LETTER TO THE EDITOR

Glomerular filtration rate is the main predictor of urine volume in autosomal dominant polycystic kidney disease patients treated with tolvaptan when daily osmolar excretion is expressed as urinary osmolality/creatinine ratio

Francisco José Borrego Utiel and Enoc Merino García

Unidad de Gestión Clínica de Nefrología, Complejo Hospitalario Universitario de Jaén, Jaén, Spain

Correspondence to: Francisco José Borrego Utiel; E-mail: fjborregou@gmail.com

Tolvaptan was recently approved to treat autosomal dominant polycystic kidney disease (ADPKD) [1], as it slows the rate of kidney growth and renal function decline [2, 3]. Tolvaptan blocks the V2 vasopressin receptor in renal collecting ducts and distal nephron causing intense polyuria, which is the main adverse effect [2, 3]. Guidance on how to optimize tolvaptan prescription is available and continues to evolve [4, 5].

Recently, Kramers et al. [6] searched for factors associated with increased urine volume in 27 ADPKD patients on tolvaptan, most of them at the highest dose (90/30 mg). They observed an increase in urine volume in three periods (day, evening and night), with a greater increase in the evening, and this was paralleled by a reduction in urinary osmolality, while total osmolar excretion was unchanged by tolvaptan. Daily urine output correlated with both glomerular filtration rate (GFR) and daily solute excretion of individual molecules (= solute concentration × urine output, e.g. for sodium, potassium and urea) or of all solutes (daily osmolar excretion = urinary osmolality × urine output). In multivariable analysis with linear regression to predict urine output, initial predictors included GFR and daily solute excretion of individual molecules. They concluded that only daily osmolar excretion is predictive of urine output, while GFR was not. They used this observational conclusion to infer causality and to suggest that reducing osmolar intake may reduce urine volume.

We disagree with this conclusion as in correlation and regression analyses, a predictor variable cannot be introduced that predicts itself: the same variable cannot be placed on both sides of the regression equation. Daily urinary osmolality was calculated from urinary osmolality and urine output and used to predict urine output. Thus, urine output was on both sides of the equation: urine output is predicted by urine output! It is the same scenario as predicting body weight from body mass index (weight/height²).

To address this issue and get rid of the urine output component while still estimating the potential impact of solute intake on urine volume, we have expressed solute concentrations in urine as solute/creatinine ratio, as done with albuminuria/creatinine, calcium/creatinine or uric acid/creatinine ratios, in 24-h urine samples. With total osmolar excretion as the osmolality/creatinine ratio, the influence of the volume of diuresis is avoided.

We studied 24-h urine samples from 18 ADPKD patients on chronic treatment with tolvaptan and who had received the three doses: 45/15, 60/30 and 90/30 mg. Each patient was represented once per dose for a total of 54 urine samples (Table 1).

As expected, tolvaptan increased urine volume, which was roughly doubled, and roughly halved urine solute concentrations expressed by volume and calculated osmolality. In contrast, solute concentrations expressed as ratios with creatinine remained constant as did osmolality corrected with urinary

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Urine was correlated with urinary osmolar load, calculated from osmolality and urine volume. (osmolality/creatinine ratio. The correlation of urine volume with osmolar excretion (reflecting solute intake) after tolvaptan did not predict urine volume.

Table 1. Comparisons between baseline (without tolvaptan) and after different doses of tolvaptan for renal function and urinary determinations in patients with ADPKD

