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Pharmacokinetic and pharmacodynamic analyses of terlipressin in patients with hepatorenal syndrome

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Abstract

The objective of this population pharmacokinetics (PK) analysis was to characterize the PK of terlipressin and its active metabolite, lysine-vasopressin (L-VP), in patients with hepatorenal syndrome (HRS), following intravenous administration of terlipressin 1 mg to 2 mg every 6 h. Sparse PK samples from 69 patients with HRS who participated in terlipressin phase 3 clinical studies were used for model development. In addition, mean arterial pressure (MAP) and heart rate (HR) from 40 patients with HRS were available to explore the relationship between terlipressin and L-VP plasma concentrations and pharmacodynamic (PD) response. A two-compartment model with first-order elimination adequately described the PK of terlipressin. L-VP was well characterized as the active metabolite of terlipressin by a one-compartment model with first-order elimination. The population PK modeling results showed that the estimated clearances for terlipressin and L-VP are 27.4 L/h and 318 L/h, respectively, for a typical patient with a body weight of 86 kg. Body weight was identified as the only covariate for the clearance of terlipressin. However, simulation suggested that body weight had no clinically meaningful effects on the exposure of L-VP through terlipressin. Therefore, no weight-based dose is needed for terlipressin to treat HRS patients. PD response, change in MAP, and HR were well correlated to L-VP concentrations; compared with baseline values, the estimated maximum decrease in HR would be 10.6 bpm and the estimated maximum increase in MAP would be 16.2 mm Hg.

Keywords: Terlipressin, Lysine-vasopressin, Nonlinear mixed-effects modeling, Vasopressin analog

Introduction

Hepatorenal syndrome (HRS), a potentially reversible renal failure, is a serious, rapidly progressing disease complicating decompensated chronic liver disease associated with cirrhosis (Arroyo et al. 2006; Salerno et al. 2007; Angeli et al. 2015). If left untreated, patients with HRS have a poor prognosis (Gines et al. 1993; Alessandria et al. 2005). At present, there are no approved therapies available in the United States or Canada for the treatment of HRS. An increasing body of knowledge of the pathophysiology of HRS has demonstrated that vasoconstrictive drug therapy may improve renal function in patients with HRS (Salerno et al. 2007; European Association for the Study of the Liver 2018).

Terlipressin, a synthetic vasopressin analog, is a 12-amino-acid peptide with the chemical name N-[N-(N-glycylglycyl)glycyl]-8-L-lysinevasopressin (Jamil et al. 2018; Forsling et al. 1980) with an average molecular mass of 1227.4 Da (as a free base). It differs from endogenous human vasopressin by the substitution of lysine for arginine at the eighth position of the endogenous molecule (lys^8) and the addition of 3 glycyl residues at the amino terminus (Jamil et al. 2018). Terlipressin acts as a systemic vasoconstrictor via the vascular vasopressin V_1 receptors, primarily due to its metabolite

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lysine-vasopressin (L-VP), albeit of its own low potency. Results from the binding of terlipressin and L-VP investigation suggest that the binding affinity of L-VP to the V_1 or V_2 receptor is 600–700-fold greater than that of terlipressin. Cellular activity indicates that terlipressin is a partial agonist at V_{1a}, and a full agonist at V_2; while L-VP is a full agonist at both V_1 and V_2 receptors. It is believed that the in vivo response to terlipressin administration is likely due to partial V_{1a} agonist activity of terlipressin and full V_1 agonist activity of L-VP (Jamil et al. 2018; Forsling et al. 1980; Pliska et al. 1976; Nilsson et al. 1990; Wisniewski et al. 2006; Colson et al. 2016; Bernadich et al. 1998). In patients with HRS, the potent agonist activity of terlipressin and L-VP at V_1 receptors leads to splanchnic vasoconstriction that results in increased mean arterial pressure (MAP) and effective intravascular volume, as well as decreased heart rate (HR), which improves renal function (European Association for the Study of the Liver 2018; Jamil et al. 2018; Serpa Neto et al. 2012; Narahara et al. 2009; Boyer et al. 2016; Sanyal et al. 2008).

