Short-term effects of tolvaptan on renal function and volume in patients with autosomal dominant polycystic kidney disease

Maria V. Irazabal[1], Vicente E. Torres[1], Marie C. Hogan[1], James Glockner[2], Bernard F. King[2], Troy G. Ofstie[1], Holly B. Krasa[3], John Ouyang[3] and Frank S. Czerwiec[3]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA and [3]Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, Maryland, USA

Tolvaptan and related V_2-specific vasopressin receptor antagonists have been shown to delay disease progression in animal models of polycystic kidney disease. Slight elevations in serum creatinine, rapidly reversible after drug cessation, have been found in clinical trials involving tolvaptan. Here, we sought to clarify the potential renal mechanisms to see whether the antagonist effects were dependent on underlying renal function in 20 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) before and after 1 week of daily split-dose treatment. Tolvaptan induced aquaresis (excretion of solute-free water) and a significant reduction in glomerular filtration rate (GFR). The serum uric acid increased because of a decreased uric acid clearance, and the serum potassium fell, but there was no significant change in renal blood flow as measured by para-aminohippurate clearance or magnetic resonance imaging (MRI). No correlation was found between baseline GFR, measured by iothalmate clearance, and percent change in GFR induced by tolvaptan. Blinded *post hoc* analysis of renal MRIs showed that tolvaptan significantly reduced total kidney volume by 3.1% and individual cyst volume by 1.6%. Preliminary analysis of this small cohort suggested that these effects were more noticeable in patients with preserved renal function and with larger cysts. No correlation was found between changes of total kidney volume and body weight or estimated body water. Thus, functional and structural effects of tolvaptan on patients with ADPKD are likely due to inhibition of V_2-driven adenosine cyclic 3′,5′-monophosphate generation and its aquaretic, hemodynamic, and anti-secretory actions.

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Correspondence: *Vicente E. Torres, Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota 55901, USA. E-mail: torres.vicente@mayo.edu*

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Tolvaptan is an orally effective, non-peptide arginine vasopressin (AVP) V_2 receptor antagonist currently approved in the United States and EU for the treatment of hyponatremia associated in euvolemic and hypervolemic states and SIADH, respectively, and in Japan for the treatment of cardiac edema resistant to diuretics. Tolvaptan is also being studied as an adjunct therapy for volume overload in patients with heart failure and as a primary therapy to delay progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Both tolvaptan and a related V_2-specific AVP receptor antagonist have been shown to delay disease progression in animal models of human polycystic kidney disease.[1–3] The mechanism of these effects is proposed to involve inhibition of the AVP V_2 receptor and the subsequent decrease in adenosine cyclic 3′,5′-monophosphate concentrations in the kidney. Elevated adenosine cyclic 3′,5′-monophosphate in the kidney is thought to promote cyst fluid accumulation and the epithelial cell growth, thereby displacing normal kidney and accelerating renal failure.[4,5]

Transient decreases in blood urea nitrogen and increases in serum creatinine and uric acid have been observed during tolvaptan's evaluation for indications involving patients with hyponatremia and heart failure.[6,7] In these studies, the incidence of adverse events related to acute or chronic renal failure have been similar, but consistently numerically lower in those treated with tolvaptan than with placebo. Similar changes have been seen in ADPKD patients who have been given twice-daily tolvaptan (to consistently inhibit AVP action at the kidney's AVP V_2 receptors) over the last 4 years in an open-label study.[8]

Because renal function is critically important to those diagnosed with ADPKD, we sought to clarify the possible mechanisms of these changes in serum creatinine by studying renal hemodynamics and function in ADPKD patients given daily, split-dose tolvaptan administration over 1 week. We also sought to determine whether the level of residual renal function impacts the effect of tolvaptan on glomerular filtration rate (GFR) and creatinine clearance. Analysis of renal structure, along with correlations to hemodynamics and function were added *post hoc*.

RESULTS

Baseline clinical and laboratory parameters and kidney volumes

The baseline (day 0) clinical and laboratory parameters are shown in Table 1. Baseline total kidney volume (TKV) was inversely correlated with baseline para-aminohippurate (PAH)-renal blood flow (RBF) (and, not shown, magnetic resonance (MR)-RBF) and GFR, and directly correlated with urine albumin excretion (Figure 1a–c). PAH- and MR-RBFs were highly correlated ($r = 0.958$, $P < 0.001$), but the ratio of PAH-RBF to MR-RBF was lower in the patients with a GFR < 60 ml/min per 1.73 m^2 possibly because the 90% renal extraction of PAH used to estimate RBF-PAH is too high when renal function is low (results not shown).

Short-term effects of tolvaptan on clinical and laboratory parameters and kidney volumes

As expected the administration of tolvaptan induced aquaresis, which was accompanied by reductions in body weight of 1.6% and increases in plasma sodium concentration of 1.1% (Table 1). Estimated total body water decreased by 1.1% (not shown). No significant changes were observed in blood pressure, hematocrit or serum protein, and albumin concentrations (Table 1).

Serum creatinine, cystatin C, and uric acid increased by 8.9, 8.9, and 13.0% (Table 1), respectively. The percent increase in serum uric acid was numerically greater than creatinine or cystatin C but not significantly so ($P = 0.16$ and 0.30). Serum blood urea nitrogen and plasma renin activity and aldosterone did not change significantly (not shown).

