COMPARISON OF THE RELATIVE ORAL BIOAVAILABILITY OF TOLVAPTAN ADMINISTERED VIA NASOGASTRIC TUBE TO TOLVAPTAN TABLETS SWALLOWED INTACT

Elizabeth B. McNeely, PharmD, Kirkwood F. Adams, Jr., MD, Jasmine Talameh, PharmD, J. Heyward Hull, PharmD, MS, Brian Simmons, PharmD, Jill Henry, PharmD, Kim L. R. Brouwer, PharmD, PhD, J. Herbert Patterson, PharmD, FCCP
University of North Carolina, Eshelman School of Pharmacy and School of Medicine, Chapel Hill, NC

UNC ESHELMAN SCHOOL OF PHARMACY

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INTRODUCTION

Tolvaptan (Samsca®, Otsuka America Pharmaceuticals) is an orally active nonpeptide arginine vasopressin (AVP) V2 receptor antagonist approved for the treatment of hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. Tolvaptan is administered orally as 15 mg or 30 mg tablets. The estimated bioavailability of tolvaptan after oral administration in humans is ~40%. After absorption, tolvaptan is 99% bound to circulating plasma proteins and is hepatically eliminated by CYP 3A4. Since tolvaptan is only available orally, administration to patients who may not be able to swallow a tablet is challenging. Being able to administer the crushed tablet via a nasogastric (NG) tube is clinically important, but the relative bioavailability of tolvaptan administered in this manner is unknown.

PURPOSE

To compare the relative bioavailability and pharmacokinetics of tolvaptan administered as a 15 mg tablet orally versus NG tube administration of a 15 mg crushed tablet in healthy adults.

METHODS

- Study was an open, 2-treatment, 2-period, 2-sequence crossover design.
- Inclusion: healthy, adult men and women 18 to 40 years old; body mass index <30 kg/m^2; with no clinically significant findings on screening evaluation.
- Exclusion: serum Na^+ <135 mEq/L; pregnant or breastfeeding; intestinal or gastrointestinal disorders; use of CYP3A4 inhibitors or inducers; or clinically significant laboratory abnormalities.
- 15 mg dose tablet of tolvaptan swallowed intact and 15 mg crushed tablet administered by NG tube with a minimum of a 7-day washout period between doses.
- Randomization of sequences was balanced for gender and blocked (4) for subject enrollment.
- For tolvaptan administered via NG tube:
  - Tablet was crushed in a standardized pill crusher (Silent Knight®)
  - Crushed tablet was mixed with 60 mL of water and solution administered into the NG tube with 60 mL syringe
  - Dosing cup was repeatedly rinsed with water to 240 mL and flushed through NG tube
- Tolvaptan was administered with 240 mL of water during oral administration.
- Blood was collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30 and 36 hours after the dose of study drug for both administrations.
- Tolvaptan concentrations were determined by validated LC-MS/MS assay by ICON plc.
- Noncompartmental pharmacokinetic analysis and summary statistics [Phoenix-WinNonlin, v. 6.0].
- Relative tolvaptan absorption by the two routes was compared using a repeated-measures, mixed-effects ANOVA. Cmax and AUC data were $\log_e$ transformed prior to analysis.

RESULTS

Demographics. Of 29 subjects enrolled, 28 subjects completed both periods and were included in the analysis (1 subject removed from study due to vasovagal reaction from NG tube placement): 15 males and 13 females; 20 whites, 7 blacks, and 1 asian. Median age was 27 years old (range, 18-40 years.) Median BMI was 23.5 kg/m^2 (range, 19-29 kg/m^2). All dosing was confirmed by direct observation.

Pharmacokinetic Summary. Geometric mean values of tolvaptan pharmacokinetic parameters following NG tube and oral administration are presented in Table 1. The primary statistical results for the C_{max}, AUC_t, and AUC_∞ of tolvaptan after NG tube and oral administration are summarized in Table 2. Compared to the oral tablet, C_{max}, AUC_t, and AUC_∞ % ratios after NG tube administration were 88.9%, 74.3%, and 74.2%, respectively. The 90% confidence intervals for AUC_t and AUC_∞ were outside of the 80-to-125% standard bioequivalence range.

TABLE 1. Tolvaptan pharmacokinetic parameters.

Parameter	Geometric Mean Values			
	NG	$CI_{90\%}$	ORAL	$CI_{90\%}$
C_{max} (ng/mL)	77.6	69.5, 86.6	87.3	75.3, 101
T_{max} (h)	1.5 [a]	0.5, 4.0 [b]	2.0 [a]	1.0, 6.0 [b]
AUC_t (ng*h/mL)	381	335, 432	512	444, 592
AUC_∞ (ng*h/mL)	391	344, 443	527	456, 607
$T_{1/2}$ (h)	4.41 [c]	3.84, 4.98	5.39 [c]	4.64, 6.13

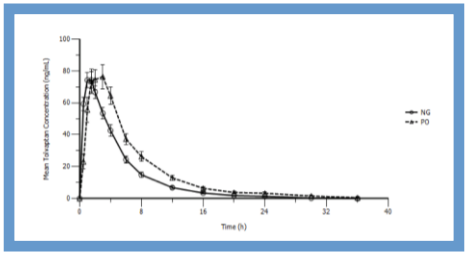
[a] Median [b] Range [c] Arithmetic Mean

Table 2. Primary statistical analysis: tolvaptan relative oral bioavailability.

Parameter	Estimated Ratio (%) of Geometric Means [a]	$CI_{90\%}$
C_{max} (ng/mL)	88.9	80.1 – 98.6
AUC_t (ng*h/mL)	74.3	68.1 – 81.0
AUC_∞ (ng*h/mL)	74.2	68.1 – 80.9

[a] Tablets swallowed intact (reference)

Figure 1. Mean (±SEM) plasma concentration-time profiles of tolvaptan.



While the trial was not designed to evaluate the pharmacodynamic properties of tolvaptan, there appeared to be similar aquaresis with each route of administration (2.8% decrease in 24-hour urine output after NG tube administration (6659 mL) compared to oral administration (7042 mL)).

SAFETY

- A total of 7 study related adverse events (AEs) were reported in 6 subjects, 4 in the NG tube administration phase and 2 in the oral administration phase.
- Of the 7 AEs, 3 occurred prior to study drug administration.
- The remaining 4 treatment emergent AEs were:
  - NG – dental pain, epistaxis, pharyngitis
  - Oral – dehydration (post ironman triathlon)
- All AEs were considered mild to moderate and none were considered related to study drug.

CONCLUSIONS

- After dedicated NG tube administration of a 15-mg crushed tablet, the 90% confidence intervals for AUCs were not within 80-125%, therefore bioequivalence to an oral tablet cannot be concluded.
- Nevertheless, with appropriate clinical monitoring, NG tube administration appears to be a viable approach to administer tolvaptan as a crushed tablet to patients who are unable to swallow a tablet.
- Further studies are underway to determine the basis for reduced tolvaptan bioavailability when administered as a crushed tablet by NG tube.

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