After intravenous (IV) administration of terlipressin, the glycyl residues of terlipressin are cleaved by endogenous tissue proteases resulting in a rapid decrease of terlipressin levels in blood circulation. Terlipressin is almost completely metabolized in the tissues by ubiquitous peptidases and L-VP is released gradually from tissues into the circulation, which likely contributes to the longer duration of action of terlipressin than that of vasopressin. The prolonged pharmacologic effect following injection of terlipressin at 7.5 μg/kg was from the conversion of terlipressin to L-VP in humans. Further, the clinical use of terlipressin lies in its ability to generate L-VP over a prolonged period. Adding amino acid residues to the amino terminus can prolong the duration of biological activity of vasopressin (Forsling et al. 1980; Cort et al. 1975; Kyncl and Rudinger 1970). The pharmacokinetics (PK) of terlipressin and L-VP has been characterized in healthy subjects (Forsling et al. 1980; Nilsson et al. 1990). Plasma concentrations of L-VP peak at 60 to 120 min after IV administration of terlipressin (Forsling et al. 1980). There is a biphasic decline in plasma terlipressin concentration with a rapid initial distribution phase (half-life of 8 min) followed by a slower second phase with an elimination half-life of 50 min (Nilsson et al. 1990). The volume of distribution is 0.7 L/kg and the plasma clearance is 9 mL/kg/min (Nilsson et al. 1990). Less than 1% of administered terlipressin is excreted in urine, and less than 0.1% is excreted as L-VP in urine (Forsling et al. 1980).

Based on the elimination half-life of 50 min (Nilsson et al. 1990) and its prolonged pharmacological effect due to the conversion to L-VP (Forsling et al. 1980; Cort et al. 1975), terlipressin is given as a bolus injection every 4 to 6 h (2 to 6 mg/day, up to 8 to 12 mg/day). More recently, a continuous intravenous infusion (CIV) of terlipressin has been used in HRS in bovine sepsis models, as well as in several small clinical studies. A recent Australian study in five patients with refractory ascites, using 3.4 mg/24 h CIV therapy of terlipressin for 4 weeks, resulted in promising clinical response and safety profiles (Gow et al. 2016).

Owing to the restriction of blood sampling in target patients, the PK data of terlipressin and L-VP are very limited. Understanding the PK and pharmacodynamic (PD) characteristics of terlipressin and L-VP in patients with HRS is necessary to guide the usage of terlipressin, such as dosing regimen and dose adjustment, in a clinical setting. Using the PK and PD data from two clinical studies in patients with HRS, the objectives of this analysis were to characterize the PK and PD, as measured by MAP and HR, of terlipressin and L-VP.

Materials and methods

Data

The data used for population PK/PD model development are from two phase 3 randomized, multicenter, double-blind, placebo-controlled studies of IV bolus administration of terlipressin in patients with HRS (study 1: OT-0401, NCT00089570; study 2: REVERSE, NCT01143246) (Boyer et al. 2016; Sanyal et al. 2008). Each study protocol was reviewed and approved by an institutional review board at each study site and written informed consent was obtained from each patient before enrollment in the studies. A summary of the study designs is provided in Supplementary Appendix 1.

In study 1, patients received up to 14 days of study treatment with terlipressin or matched placebo. Terlipressin was administered as slow IV bolus doses of 1 mg every 6 h (4 mg/day), with a dose increase to 2 mg every 6 h if serum creatinine (SCr) decreased by less than 30% after a minimum of 10 doses were administered. One baseline sample and additional 2 samples per day were collected on days 3, 6, 9, and day 14 (or last treatment day, whichever came first). The sampling time points for each day included one time point from TIMEPOINT 1 (0.083, 0.5, 1.0, and 2.0 h) and one time point from TIMEPOINT 2 (3.0, 4.0, 5.0, and 6.0 h) (Table 1).