The administration of tolvaptan increased urine flow and free water clearance, and induced an 8.6% reduction in GFR, without a consistent or significant change in RBF-PAH or RBF-magnetic resonance imaging (MRI; Table 1). There was no correlation between percent changes in GFR and GFR values at baseline ($P = 0.398$). Consistent with its effect on GFR, tolvaptan significantly reduced the osmolar and uric acid clearances, but only the reduction in uric acid clearance remained significant when these clearances were adjusted for the reduction in GFR (Table 1). Moreover, the percent reduction in uric acid clearance was significantly larger than the reduction in GFR, indicating that a change in the rates of uric acid reabsorption and/or secretion contributes to the reduction in uric acid clearance in addition to the reduction in GFR.

Changes in TKV were not an initial focus for this study, as it had been believed that it would take months to detect the effects due to inhibition of cell proliferation or fluid secretion. Unexpectedly, however, a *post hoc*-blinded analysis of the renal MRI obtained for measurement of renal blood flow and to document disease progression showed a 3.1% reduction in TKV from baseline after 1 week of tolvaptan therapy ($P < 0.001$; Table 1, Figure 2). The percent change in right and left kidney volumes were significantly correlated

Table 1 | Short-term effects of tolvaptan on clinical and laboratory parameters and on TKVs

	All study participants			
	Pre	Post	%△	*P*-value
Age (years)	47.8 ± 8.7			
Weight (kg)	84.0 ± 22.0	82.7 ± 21.7	−1.6 ± 1.3	**<0.001**
MAP (mm Hg)	92.0 ± 10.1	90.0 ± 10.8	−1.7 ± 10.1	0.390
RKV (ml)	1236 ± 1538	1211 ± 1533	−4.0 ± 4.1	**<0.001**
LKV (ml)	1081 ± 1211	1064 ± 1201	−2.5 ± 2.9	**0.003**
TKV (ml)	2316 ± 2715	2274 ± 2700	−3.1 ± 3.0	**<0.001**
Hb (g/dl)	13.0 ± 1.1	13.0 ± 1.0	0.1 ± 5.4	0.925
Protein (g/dl)	7.0 ± 0.6	7.1 ± 0.4	2.8 ± 7.8	0.153
Albumin (mg/l)	4.4 ± 0.2	4.4 ± 0.3	0.9 ± 4.1	0.323
GFR (ml/min per 1.73 m^2)	69.3 ± 34.8	62.4 ± 28.7	−8.6 ± 13.9	**0.018**
PAH (ml/min per 1.73 m^2)	345.7 ± 184.4	320.5 ± 156.7	−5.7 ± 13.1	0.071
RBF-PAH (ml/min per 1.73 m^2)	619 ± 338	570 ± 286	−5.9 ± 15.6	0.109
RBF-MRI (ml/min per 1.73 m^2)	536 ± 266	514 ± 221	1.0 ± 18.9	0.459
SCr (mg/dl)	1.4 ± 0.8	1.5 ± 0.8	8.9 ± 10.5	**0.004**
Cystatin C (mg/l)	1.2 ± 0.6	1.3 ± 0.6	8.9 ± 10.4	**0.011**
BUN (mg/dl)	21.7 ± 10.7	21.1 ± 10.0	−1.3 ± 16.4	0.564
Uric acid (mg/dl)	5.6 ± 2.1	6.2 ± 2.2	13.0 ± 14.1	**0.002**
Sodium (mmol/l)	137.9 ± 2.3	139.5 ± 2.7	1.1 ± 1.2	**<0.001**
Potassium (mmol/l)	4.6 ± 0.5	4.4 ± 0.6	−4.8 ± 5.5	**0.001**
Urine flow (ml/min)	7.3 ± 3.2	8.5 ± 3.1	23.8 ± 43.9	**0.012**
CH_2O (ml/min)	4.1 ± 2.7	6.0 ± 2.8	91.7 ± 160.7	**<0.001**
(CH_2O/GFR) × 100	5.6 ± 2.7	9.1 ± 2.2	107 ± 131	**<0.001**
Cosm (ml/min)	3.3 ± 0.8	2.7 ± 0.8	−16.0 ± 16.9	**0.001**
(Cosm/GFR) × 100	5.1 ± 2.2	4.8 ± 2.2	−6.6 ± 16.7	0.121
Curi (ml/min)	9.6 ± 4.9	6.8 ± 3.0	−26.8 ± 14.8	**<0.001**
(Curi/GFR) × 100	12.8 ± 3.6	10.6 ± 4.5	−18.7 ± 17.2	**<0.001**

Abbreviations: BUN, blood urea nitrogen; CH_2O, free water clearance; Cosm, osmolar clearance; Curi, uric acid clearance; GFR, glomerular filtration rate determined by iothalamate clearance; Hb, serum hemoglobin; LKV, left kidney volume; MAP, mean arterial pressure; PAH, para-aminohippurate clearance; RKV, right kidney volume; RBF-PAH, renal blood flow determined by para-aminohippurate clearance; RBF-MRI, renal blood flow determined by magnetic resonance imaging; SCr, serum creatinine; TKV, total kidney volume.
Bold denotes statistical significance.