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Pharmacokinetic/Pharmacodynamic (PK/PD) Model for Tolvaptan in Healthy Subjects

S.A. Van Wart,[1] B.B. Cirincione,[1] E.A. Ludwig,[1] T.H. Grasela,[1] X. Chen,[2] S. Shoaf,[2] S. Mallikaarjun[2]

[1]Cognigen Corporation, Buffalo, NY and [2]Otsuka Maryland Research Institute (OMRI), Rockville, MD

ABSTRACT

AIM. Direct effect, indirect effect, and competitive antagonism models were evaluated to describe plasma tolvaptan concentration effect on urine flow rate (UFR), with consideration of water intake rate (WIR) and concurrent diuretic use. Tolvaptan is a vasopressin (V_2) receptor antagonist under development for congestive heart failure (CHF) and hyponatremia (HYP).

Methods. Data (1956 timed urine collections from 101 subjects) were pooled from 3 Phase 1 studies in healthy adults given single oral doses of placebo or tolvaptan (30 to 480 mg). Serial blood samples were collected to determine tolvaptan and vasopressin concentrations in plasma. Urine output and water intake were recorded for 2 days prior to, and for up to 3 days after the tolvaptan dose. WIR was calculated using a 1 hour delay for the urine output lag after water consumption. Previous models were used for tolvaptan PK and the non-constant baseline UFR.

Results. A direct effect model, with UFR estimated as a linear function of plasma tolvaptan concentration (slope = 0.941 mL/hr per ng/mL) best described the data. E_0 was estimated as a linear function of WIR (intercept = 52.6 mL/hr, slope = 0.42), with shifts for concurrent use of loop (483 mL/hr) or thiazide diuretics (88.4 mL/hr), for each urine collection. Urine volumes predicted by the model during each interval were generally unbiased (median PE% = –1.27%) and reasonably precise (median |PE|% = 30%).

Conclusions. This PK/PD model demonstrates the effect of tolvaptan concentrations on UFR in healthy subjects, and provides a basis for estimating net fluid loss in Phase 2 patients with CHF and HYP.

INTRODUCTION

- Tolvaptan (OPC-41061) is an orally administered, selective V_2-receptor antagonist clinically shown to increase urinary output.
- Tolvaptan is currently under development as an adjunct to diuretic therapy in the treatment of volume overload in patients with CHF, and for the treatment of hyponatremia (HYP).
- AVP antagonism by tolvaptan appears to produce effective and sustained reductions in congestion without the potential for potassium depletion, hypotension, or worsening renal function.

OBJECTIVES

The main objectives of this work were to:

1. identify a population PK/PD model (direct effect, competitive antagonism, or indirect effect model) that best characterizes the relationship between plasma tolvaptan concentrations (C_{TLV}) and urine flow rate (UFR) using timed urine collections from healthy subjects, and thus serve as the basis for future estimation of this relationship in Phase 2 patients with CHF and/or HYP; and
2. quantitate the influence of other factors on UFR, such as concurrent diuretic use and daily variations in water intake, so that the model is more reflective of net fluid loss due to tolvaptan.

METHODS

Data

- Data were pooled from three Phase 1 studies conducted by OMRI (**TABLE 1**).

Tolvaptan Pharmacokinetics

- Serial blood samples were collected to determine tolvaptan concentrations in plasma using HPLC with either ultraviolet (Study 1) or mass spectrometric detection (Studies 2 and 3).
- A population PK model in healthy subjects (2-compartment (CMT) model with first-order absorption and elimination as shown in **FIGURE 1A**) was previously developed by OMRI.
- The mean of the individual predicted plasma tolvaptan concentration-time profiles for each dose group at each of the scheduled sampling times is shown in **FIGURE 2**.

