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What is the Appropriate Dose of Tolvaptan in ADPKD?

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The half-life of tolvaptan is dose-dependent, with the half-life increasing from 3.3 hours after a 15 mg dose to 11 hours after a 120 mg dose.[1] Daily split dosing ensures V2 receptor antagonism throughout the day, whereas a higher morning dose and lower afternoon dose helps minimize nocturia.[2] Early trials to establish dose and efficacy of tolvaptan showed that twice daily dosing was critical for continuous vasopressin suppression, and that urine osmolarity remained low from 4 to 16 hours after treatment with 15 mg/15 mg, 30 mg/15 mg, and 30 mg/30 mg dosing.[2] Subjects were increasingly intolerant of higher tolvaptan dosing because of aquaretic side effects, with those with lower estimated glomerular filtration rate (eGFR) more likely to consent to increased dosing.

The starting dose in TEMPO 3:4[3] was 45 mg followed by 15 mg approximately 8 hours later. This dosing regimen was titrated up to 60 mg/30 mg and 90 mg/30 mg as tolerated. The rationale for increasing dosing despite the increasing aquaretic side effects was that the 90 mg/30 mg dosing resulted in more patients (85%) having a premorning dose urine osmolarity <300 mOsm/kg.[2] Comparisons of 24-hour measurements of urine volume, urine osmolarity, and total osmolar load show that urine volume increases and urine osmolarity decreases, but total osmolar load remains the same with increasing doses of tolvaptan.[4]

In the 2 pivotal clinical trials (TEMPO 3:4[3] and REPRISE[5]) the dose was titrated up to 90 mg/30 mg as tolerated and down-titrated as needed. Patients were encouraged to stay on the maximum tolerated dose. REPRISE patients who did not tolerate 60 mg/30 mg dosing in the single-blind period were excluded from the double-blind study. In routine clinical practice however, doses are generally much lower than those in the trials. In a post-marketing analysis of tolvaptan including over 6000 individuals, 45 mg/15 mg was the most common dose (63%), with 15% at 60 mg/30 mg, and 17% at 90 mg/30 mg.[6] The ideal dose of tolvaptan might be that which achieves suppression of vasopressin as measured by a lower 24-hour urine osmolarity and is tolerated by the patient.

However, a recent paper noted that increasing weight-adjusted daily dosing of tolvaptan positively correlated with lower percentage change in eGFR.[7] Concerns with this study include reported percent changes in GFR in 3 of the 79 patients which were unusually high (>40% per year); and all had lower tolvaptan dosing, raising the question of whether the lower doses in this study were merely correlated with cautious prescribing for those with variable eGFR or if there is true causation between lower dosing and faster eGFR decline.

Urine osmolality (Uosm), which serves as a marker of vasopressin suppression may have a role in guiding appropriate tolvaptan dose. A greater reduction in Uosm in response to tolvaptan correlates with less disease progression.[8] This finding, based on a *post hoc* analysis of TEMPO 3:4 data showed that there was no further benefit (in eGFR decline) of decreasing Uosm below 250 mOsm/kg.[8] These findings suggest that an appropriate tolvaptan dose may be that which correlates to a Uosm <280 mOsm/kg (value chosen to ensure the urine osmolarity less than serum osmolarity). In this analysis, a spot, nonfasting urine (preferably the second morning void, prior to taking the morning tolvaptan dose) was used for urine osmolarity measurements. The 24-hour urine osmolarity measurements were not collected in TEMPO 3:4 or REPRISE because these urine collections could have unblinded participants and investigators to the treatment versus placebo arm allocation.

There are limitations of spot urine osmolarity measurements compared to 24-hour measurements, as nicely illustrated by Gobburu *et al.*,[9] who found that

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change in a spot Uosm at 3 weeks in TEMPO 3:4 explained only about 15% of the tolvaptan effect on total kidney volume, however 24-hour measurements (Uosm AUC_{24}) had better correlation. This paper also showed that a spot urine osmolarity in controls versus those treated with tolvaptan does not reflect the 24-hour blockade of vasopressin activity in the kidney.

