	0.5

Note: St β and *P* values were calculated using univariable linear regression; St β is the Pearson correlation coefficient. Non-normally distributed variables were natural logarithm–transformed to fulfill the criteria of linear regression. Independent variables were baseline values in all models except for sodium, potassium, urea, and osmolar excretion and pharmacokinetic variables. In the "without V2RA" analysis, urinary excretions are an average of the baseline and washout values. In the "V2RA" analysis, urinary excretions, C_{max} tolvaptan, and $AUC_{0\text{-}5h}$ were measured during the V2RA visit. The dependent variable is 24-hour urine volume.
Abbreviations: AUC, area under the curve of tolvaptan; C_{max}, maximum tolvaptan concentration; mGFR, measured glomerular filtration rate; NA, not available; St β, standardized β; TKV, total kidney volume; V2RA, vasopressin V2 receptor antagonist.
[a]Statistically significant at $P < 0.1$.

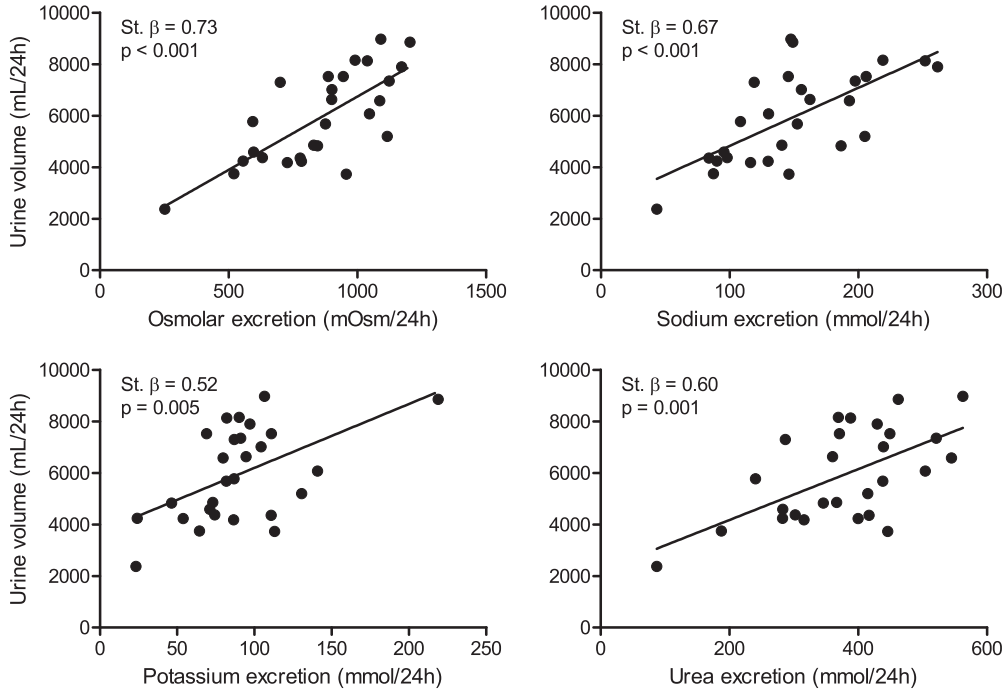

Figure 3. Associations of 24-hour excretions of osmoles, sodium, potassium, and urea with 24-hour urine volume while using tolvaptan. Abbreviation: St β, standardized β.

day and evening and increased slightly but significantly to a median of 154 mOsm/kg during the night. This has been described previously.[17] The high V2RA dose (90 mg) was taken around 08:00, and the lower dose (30 mg), around 17:00, likely leaving the V2 receptor maximally inhibited during the day and evening, only to fall below maximal during the night.[17] Consistent with this, hourly urine volume was lowest during the night. Evening urine volume was 41% higher compared to the day despite similar urine osmolality due to higher hourly osmolar excretion. These findings indicate that the main meal in the evening, with highest osmolar intake, may have contributed to higher urine output.