TABLE 1. Study Designs, Tolvaptan Doses Administered, and Urine Collection Intervals

Study	Design	Dosing Regimen	Urine Collection Intervals
1 (n=12)	Single center, randomized, open-label, parallel-arm, three-way cross-over study to assess potential PK and PD interactions between oral tolvaptan and furosemide or HCTZ	Arm 1: (A) 30 mg tolvaptan (B) 80 mg furosemide (C) 80 mg furosemide + 30 mg tolvaptan Arm 2: (A) 30 mg tolvaptan (B) 100 mg HCTZ (C) 30 mg tolvaptan + 100 mg HCTZ	Days –1 and 1 of each period: 0-1,1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-12 & 12-24 hr
2 (n=48)	Open-label, single and multiple-dose study of the safety, PK and PD of oral tolvaptan	Day 1: 60 mg Days 4-10: 60 mg QD	Days –1, 2 and 3: Pooled 24-hr Day 1: 0-4, 4-8, 8-12 & 12-24 hr
3 (n=56)	Single center, placebo-controlled, double-blind, crossover, randomized ascending single dose study of oral tolvaptan	Days 1[a] and 8: Placebo or 60, 90, 120, 180, or 240 mg tolvaptan	Days –1, 2 and 3: 0-2, 2-4, 4-6, 6-8, 8-12, & 12-24 hr Day 4: Pooled 24-hr

[a]Fluid replacement was implemented on Day 1; this data was excluded from all analyses.

- Bayesian estimates of the absorption rate constant (k_a), apparent oral clearance (CL), central and peripheral volumes of distribution (V_2 and V_3, respectively), and transfer rates from the central to peripheral CMT (k_{23}) and from the peripheral to the central CMT (k_{32}) were obtained for each subject and included in each PD/PD analysis dataset.

Plasma AVP Concentrations

- Serial blood samples were collected to determine AVP concentrations in plasma using a radio-immunoassay (RIA).
- Plasma AVP concentrations tended to increase from baseline in a dose-related manner during tolvaptan therapy, and were considered as a time-varying covariate for up to 12 hr post-dose.
- AVP levels measured prior to dosing were retained for all records on Day –1; AVP levels reported as zero were assigned a value of one-half the LOQ (0.25 pg/mL).

Urine Output and Fluid Intake Recordings

- Urine output and fluid intake (mL) were recorded on the day prior to and for up to 3 days during therapy; fluid intake was restricted only around the time of dosing.
- The start and stop times for each epoch were used to calculate the interval duration (hr) and to reset the predicted urine volume for the start of the next interval.
- Water intake was delayed by 1 hr in each epoch to account for a lag in urine output due to water that may have been consumed toward the end of an interval.
- A linear relationship was observed between the baseline UFR and the 60-min adjusted WIR, as shown in **FIGURE 3** for a subject given placebo.

FIGURE 2: Mean of the individual predicted plasma tolvaptan concentrations at each PK sampling time

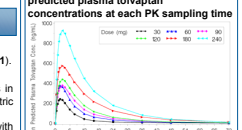
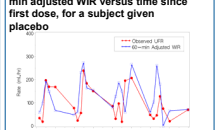


FIGURE 3: Observed UFR and 60-min adjusted WIR versus time since first dose, for a subject given placebo



Concurrent Diuretic Use

- UFR appeared to increase in subjects given either 80 mg furosemide or 100 mg hydrochlorothiazide (HCTZ), therefore two indicator variables were created for this analysis to test for the effect of these medications:
- FURO=1 for urine collected ≤ 4 hr after a furosemide dose and 0 otherwise, and
- HCTZ=1 for urine collected ≤ 8 hr after a HCTZ dose and 0 otherwise.

Statistical Methods

- Population PK/PD analyses were performed using NONMEM®, Version 5 Level 1.1 (FOCE method with interaction).
- Model discrimination criteria included graphical examination of goodness-of fit (GOF), the precision of the parameter estimates (%SEM), reductions in IIV and RV, and comparison of Akaike Information Criteria (AIC).
- Differences between observed and individual predicted urine volumes were also calculated as a percentage of the observed urine volumes (PE%), and summary statistics of both PE% and |PE|% were generated to assess the bias and precision.

PD Analysis

Direct Effect Model

- An E_{max} model was initially evaluated (**FIGURE 1B**) where:
  - E_0 = additive baseline effect in the absence of tolvaptan;
  - E_{max} = maximal increase in UFR from E_0 due to tolvaptan; and
  - EC_{50} = plasma tolvaptan concentration producing half-maximal effect.
- E_0 was evaluated as a linear function of WIR during each time interval, with an additive shift for concurrent furosemide or HCTZ use.

