Short-Term Tolvaptan Increases Water Intake and Effectively Decreases Urinary Calcium Oxalate, Calcium Phosphate and Uric Acid Supersaturations

Wisit Cheungpasitporn, Stephen B. Erickson, Andrew D. Rule, Felicity Enders and John C. Lieske*,†

From the Division of Nephrology and Hypertension (WC, SBE, ADR, JCL), Department of Health Sciences Research (ADR, FE), and Department of Laboratory Medicine and Pathology (JCL), Mayo Clinic, Rochester, Minnesota

Abbreviations and Acronyms

ADPKD = autosomal dominant polycystic kidney disease
AVP = arginine vasopressin
CaOx = calcium oxalate
CaP = calcium phosphate
SS = supersaturation
UA = uric acid

Accepted for publication November 10, 2015.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Mayo Clinic O'Brien Urology Research Center (U54 DK100227), National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Advancing Translational Sciences and Rare Kidney Stone Consortium (U54KD083908), a member of the National Institutes of Health Rare Diseases Clinical Research Network, and Otsuka Pharmaceuticals, Inc.

* Correspondence: Division of Nephrology and Hypertension, Mayo Clinic, 200 First St. SW, Rochester, Minnesota 55905 (telephone: 507-266-7960; FAX: 507-266-7891; e-mail: lieske.john@mayo.edu).

† Financial interest and/or other relationship with Otsuka America Pharmaceutical, Inc.

Purpose: Some patients cannot effectively increase water intake and urine volume to prevent urinary stones. Tolvaptan, a V2 receptor antagonist, blocks water reabsorption in the collecting duct and should decrease urinary supersaturation of stone forming solutes, although this action has never been proved.

Materials and Methods: We conducted a double-blind, randomized, placebo controlled, crossover study of 21 calcium urinary stone formers stratified into majority calcium oxalate (10 patients) and calcium phosphate (11) groups. Patients received 45 mg tolvaptan per day or placebo for 1 week, followed by a washout week and crossover to tolvaptan or placebo for week 3. A 24-hour urine sample was collected at the end of weeks 1 and 3.

Results: Tolvaptan vs placebo decreased urinary osmolality (mean ± SD 204 ± 96 vs 529 ± 213 mOsm/kg, $p < 0.001$) and increased urinary volume (4.8 ± 2.9 vs 1.8 ± 0.9 L, $p < 0.001$). The majority of urinary solute excretion rates, including sodium and calcium, did not change significantly, although oxalate secretion increased slightly (from mean ± SD 15 ± 8 to 23 ± 8 mg per 24 hours, $p = 0.009$). Mean ± SD urinary calcium oxalate supersaturation (−0.01 ± 1.14 vs 0.95 ± 0.87 dG, $p < 0.001$), calcium phosphate supersaturation (−1.66 ± 1.17 vs −0.13 ± 1.02 dG, $p < 0.001$) and uric acid supersaturation (−2.05 ± 4.05 vs −5.24 ± 3.12 dG, $p = 0.04$) all dramatically decreased. Effects did not differ between the calcium oxalate and calcium phosphate groups ($p > 0.05$ for all interactions).

Conclusions: Tolvaptan increases urine volume and decreases urinary supersaturation in calcium stone formers. Further study is needed to determine if long-term use of V2 receptor antagonists results in fewer stone events.

Key Words: kidney calculi, osmolar concentration, vasopressins, water-electrolyte balance

URINARY stone disease is a common metabolic disorder, with a prevalence of 7.2% to 7.7% in the adult population, and a 10-year recurrence rate of 30% or greater.[1,2] The costs to treat patients with urinary stone disease exceed $10.3 billion yearly.[3] Evidence suggests that the incidence of urinary stone disease is increasing in industrialized countries, with a current estimated global prevalence of 10% to 15%.[4] The precise biological pathways to calcium stone formation are many.[5] However, a common

0022-5347/16/1955-1476/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.11.027
Vol. 195, 1476-1481, May 2016
Printed in U.S.A.

underlying feature is often increased urinary supersaturation for calcium oxalate, calcium phosphate and/or uric acid.[6]

Increasing urinary volume is a useful measure to decrease kidney stone risk since it dilutes the components that drive urinary SS. Indeed, a recent meta-analysis confirmed that increasing urinary volume by drinking more fluid reduced the risk of incident and recurrent events.[7] Nevertheless, not all patients can effectively increase fluid intake despite consistent counseling.

