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Original Investigation

Short-term Effects of Tolvaptan in Individuals With Autosomal Dominant Polycystic Kidney Disease at Various Levels of Kidney Function

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Background: A recent study showed that tolvaptan, a vasopressin V_2 receptor antagonist, decreased total kidney volume (TKV) growth and estimated glomerular filtration rate (GFR) loss in autosomal dominant polycystic kidney disease (ADPKD) with creatinine clearance $\geq$ 60 mL/min. The aim of our study was to determine whether the renal hemodynamic effects and pharmacodynamic efficacy of tolvaptan in ADPKD are dependent on GFR.

Study Design: Clinical trial with comparisons before and after treatment.

Setting & Participants: Patients with ADPKD with a wide range of measured GFRs (mGFRs; 18-148 mL/min) in a hospital setting.

Intervention: Participants were studied at baseline and after 3 weeks of treatment with tolvaptan given in increasing dosages, if tolerated (doses of 60, 90, and 120 mg/d in weeks 1, 2, and 3, respectively).

Outcomes: Change in markers for aquaresis (free-water clearance, urine and plasma osmolality, 24-hour urine volume, and plasma copeptin) and kidney injury (TKV and kidney injury biomarkers).

Measurements: GFR was measured by ^{125}I-iothalamate clearance; TKV, by magnetic resonance imaging; biomarker excretion, by enzyme-linked immunosorbent assay; and osmolality, by freezing point depression.

Results: In 27 participants (52% men; aged 46 $\pm$ 10 years; mGFR, 69 $\pm$ 39 mL/min; TKV, 2.15 [IQR, 1.10-2.77] L), treatment with tolvaptan led to an increase in urine volume and free-water clearance and a decrease in urine osmolality, TKV, and kidney injury marker excretion. Changes in urine volume and osmolality with treatment were less in participants with lower baseline mGFRs (both $P < 0.01$). However, change in fractional free-water clearance was greater at lower baseline mGFRs ($P = 0.001$), suggesting that participants with decreased GFRs responded more to tolvaptan per functioning nephron.

Limitations: Limited sample size, no control group.

Conclusions: In patients with ADPKD with decreased kidney function, response to tolvaptan is lower for TKV, urinary volume, and osmolality, but larger for fractional free-water clearance. This latter finding suggests that patients with ADPKD with lower GFRs might benefit from long-term treatment with tolvaptan, as has been observed for patients with preserved GFRs.

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Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disease that leads to cyst formation, especially in the kidneys, resulting in kidney enlargement and function loss. Fifty percent of affected individuals need renal replacement therapy in their sixth decade of life.[1]

Experimental studies have suggested that arginine vasopressin (AVP) may have a central role in the pathophysiology of this disease. Studies of humans have shown that in patients with ADPKD, higher AVP levels are associated with a decrease in kidney function and an increase in total kidney volume (TKV) during follow-up.[2] Blocking the AVP V_2 receptors therefore is a promising therapeutic intervention in this disease. Several experimental studies have demonstrated that AVP V_2 receptor antagonists

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slow the rate of cyst development and kidney growth in various models for cystic kidney disease.[3-7] In a study involving 20 patients with ADPKD, the AVP V_2 receptor antagonist tolvaptan given at low dose (45/15-mg split dose) was reported to cause a decrease in TKV after 1 week of treatment.[8] A study by Higashihara et al[9] suggested that long-term use of this drug is associated with less increase in TKV and less decrease in kidney function when compared with historical control patients with ADPKD who were matched for several patient characteristics. Recently, the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3:4 Study[10] prospectively showed that use of tolvaptan, given in dosages between 45/15 and 90/30 mg/d as a split dose, slowed the increase in TKV and decline in kidney function over a 3-year period in 1,445 patients with ADPKD.[11] All 3 mentioned studies were performed in patients with ADPKD with relatively preserved kidney function. Studies of animals and humans have suggested that the efficacy of AVP receptor antagonists may be lower when given at later stages in the disease.[6,8]

We recently completed a study of short-term renal hemodynamic effects of tolvaptan in patients with ADPKD (ClinicalTrials.gov identifier NCT01336972).[12] The renal hemodynamic results showed that changes in glomerular filtration rate (GFR), effective renal plasma flow, and filtration fraction were not different between patients with lower compared to higher GFR kidney function. The aim of the present analyses was to determine whether the pharmacodynamic efficacy of tolvaptan in patients with ADPKD is dependent on kidney function, which would give information about the efficacy of tolvaptan in patients with decreased kidney function. For that reason, we investigated short-term responses on various efficacy parameters to target therapeutic doses of this drug in patients with ADPKD with a wide range of kidney function, including those with GFRs < 30 mL/min/1.73 m^2, and we investigated whether therapy-induced changes in these parameters are dependent on baseline kidney function.