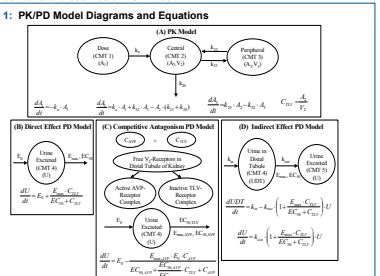
Competitive Antagonism Model

- A competitive antagonism inhibitory E_{max} model (**FIGURE 1C**) reflecting reversible and competitive binding of both AVP (agonist) and tolvaptan (antagonist) to V_2-receptors in the kidney was also examined where:
  - E_0 = baseline effect in the absence of both plasma tolvaptan and AVP concentrations;
  - $E_{max,AVP}$ = maximum fractional decrease in UFR from E_0 attributed to AVP ($0 < E_{max,AVP} \leq 1$);
  - $EC_{50,AVP}$ = plasma AVP concentration producing half-maximal effect;
  - $EC_{50,TLV}$ = plasma tolvaptan concentration ($EC_{50,TLV}$) that would require a doubling of $EC_{50,AVP}$ in order to produce the same level of effect.
- E_0 was evaluated as a linear function of WIR during each time interval; diuretic use was not investigated.

Indirect Effect (IDR) Model

- An IDR model (**FIGURE 1D**) was also evaluated given a delay in the maximal change in UFR relative to peak plasma tolvaptan concentrations observed for some subjects.
- A hypothetical compartment represented the urine volume in the distal tubules of the kidney (UDT) where water re-absorption is governed by AVP. PD steady-state was assumed such that baseline UFR was equal to the ratio of the transfer rate of urine to (k_{in}) and the elimination rate of urine from the distal tubule (k_{out}).
- An E_{max} equation was utilized to stimulate k_{out} where:
  - E_{max} = maximal increase in k_{out} attributed to tolvaptan; and
  - EC_{50} = plasma tolvaptan concentration producing a half-maximal increase in k_{out}.
- k_{in} was evaluated as a linear function of WIR during each time interval, with an additive shift for concurrent furosemide or HCTZ use.

FIGURE 1: PK/PD Model Diagrams and Equations



RESULTS

Data

- 1956 timed urine collections from 101 subjects were used to develop the direct and IDR models; 1136 timed urine collections from 88 subjects were used to develop the competitive antagonism model.
- The population was 66% male and 93% White, with a median (min-max) age of 29 yr (18-91 yr), weight of 74 kg (45-103 kg), and CrCL of 109 mL/min (35-176 mL/min).

Direct Effect Model

- A direct effect model in which a slope term (E_{SLP}) linearly related plasma tolvaptan concentrations to UFR provided the best fit to the data. (**TABLE 2**)
- Observed UFR, along with the predicted UFR from the linear direct effect model, are shown for a subject given placebo (**FIGURE 4A**) or 180 mg tolvaptan (**FIGURE 4B**).
- GOF plots for the linear direct effect model are shown in **FIGURE 5**.
- This model was generally unbiased (median PE = 1.27%), had the best precision (median |PE| = 30%), and was preferred over the IDR model based upon AIC.
- E_{max} models yielded no further advantage over the linear model.

TABLE 2: Parameter Estimates for the Linear Direct Effect Model[a,b]

Parameter	Final Estimate (%SEM)
E_0	
Intercept (mL/hr)	52.6 (8.3)
Slope for WIR	0.420 (8.1)
Additive Shift during furosemide use (mL/hr)	483 (13.0)
Additive Shift during HCTZ use (mL/hr)	88.4 (24.7)
E_{slope} (mL/hr per ng/mL)	0.941 (5.5)
IIV of E_0 (%CV)	20.3 (19.7)
IIV of concentration-effect slope (SD)	0.37 (21.6)

[a] RV ranged from 116 to 36.9 %CV for predicted urine volumes from 0.1 to 8 L.
[b] UFR = E_0 + 0.941×C_{TLV} , where: E_0 = 52.6 + 0.420×WIR + 483×FURO + 88.4×HCTZ

FIGURE 4: Observed and predicted UFR from the linear direct effect model versus time since first dose for a subject given placebo (A) or 180 mg of tolvaptan (B). The shaded region is the difference between the total and baseline UFR, representing net urine output due to tolvaptan.

