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Pharmacokinetics and pharmacodynamics of oral tolvaptan in patients with varying degrees of renal function

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The selective vasopressin V2–receptor antagonist tolvaptan is eliminated almost exclusively by non-renal mechanisms. As renal impairment can influence the pharmacokinetics of drugs even when eliminated by non-renal mechanisms, we evaluated the effect of renal insufficiency on the pharmacokinetics/pharmacodynamics of tolvaptan. Thirty-seven patients were grouped by a 24-h creatinine clearance (CrCL) and evaluated for 48 h after a single 60 mg oral dose in the fasting state. Mean tolvaptan exposure was 90% higher in the under 30-ml/min group compared with the over 60-ml/min group with individual values significantly but negatively correlated with increasing baseline CrCL. There was a greater and more rapid increase in urine output and free water clearance in the over 60-ml/min compared with the renal impaired groups, but they returned to baseline more quickly. Serum sodium increased more rapidly in the over 60 as opposed to the under 30-ml/min group, but overall maximum increases were similar across groups. Small decreases in mean CrCL and small increases in mean serum creatinine/potassium were independent of baseline CrCL. The percent fractional free water clearance with respect to CrCL was significantly but negatively correlated with increasing baseline CrCL. No unexpected adverse events were reported. Thus, renal impairment attenuated the increase in 24-h urine volume and free water clearance caused by tolvaptan, consistent with decreased nephron function in renal impairment. The delay in serum sodium increase was consistent with the longer duration needed to excrete sufficient water to cause the increase.

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Tolvaptan is an orally active vasopressin V2–receptor antagonist, which is approved for treatment of specific forms of hyponatremia in the United States and Europe.[1–3] The recommended starting dose for hyponatremia is 15 mg once daily, which can be titrated to a maximum of 60 mg once daily, as needed, to raise serum sodium.[4] Tolvaptan is also used in clinical testing in subjects with autosomal dominant polycystic kidney disease.[5–8]

The pharmacokinetics and pharmacodynamics of tolvaptan have been evaluated in multiple trials in healthy subjects. Dose-proportional increases in exposure to tolvaptan, as measured by area under the curve to infinity (AUC_{∞}) and maximum plasma concentration (C_{max}), were observed for doses of 15–60 mg.[9–11] After oral administration, tolvaptan produced aquaresis characterized by increases in urine volume and free water clearance (FWC), and consequent increases in serum osmolality and serum sodium within the 24-h period after dosing.[10] These effects were not accompanied by significant changes in serum potassium, creatinine clearance (CrCL), or urine electrolyte excretion. A recently published trial showed that the pharmacokinetics and pharmacodynamics of tolvaptan 30 mg were not clinically significantly affected by race or by administration with food.[12]

Tolvaptan is eliminated almost exclusively by non-renal routes, with $<1\%$ of the administered dose excreted unchanged in urine.[10] Renal impairment can, however, influence the pharmacokinetics of drugs predominantly eliminated by non-renal mechanisms through effects on drug metabolism enzymes and the activities of drug transporters.[13] Therefore, the present trial investigated whether renal impairment influences the pharmacokinetics and pharmacodynamics of tolvaptan following administration of a single 60-mg oral dose.

RESULTS

Subject disposition and characteristics

Thirty-seven subjects were enrolled and given a single 60-mg dose of tolvaptan, including 12 subjects with CrCL <30 ml/min, 12 subjects with CrCL of 30–60 ml/min, and 13 subjects with CrCL >60 ml/min. All subjects completed the

trial as planned. The demographics of the CrCL <30- and >60-ml/min groups were well balanced, consistent with the protocol-specified matching of these groups by age, weight, and sex (Table 1). In comparison, the CrCL 30- to 60-ml/min group had a higher mean age, fewer women, and more Hispanic/Latino subjects than the other groups. The mean CrCL values in the CrCL <30-, 30- to 60-, and >60-ml/min groups were 20.6, 49.6, and 95.8 ml/min, respectively. As expected, higher mean cystatin C concentrations were seen in subjects with greater degrees of renal impairment. One subject in the CrCL >60-ml/min group had diabetes and was taking daily medication in violation of the eligibility criteria. This subject was excluded from the pharmacokinetic and pharmacodynamic analyses but was included in the safety analysis.

Pharmacokinetics

Tolvaptan plasma concentrations reached maximal levels by 2–3 h after dosing and then decreased in an exponential manner (Figure 1). Subjects with renal impairment (CrCL <30 and 30–60 ml/min) had slightly higher plasma concentrations than those with preserved renal function (CrCL >60 ml/min) throughout most of the 48-h evaluation period. When measured by AUC_{∞}, exposure to tolvaptan, on average, was 90% higher in the CrCL <30-ml/min group and 83% higher in the CrCL 30- to 60-ml/min group than in the CrCL >60-ml/min group (Table 2). Mean C_{max} values were somewhat higher and mean values for clearance (CL/F) were lower in the groups with renal impairment than in the preserved renal function group. Individual AUC_{∞} values were negatively correlated with increasing baseline CrCL ($r^2 = 0.132$; $P = 0.028$) (Figure 2). Individual C_{max} values showed a trend for being negatively correlated with baseline CrCL ($P = 0.087$), whereas CL/F showed a trend for being positively correlated with baseline CrCL ($P = 0.059$). Neither terminal-phase elimination half-life nor percent fraction of unbound drug (%f_u) was correlated with baseline CrCL.