Table 4. Multivariable Linear Regression Analysis With 24-Hour Urine Volume as Dependent Variable

	Without V2RA		V2RA	
	St β	*P*	St β	*P*
Male sex	—	>0.05	—	NA
mGFR, mL/min/1.73 m^2	−0.62	<0.001	—	>0.05
Ln(TKV)	—	>0.05	—	NA
Osmolar excretion, mmol/24 h	0.46	0.005	0.73	<0.001
Plasma osmolality, mOsm/kg	—	>0.05	—	NA
Ln(copeptin)	—	>0.05	—	NA

Note: St β and *P* values were calculated using multivariable linear regression. The dependent variable is 24-hour urine volume. Independent variables were chosen based on univariable associations with $P < 0.1$, the model using stepward backward elimination. Sodium, potassium, and urea excretion were not entered because these are components of osmolar excretion. Variables labeled NA were not entered into the model because their univariable association was $P > 0.1$.
Abbreviations: mGFR, measured glomerular filtration rate; NA, not available; St β, standardized β; TKV, total kidney volume; V2RA, vasopressin V2 receptor antagonist.

At metabolic steady state, 24-hour excretions of osmoles, sodium, and urea are a measure of intake. Initiation of V2RA treatment influences sodium, potassium, and urea reabsorption.[18,19] However, during longer use, compensatory mechanisms will cause excretions to match intake again, such that a new steady state will be reached. The similar values for 24-hour osmolar, sodium, and urea excretions with and without tolvaptan indicate that 3 weeks was sufficient to reach steady state.

Without V2RA, in multivariable analysis, only 24-hour osmolar excretion and mGFR were significantly associated with urine volume. Earlier studies have shown that as ADPKD progresses, patients develop a urine-concentrating defect and polyuria.[20,21] A post hoc analysis of the TEMPO 3:4 trial also showed that patients with worse eGFRs and larger TKVs were more likely to have lower urine osmolality.[22] This is consistent with our finding of an independent association between 24-hour urine volume and mGFR. Because 24-hour osmolar excretion is a measure of osmolar intake, this finding suggests that osmolar intake may also be involved in determining urine volume in ADPKD. In healthy individuals, it has been shown that higher osmolar intake results in higher urine osmolality without an effect on urine volume in steady state[23,24]; more dilute urine enters the collecting duct, but this is counterbalanced by increased water reabsorption in the collecting duct resulting in a (more) negative free-water clearance.[18,21] However, in progressive ADPKD, the ability to concentrate urine and increase urine osmolality is impaired. This is consistent with our findings: when water cannot be sufficiently reabsorbed, higher osmolar

excretion results in higher urine volume. In line with this, there was no significant correlation between osmolar excretion and urine volume in the stratum of patients with the highest eGFR (St $\beta = 0.3$; $P = 0.4$), for whom a urine concentrating defect has not occurred yet, whereas this correlation became highly significant in the stratum of patients with the lowest eGFR (St $\beta = 0.9$; $P = 0.001$).

The increase in urine volume after V2RA treatment initiation was higher in patients with greater eGFRs due to a greater decline in urine osmolality (Table S3). Urine osmolality and urine volume while using the V2RA were the same across eGFR strata; hence, the difference in decline in urine osmolality was due to differences in baseline urine osmolality. It has been suggested that the decrease in urine osmolality under V2RA treatment is predictive of the renoprotective effect.[22] The duration of our study was too short to evaluate this.

While using the V2RA, univariable associations with higher urine volume were found for higher mGFR (in contrast to the situation without using the V2RA) and higher 24-hour excretions of osmoles, sodium, potassium, and urea (Fig 3). Tolvaptan plasma concentrations were not associated with urine volume, possibly due to interindividual variation in pharmacodynamic response. In multivariable regression analysis, the only association with urine volume that remained significant was 24-hour osmolar excretion. When instead of 24-hour osmolar excretion, its individual components were entered into the analysis, 24-hour sodium and potassium excretion remained highly significantly associated. This finding indicates that osmolar intake plays a vital role in determining urine volume while using a V2RA. Osmoles (sodium, potassium, and urea) deliver water to the thick ascending limb of the loop of Henle, where solutes get reabsorbed and solute-free water reaches the collecting duct.[21,25] In the presence of vasopressin and functioning vasopressin V2 receptors, most water will be reabsorbed in the distal collecting duct, resulting in more concentrated urine.[26] However, in the scenario of V2RA treatment, water cannot be reabsorbed. Thus, after V2RA treatment initiation, osmolar excretion becomes the major determinant of urine volume. Urine osmolality cannot increase and is set within a relatively small range, whereas osmolar excretion can vary greatly according to intake, resulting in variation in urine volume (Fig S1). This is very similar to nephrogenic diabetes insipidus, in which the vasopressin V2 receptor is defective.[27] In diabetes insipidus, the importance of reduced osmolar intake to reduce daily urine volume is well recognized.[27]