Tolvaptan, an orally administered AVP V2 receptor antagonist, causes dose related polyuria.[8] Thus, urinary free water losses increase, which, in turn, leads to a slight increase in serum osmolality, and stimulates thirst and increased water intake to replace that lost in the urine. Therefore, tolvaptan could potentially induce patients with urinary stones to drink more fluid. However, the effect of tolvaptan on urinary excretion of calcium, oxalate and other determinants of urinary SS is untested. We evaluated the net result of short-term tolvaptan administration on overall urinary SS and the excretion of key components of calcium based stones.

MATERIALS AND METHODS

This randomized, double-blind, placebo controlled, crossover study was conducted at our stone clinic between September 2013 and January 2015. The study received institutional review board approval (https://clinicaltrials.gov/ct2/show/results/NCT02096965).

Study Population

We enrolled 21 patients 18 years or older who were idiopathic calcium kidney stone formers. Patients were stratified to achieve near equal numbers of majority CaOx and CaP. Patients with chronic kidney disease (estimated glomerular filtration rate less than 60 ml/minute/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation) were excluded, as were those with a history of hyponatremia or hypernatremia, hypotension or orthostatic dizziness, or congestive heart failure, and women who were pregnant. Stones were confirmed by computerized tomography and analysis by infrared spectroscopy at our metals laboratory.

Tolvaptan Regimen and Dosage

After informed written consent was obtained subjects received tolvaptan or placebo in a randomized fashion. A daily dose of 45 mg (30 mg at 8:00 a.m. and 15 mg at 4:00 p.m.) was chosen since this dose had adequate tolerability (96% of patients are willing to adhere to this regimen for the rest of their lives) and efficacy (60% of patients maintain persistently hypotonic urine for 24 hours) in a phase II ADPKD trial (156-04-250),[9] and this dose could be safely initiated in outpatients.[10] This varied dose is designed to produce maximal AVP inhibition on waking with a gradual falloff of effect overnight to allow better sleep.

Patients were maintained at each phase for 1 week to allow for a new steady state (fig. 1).[11] All patients completed a baseline 24-hour urine collection, received drug or placebo for 1 week and then completed another urine collection. Following a washout week, a third week of drug or placebo (whichever was not received initially) and a final urine collection followed. The order of drug and placebo was randomized. Serum electrolytes were monitored at each stage of the study. All patients were instructed to drink to thirst and maintain their usual diet. No medications were altered, including those already taken for urinary stone disease.

Outcomes

The primary outcome was urinary CaOx and CaP supersaturation on drug vs placebo. Secondary outcomes included urinary UA SS; volume and osmolality; urinary excretions of calcium, oxalate, citrate, uric acid and phosphate; urinary pH; and serum sodium.

The 24-hour urinary concentrations of oxalate, calcium and other determinants of SS were measured at our renal testing laboratory, and serum electrolytes were measured at our central clinical chemistry laboratory. SS was calculated using EQUIL® 2.0.[12]

Statistical Analysis

Continuous variables are reported as means with standard deviations or medians with interquartile ranges, as appropriate. All categorical variables are reported as counts with percentages. In the event of missing information, data were not imputed. A Wilcoxon matched pairs signed-rank test was used to compare the end point changes while on drug vs placebo. Linear regression was used to test for the potential effect of the baseline level and a treatment order effect. The primary end point analysis was performed for the entire group to maximize power. Interactions between treatment group and stone type (CaOx vs CaP) on urinary SS profiles were assessed by adding interaction terms to the linear regression models. A 2-sided p value of less than 0.10 was considered statistically significant for the carryover effect test since this test has low power. Otherwise, a 2-sided p value of less than 0.05 was considered statistically significant. All analyses were performed using JMP®, version 9.0. A sample of 20 patients provided 80% power to detect a 50% change in urinary phosphate and urinary oxalate.[13]

	Week 1	Week 2	Week 3
Baseline	Drug or placebo	Washout	Drug or placebo
24 hr urine *	*		*
Diet Diary *	*		*
Serum electrolytes *	*		*
Creatinine *	*		*

Figure 1. Study design. Subjects collected 2 baseline 24-hour urine samples, were randomized to placebo or tolvaptan for 1 week, then completed 2 more 24-hour urine collections. After washout week subjects crossed over from tolvaptan or placebo, then completed 2 final 24-hour urine collections.