METHODS

Study Population

Study participants were eligible when ADPKD was diagnosed based on the Ravine criteria[13] and were aged 18 to 70 years. Patients were given information about this study at the outpatient clinic by their nephrologists. If they were interested, an appointment with the study physician was made. Participants were included by estimated GFR (eGFR; isotope-dilution mass spectrometry–traceable 4-variable MDRD [Modification of Diet in Renal Disease] Study equation[14]) in 3 strata (>60, 30-60, and <30 mL/min/1.73 m^2) to ensure that inclusion was balanced to cover a wide range of kidney function. We used eGFR only for inclusion. In all analyses, we used measured GFR (mGFR; iothalamate clearance).

Main exclusion criteria were as follows: diuretic use, pregnancy or breast-feeding, previous exposure to tolvaptan, risk factors for decreased kidney function other than ADPKD (eg, renal cancer, single kidney, active glomerular nephritides, and nephrotoxic drugs), recent renal surgery, diabetes mellitus, contraindications to magnetic resonance imaging (MRI; ferromagnetic prostheses, aneurysm clips, severe claustrophobia, and body mass index > 35 kg/m^2), critical electrolyte imbalances, and uncontrolled hypertension. Participants with hypertension were treated with an angiotensin I–converting enzyme inhibitor or angiotensin II receptor blocker, with the addition of any other antihypertensive drug if needed (except diuretics).

This study was approved by the ethics board at the University Medical Center Groningen (METc 2010.187) and performed in adherence to the ICH-GCP (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use−Good Clinical Practice) guidelines. Written informed consent was obtained from all participants.

Study Design

Participants were screened 2 to 42 days before tolvaptan was administered. They were instructed to collect urine for 24 hours before every kidney function measurement test and not to drink alcohol or use food or beverages containing methyl xanthines within 24 hours of kidney function testing to avoid effects on AVP signaling. Because tolvaptan is a weak cytochrome P450 3A4 (CYP3A4) substrate, participants were instructed not to consume grapefruit or Seville oranges within 72 hours prior to receiving tolvaptan.

One day before initiating tolvaptan treatment, participants visited the clinic for kidney function and TKV measurements (baseline visit). The day after the baseline visit, participants initiated tolvaptan treatment in a split-dose regimen with 45 mg in the morning and 15 mg approximately 8 hours after the first dose. After 1 week of treatment, if this low dosage was tolerated, participants started an intermediate dosage (60/30-mg/d split dose), which after another week, if tolerated, was uptitrated to a split-dose regimen with 90/30 mg/d. On the last day of this 3-week treatment period, as well as 3 weeks after the last dose of tolvaptan, kidney function and TKV were measured again. On the last day of treatment, the highest tolerated dose of tolvaptan was administered 30 minutes after the start of kidney function tracer infusion.

Because of the large number of variables measured in this intensive study protocol, the present study focuses on effects of tolvaptan on efficacy variables, whereas the effects on renal hemodynamics, adverse events, and safety are reported in detail elsewhere.[12]

Measurements and Calculations

On kidney function and TKV measurement days, participants visited our clinic at about 7:45 AM, by which time they had been fasting for 4 hours (but drinking water ad libitum). Blood samples were drawn at around 8:00 AM, in which creatinine (Roche enzymatic assay), effective plasma osmolality ($2 \times$ (plasma sodium + plasma potassium) + plasma glucose), plasma and urine osmolality (freezing point depression), and copeptin were measured. Copeptin is a surrogate for AVP and was measured using a chemiluminescence immunoassay (CT-proAVP LIA; Thermo Fisher Scientific Inc) as described previously.[15] Free-water clearance was calculated as urine flow minus osmolar clearance. Osmolar clearance was calculated by the formula (urine osmolality $\times$ urine volume)/plasma osmolality. Fractional free-water clearance was calculated by dividing free-water clearance by GFR.

Kidney function measurements used the constant infusion method of ^{125}I-iothalamate and ^{131}I-hippuran.[16-18] After drawing a time-0 blood sample at about 8:00 AM, a priming solution containing