| Tolvaptan doses of mg | Baseline | 45/15 mg | 60/30 mg | 90/30 mg |
|---------------------|----------|----------|----------|----------|
| Patients            | 18       | 18       | 18       | 18       |
| Serum creatinine, mg/dL | 1.7 ± 0.6 | 1.9 ± 0.9 | 1.9 ± 0.9 | 2.1 ± 1.0 |
| GFR-MDRD4, mL/min/1.73 m² | 50 ± 18  | 45 ± 19  | 48 ± 22  | 43 ± 20  |
| Urine               |          |          |          |          |
| Output, mL/day      | 2683 ± 675  | 5419 ± 1674 | 6400 ± 2100 | 6511 ± 1694 |
| Creatinine, mg/dL   | 55.9 ± 17.6 | 27.9 ± 8.2 | 23.0 ± 4.9 | 21.8 ± 5.0 |
| Urea, mg/dL         | 893 ± 257   | 446 ± 141  | 395 ± 78  | 391 ± 82  |
| Urea/Cr, g/gCr      | 16.9 ± 4.5  | 16.2 ± 3.6 | 17.5 ± 3.3 | 18.1 ± 2.6 |
| Sodium, mmol/L      | 71.9 ± 27.3 | 34.0 ± 13.9 | 33.3 ± 9.3 | 31.4 ± 11.3 |
| Sodium/Cr, mEq/gCr  | 134 ± 41    | 123 ± 44   | 150 ± 54  | 144 ± 41  |
| Potassium, mmol/L   | 27.1 ± 12.6 | 12.4 ± 3.4 | 10.6 ± 2.4 | 11.4 ± 3.2 |
| Potassium/Cr, mmol/gCr | 50.8 ± 21 | 46.2 ± 12.8 | 47.9 ± 15.0 | 52.7 ± 13.2 |
| Urinary osmolality  |          |          |          |          |
| Calculated, mOsm/kg  | 353 ± 118  | 170 ± 48   | 156 ± 24  | 153 ± 37  |
| Osmolal load, mOsm/day | 929 ± 316 | 918 ± 394  | 1002 ± 377 | 976 ± 291 |
| Osmolality/Cr, mOsm/gCr | 666 ± 180 | 618 ± 113  | 697 ± 139 | 705 ± 110 |

MDRD: modification of diet in renal disease.

*p < 0.001. Baseline without tolvaptan compared with each dose using Wilcoxon test.

* Calculated osmolality = 2 × (Na + K) + urea/5.8.

FIGURE 1: Correlates of urine volume in patients with ADPKD treated with tolvaptan. (A) Urine volume is significantly correlated with GFR. (B) Urine volume is highly correlated with urinary osmolar load, calculated from osmolality and urine volume. (C) Urine volume is not correlated with urinary osmolar load expressed by urinary osmolality/creatinine ratio.

Urine volume was correlated with serum creatinine (Rho Spearman = −0.36, P = 0.008), urinary creatinine (Rho = −0.29, P = 0.034) and GFR estimated with the modification of diet in renal disease (MDRD4) equation (Rho = 0.44, P = 0.001; Figure 1A). Urine volume was also correlated with calculated daily osmolar excretion expressed as mOsm/day as calculated from urine osmolality and urine volume (Rho = 0.76, P < 0.001; Figure 1B). These findings were in agreement with the report by Kramers et al. [6]. However, urine volume was not correlated with calculated urinary osmolality expressed as mOsm/Kg (Rho = −0.04, P = 0.77) or as urinary osmolality/creatinine ratio (Rho = 0.23, P = 0.1; Figure 1C), that is, the correlation of urine volume with osmolar excretion was lost when urine volume was removed from the predictor variable. Urine volume was additionally not correlated with urinary urea or sodium concentrations nor their solute/creatinine ratios, and although it was correlated with urinary potassium concentration (Rho = −0.33, P = 0.014), it was not correlated with potassium/creatinine ratio.

Next, we performed a linear regression analysis using as predictors of urine volume the following variables: tolvaptan dose, GFR and urinary assessments. In the final model, only GFR and the osmolality/creatinine ratio were significant predictors of urine volume (urine volume = −55.35 × GFR + 4.74 × osmolality/ Cr; r² = 0.41, P < 0.001) but individual solute assessments or tolvaptan dose did not predict urine volume.

In a sensitivity analysis, in which correlations were performed with samples sharing the same tolvaptan dose, urine volume only correlated with GFR but it did not correlate with the osmolality/creatinine ratio.
Therefore, urine volume after initiating tolvaptan in patients with ADPKD is influenced mainly by the degree of renal function as assessed by GFR, that is, by a non-modifiable variable. There might also be a contribution of urinary solute load. However, the contribution of solute intake (and excretion) appears to be lower than estimated by Kramers et al. [6]. We propose that the urinary solute/creatinine ratio and osmolality/creatinine ratio should be used to search for predictors of urine output in patients on tolvaptan. We wonder what results might Kramers et al. [6] obtain when using creatinine ratios rather than 24-h urinary excretion values.

CONFLICT OF INTEREST STATEMENT
None declared.

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