In this issue, Roca Oporto *et al.*[10] describe the results of a prospective study with adjustment of tolvaptan dosing based on 24-hour urine osmolarity (Uosm) measurements in patients with ADPKD. Forty patients were enrolled, with tolvaptan treatment initiated at a dose of 45 mg/15 mg, and a 24-hour urine osmolarity goal of 200 mOsm/kg set as the therapeutic target. Patients had a mean age of 45 (±7) years, with 82% on treatment for hypertension, with a baseline eGFR of 51 ± 12.5 ml/min per 1.73 m^2. Two patients dropped out because of aquaretic side effects, and tolvaptan was discontinued in an additional 4 patients who had eGFR decline to <20 ml/min per 1.73 m^2.

As expected, there was a significant decrease in 24-hour Uosm with initiation of tolvaptan with a difference of −220 mOsm/Kg (95% confidence interval: −118 to −255). Five patients were uptitrated from a dose of 45 mg/15 mg to 60 mg/30 mg. No patient required a dose of 90 mg/30 mg to achieve a 24-hour Uosm <200 mOsm/kg. Patients had a median urine volume of 6000 ml/day (range: 5500–7000) on treatment.

The mean decline in eGFR prior to treatment was −7.71 (±4.15) ml/min per 1.73 m^2, and the mean decline on treatment was −3.05 (±2.41) ml/min per 1.73 m^2. No significant difference was noted in primary renal events based on chronic kidney disease stage ($P = 0.08$) or tolvaptan dose ($P = 0.20$) in this small study, and the Uosm did not differ significantly between those with a primary renal event (a >25% decrease in eGFR).

Secondary outcomes in this study were defined as composite events, including a cyst complication requiring medical care, worsening albuminuria (defined as a change in category), onset of hypertension, or increased treatment of hypertension. The most frequent secondary outcome was increased treatment of hypertension (occurring in about 22% of patients), followed by cyst complications. Those with secondary events had a higher baseline Uosm; however, there was no significant difference in the 2 groups over the 3-year treatment period.

In models with multivariate analysis, baseline eGFR was found to be protective for both primary (hazard ratio: 0.88; 95% confidence interval: 0.807–0.971) and secondary (hazard ratio: 0.92; 95% confidence interval: 0.871–0.969, respectively).

The dosing strategy was safe, with hyperuricemia (18%), hypernatremia (11%) as the most frequent side effects of those on tolvaptan. There were no cases of hepatotoxicity.

Although this study is a small, single center study, without a true control group, it provides valuable insight into tolvaptan dosing. Importantly, the study involved collecting 24-hour urines for measurement of osmolarity, which demonstrated that most patients achieved a 24-hour Uosm <200 with 45 mg/15 mg dosing, and that the 24-hour urine osmolarity was beneficial in guiding dose titration to those who ultimately went up to a 60 mg/30 mg dose.

Unfortunately, this study does not guide us on how to manage patients with preserved kidney function who have the most polyuria and aquaretic side effects to tolvaptan and may benefit from a dose lower than 45 mg/15 mg. We do not know if titration using 24-hour Uosm would allow down titration of dosing for these patients. We also do not know how well a spot morning urine osmolarity compares to a 24-hour urine measurement as a potential alternative guide in the nonclinical trial setting. However, this study does provide a rationale for starting dosing at 45 mg/15 mg for those with stage 3 chronic kidney disease and offers reassurance that most patients will not need to be uptitrated.

DISCLOSURE

NKD is a consultant for Otsuka and Natera; a member of the PKD Foun dation Scientific Advisory Committee; and a principal investigator for Vertex, Regulus, and Reata. VET is an employee of the Mayo Clinic in Rochester, MN. He has recently received research support from Mironid, Blueprint Medicines, Tribune, Palladio Biosciences, Sanofi, Reata, and Regulus. He has been a consultant for Otsuka, Vertex, uResearch Technology, and MFMER; all honoraria are paid to the Institution. He is a member of the Kaplan award committee (ISN), ASN editorial board, and PKD Foundation Advisory Board.

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