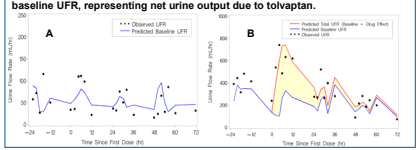
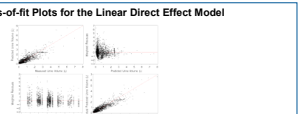


FIGURE 5: Goodness-of-fit Plots for the Linear Direct Effect Model



Competitive Antagonism Model

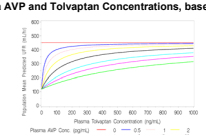
- The competitive antagonism model is presented in **TABLE 3.**
- Although this model did a reasonable job, it had a tendancy to under-predict the observed urine data (median PE = 12.2%) and had slightly lower precision than the linear direct effect model (median |PE| = 34%).
- Using this model, UFR was predicted over the range of observed plasma AVP and tolvaptan concentrations in healthy subjects as shown in **FIGURE 6**.
- Further use of this model will not be feasible since serial AVP samples were not collected in the Phase 2 and 3 clinical trials in CHF and HYP patients.

TABLE 3: Parameter Estimates for the Competitive Antagonism Model[a]

Parameter	Final Estimate (%SEM)
E_0[b]	
Intercept (mL/hr)	212 (15.0)
Slope for WIR	1.59 (14.0)
$E_{max,AVP}$ (fractional decrease from E_0)	0.74 (8.2)
$EC_{50,AVP}$ (pg/mL)	0.021 (61.7)
$EC_{50,TLV}$ (ng/mL)	0.720 (59.6)
IIV of E_0 (SD)	41.4 (87.1)
IIV of $E_{max,AVP}$ (%CV)	18.7 (60.3)
IIV of $EC_{50,AVP}$ (SD)	0.01 (162)

[a] RV ranged from 85.7 to 47.3 %CV for predicted urine volumes from 0.1 to 8 L
[b] E_0 = 212 + 1.59×WIR (refer to FIGURE 1C for full equation)

FIGURE 6: Predicted UFR from the Competitive Antagonism Model at Various Plasma AVP and Tolvaptan Concentrations, based upon a WIR of 150 mL/hr



Indirect Response Model

- The IDR model, in which a sigmoidal E_{max} model described the effect of tolvaptan on UFR via stimulation of k_{out}, is presented in **TABLE 4**.
- GOF plots for this more complex model were similar in appearance to those from the linear direct effect model.
- The IDR model was generally unbiased (median PE = 0.74%) but had a slightly lower precision than the direct effect model (median |PE| = 35%).
- Since the IDR model was determined to be more complex than needed and did not improve upon the fit provided by the linear direct effect model, it was not recommended for further evaluation in Phase 2 studies.

TABLE 4: Parameter Estimates for the Indirect Effect Model[a]

Parameter	Final Estimate (%SEM)
k_{in}[b]	
Intercept (mL/hr/hr)	15.3 (64.6)
Slope for WIR (hr^{-1})	1.06 (6.8)
Additive Shift during furosemide use(mL/hr/hr)	387 (20.2)
Additive Shift during HCTZ use (mL/hr/hr)	41.7 (55.6)
k_{out} (hr^{-1})	0.122 (13.1)
E_{max} (fractional increase in k_{out})	5.01 (10.4)
EC_{50} (ng/mL)	80.8 (26.9)
Sigmoidicity factor (γ)	2.09 (12.7)
IIV of k_{in} (%CV)	16.9 (27.1)
IIV of k_{out} (%CV)	90.4 (28.7)
IIV of E_{max} (SD)	2.34 (24.0)

[a] RV ranged from 186 to 36.1 %CV for predicted urine volumes from 0.1 to 8 L
[b] k_{in} = 15.3 + 1.06×WIR + 387×FURO + 41.7×HCTZ; (refer to FIGURE 1D for full equation)

CONCLUSIONS

- The linear direct effect model, with baseline UFR modeled as a function of both water intake and concurrent diuretic use, provided the best fit to the urine data from healthy subjects and was selected for further evaluation in Phase 2 patients with CHF and/or HYP.
- Utilization of this model allows for estimation of the net urine output due to tolvaptan after accounting for water intake and concurrent diuretic use.