In multivariable linear regression analysis, the unstandardized correlation coefficient β of 24-hour sodium excretion in relation to 24-hour urine volume while using the V2RA was 19.5. This implies that a reduction in daily intake of sodium by 100 mmol (5.6 g of table salt, NaCl) could decrease 24-hour urine volume by 1,950 mL (100×19.5). The strength of the association between 24-hour potassium excretion and 24-hour urine volume during V2RA use was similar. Remarkably, 24-hour urea excretion was not associated with urine volume in multivariable regression analysis. Because urea is an active osmol in urine, this was unexpected. It is possible that this is a false-negative finding. Patients who consume more sodium and potassium may also consume more protein. Consequently, colinearity may be the cause of not finding an association between urea excretion and 24-hour urine volume. The 24-hour sodium excretion was highly correlated to 24-hour urea excretion at baseline (St $\beta = 0.57$; $P = 0.002$) while using tolvaptan (St $\beta = 0.55$; $P = 0.003$) and after stopping tolvaptan treatment (St $\beta = 0.65$; $P = < 0.001$).

To our knowledge, there are no studies to date that have investigated a possible association between osmolar excretion and disease progression in V2RA-treated patients. We do not expect that a decrease in side effects through osmolar restriction would also decrease the renoprotective effect of V2RA. Renoprotection is thought to be a consequence of inhibition of cAMP (cyclic adenosine monophosphate) signaling.[17] cAMP is not likely upregulated by osmolar restriction. Osmolar restriction has been shown to decrease plasma copeptin levels (a marker of vasopressin) in patients with ADPKD.[28] Because V2RAs are competitive antagonists, an increase in agonist (vasopressin) at the same level of antagonist (V2RA) might further downregulate cAMP. In the TEMPO 2:4 trial, every dose increase of V2RA that was tested, from 30/15 mg up to 90/30 mg, further increased the pharmacodynamic effect on urine osmolality.[17] This suggests that also variations in agonist (vasopressin level) could affect pharmacodynamics at every dose tested. Whether osmolar restriction could sufficiently affect vasopressin level to really improve renoprotection is unknown.

There are limitations to this study. First, only 27 individuals were investigated. However, these patients were well characterized with measurement of GFR, TKV, and urine volume using gold-standard methods, with 24-hour urine collection in 3 time periods. Moreover, the study had a stratified inclusion to ensure inclusion of patients of all chronic kidney disease stages. Another limitation is the absence of a standardized diet. However, excretions of overall osmoles and of sodium and urea were highly correlated among the 3 study phases (Table S2), suggesting a stable diet per individual throughout the study. Last, our findings are observational and therefore do not allow firm conclusions with respect to causality. Prospective research is needed to fully understand the effects of osmolar intake on urine volume in patients using V2RAs.

To date, the V2RA tolvaptan is the only treatment that has been proven to slow disease progression in ADPKD. Polyuria and related side effects, such as thirst, are the most common reasons for treatment discontinuation. We found that due to the maximally dilute urine induced by use of V2RAs, osmolar excretion becomes the major determinant of urine volume. Our data suggest that

limiting osmolar intake could reduce urine volume and make treatment with V2RAs more tolerable. Furthermore, patients could be informed that they may be able to change the timing of the highest urine output by adjusting their meal schedule and the amounts of osmoles ingested, allowing them to have more control over the aquaretic side effects of tolvaptan.

Supplementary Material

Figure S1: 24-hour urine volume by urine osmolality tertile, each divided into tertiles of 24-hour osmolar excretion.

Table S1: Water clearance, plasma osmolality, and plasma sodium.

Table S2: Correlations of 24-hour urinary excretions between baseline, V2RA treatment, and the wash-out period.

Table S3: Changes in markers of urine volume and concentration per eGFR stratum.

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