Pharmacodynamics

The onset of tolvaptan action was rapid as FWC was increased in all subjects in the 0- to 4-h urine collection period. The CrCL >60-ml/min group had larger and more rapid increases in urine excretion rate and FWC after tolvaptan administration, and these parameters returned to baseline more quickly (ie, within 24 h) than in the groups with renal impairment (Figure 3).

Table 1 | Demographic and clinical characteristics

Parameter[a]	CrCL <30 ml/min ($n = 12$)	CrCL 30–60 ml/min ($n = 12$)	CrCL >60 ml/min ($n = 13$)
Age (year)	58.3 (11.2)	70.0 (8.2)	58.8 (11.4)
Sex (n (%))			
Male	7 (58.3)	10 (83.3)	8 (61.5)
Female	5 (41.7)	2 (16.7)	5 (38.5)
Race (n (%))			
White	10 (83.3)	11 (91.7)	13 (100)
Black	2 (16.7)	1 (8.3)	0 (0)
Ethnicity (n (%))			
Hispanic/Latino	5 (41.7)	10 (83.3)	5 (38.5)
Non-Hispanic/Latino	7 (58.3)	2 (16.7)	8 (61.5)
Weight (kg)	76.5 (15.1)	71.9 (11.5)	76.3 (11.5)
Height (cm)	170.3 (7.7)	165.5 (8.5)	173.2 (9.9)
BMI (kg/m^2)	26.4 (5.3)	26.1 (2.5)	25.4 (3.3)
CrCL (ml/min)	20.6 (6.4)	49.6 (7.3)	95.8 (17.5)
Serum sodium (mmol/l)	138.8 (3.2)	140.3 (2.5)	140.5 (1.4)
Serum osmolality (mOsm/kg)	315.1 (11.4)	297.7 (8.6)	292.6 (3.6)
Serum creatinine (mg/dl)	3.5 (1.0)	1.5 (0.3)	0.9 (0.2)
Cystatin C (mg/l)	3.4 (0.7)	1.3 (0.3)	0.9 (0.3)

Abbreviations: BMI, body mass index; CrCL, creatinine clearance.
[a]All values presented as mean (±s.d.), unless otherwise specified.

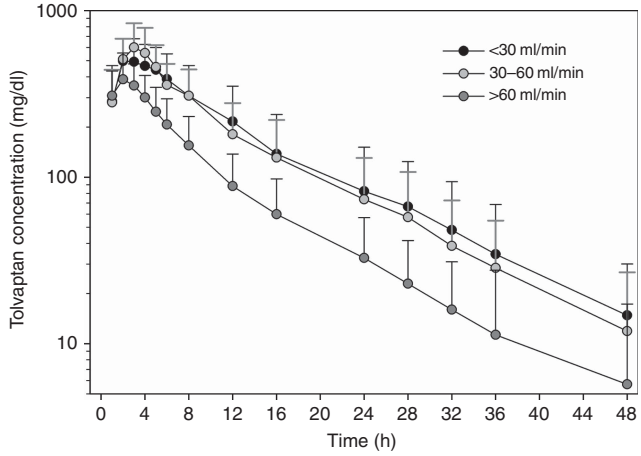

Figure 1 | Mean (±s.d.) tolvaptan plasma concentration–time profiles by creatinine clearance.

Table 2 | Pharmacokinetic parameters for tolvaptan by CrCL group

Parameter[a]	CrCL <30 ml/min ($N = 12$)	CrCL 30–60 ml/min ($N = 12$)	CrCL >60 ml/min ($N = 12$)
Total tolvaptan			
C_{max} (ng/ml)	535 (183)	621 (241)	417 (150)
t_{max} (h)	3.5 (2.0–6.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)
AUC_t (ng h/ml)	6690 (3550)	6470 (3090)	3530 (1570)
$t_{1/2,z}$ (h)[b]	9.1 (2.8)	9.2 (3.3)	10.1 (8.3)
AUC_{∞} (ng h/ml)[b]	7360 (3580)	6980 (3360)	3890 (1910)
CL/F (ml/min/kg)[b]	2.65 (2.40)	2.37 (0.80)	4.55 (2.58)
Unbound tolvaptan			
f_u (%)	1.2 (0.8)	0.6 (0.1)	1.0 (0.3)
$C_{max,u}$ (ng/ml)	5.89 (2.74)	3.35 (0.85)	4.29 (1.92)
$AUC_{\infty,u}$ (ng h/ml)[b]	71.8 (37.4)	36.4 (11.9)	37.5 (21.2)
CL/F_u (ml/min/kg)[b]	0.034 (0.038)	0.014 (0.006)	0.049 (0.036)

Abbreviations: AUC_t, area under the curve from time zero to the last sampling time; AUC_{∞}, AUC to infinity; CL/F, clearance; C_{max}, maximum plasma concentration; CrCL, creatinine clearance; f_u, fraction of unbound drug; t_{max}, time to C_{max}; $t_{1/2,z}$, terminal half-life; u, unbound.
[a]All values are mean (±s.d.), except for t_{max}, which is shown as median (range).
[b]$n = 11$ per group.