In study 2, patients received up to 14 days of study treatment with terlipressin or matched placebo, IV, every 6 h (maximum of 15 or 16 days if HRS reversal was first achieved on days 13 or 14, respectively). Blood samples were taken, one predose and three postdose, based on randomization assignments from one of each group during the first dosing interval on day 1. The first time point was randomly assigned from one of the six time points of TIMEPOINT A, (5, 6, 7, 8, 9, and 10 min [± 1 min]), the second time point from one of the four time points

Table 1 Demographic and selected characteristics of patients with HRS in the population PK analysis

Variable	Statistic or category	Study 1 ($n = 29$)	Study 2 ($n = 40$)	Total ($N = 69$)
Weight, kg	Mean	89.1	89.4	89.3
	Range	58.0–170.0	43.0–134.0	43.0–170.0
Age, years	Mean	49.9	56.4	53.7
	Range	23–66	40–73	23–73
Age Group, *n* (%)	Age <65 years	27 (93.1)	33 (82.5)	60 (87.0)
	Age ≥65 years	2 (6.9)	7 (17.5)	9 (13.0)
Sex, *n* (%)	Male	23 (79.3)	17 (42.5)	40 (58.0)
	Female	6 (20.7)	23 (57.5)	29 (42.0)
Race, *n* (%)	White	26 (89.7)	31 (79.5)	57 (83.8)
	Black	3 (10.3)	5 (12.8)	8 (11.8)
	Asian	0 (0.0)	2 (5.1)	2 (2.9)
	Other	0 (0.0)	1 (2.6)	1 (1.5)
Creatinine clearance, mL/min	Mean	33.5	28.7	30.8
	Range	10.0–57.0	9.7–57.6	9.7–57.6
Child-Pugh score	Mean	11.4	10.5	10.9
	Range	8–15	6–15	6–15
Dosing frequency	NA		Every 6 h	
PK sampling schedule	NA	Days 3, 6, 9, and 14 (or last treatment day, whichever came first). The sampling time points for each day included one time point from group A and one time point from group B. TIMEPOINT 1: 0.083, 0.5, 1.0, 2.0 h TIMEPOINT 2: 3.0, 4.0, 5.0, 6.0 h	Day 1: The sampling time points for each day included one time point from TIMEPOINTS A or B or C: TIMEPOINT A: 5, 6, 7, 8, 9, and 10 min (± 1 min) TIMEPOINT B (early phase): 0.5, 1, 1.5, and 2 h (± 5 min) TIMEPOINT C (late phase): 3, 3.5, 4, and 5 h (± 10 min)	NA

HRS, hepatorenal syndrome; *NA*, not applicable; *PK*, pharmacokinetic

of TIMEPOINT B, (0.5, 1, 1.5, and 2 h [± 5 min]), and the third time point from one of the four time points of TIMEPOINT C, (3, 3.5, 4, and 5 h [± 10 min]) for each patient (Table 1).

Bioanalytical methods

Blood samples (7 mL each) were processed within 30 min after they were obtained. Preliminary stability data indicated that terlipressin and L-VP were stable in plasma at −20 °C and plasma samples were to be stored under controlled conditions at −20 °C; however, it was later determined that terlipressin and L-VP in human plasma were stable at −20 °C only up to 148 days. Plasma samples that were stored at −20 °C and assayed within 148 days after collection were considered to be within the stability period, and the data are considered valid for PK use. Plasma samples that were stored at −20 °C and assayed after 148 days had elapsed were notated as being outside the stability period. For study 1, the lower limit of quantitation (LLOQ) was 0.5 ng/mL for terlipressin and 0.1 ng/mL for L-VP. For study 2, the LLOQ was 0.25 ng/mL for terlipressin and 0.05 ng/mL for L-VP.

Population PK and PK/PD analysis methods

Population PK and PK/PD analyses were performed using nonlinear mixed-effect modeling with NONMEM (version 7.3.0, ICON Development Solutions, Ellicott City, MD) in accordance with the Guidance for Industry: Population Pharmacokinetics of the US Food and Drug Administration. The first-order conditional estimation method, as well as the Laplace (INTER) with Method 3 (M3) to handle below LLOQ (below quantitation limit [BQL]) data, was used for the analysis (Ahn et al. 2008; Bergstrand and Karlsson 2009). The plasma concentration data, dosing history, sampling date/time, demographic data, baseline laboratory test results, and concomitant medications were merged using SAS software version 9.3 or higher (SAS Institute, Cary, NC). Data summary, plotting, and model diagnostics were completed with R, version 3.5.2.

Population PK model development

Per PK information from healthy subjects, a linear two-compartment model was adopted to describe the PK data for terlipressin. A third compartment was added to describe the PK of L-VP, as depicted in Fig. 1. Model

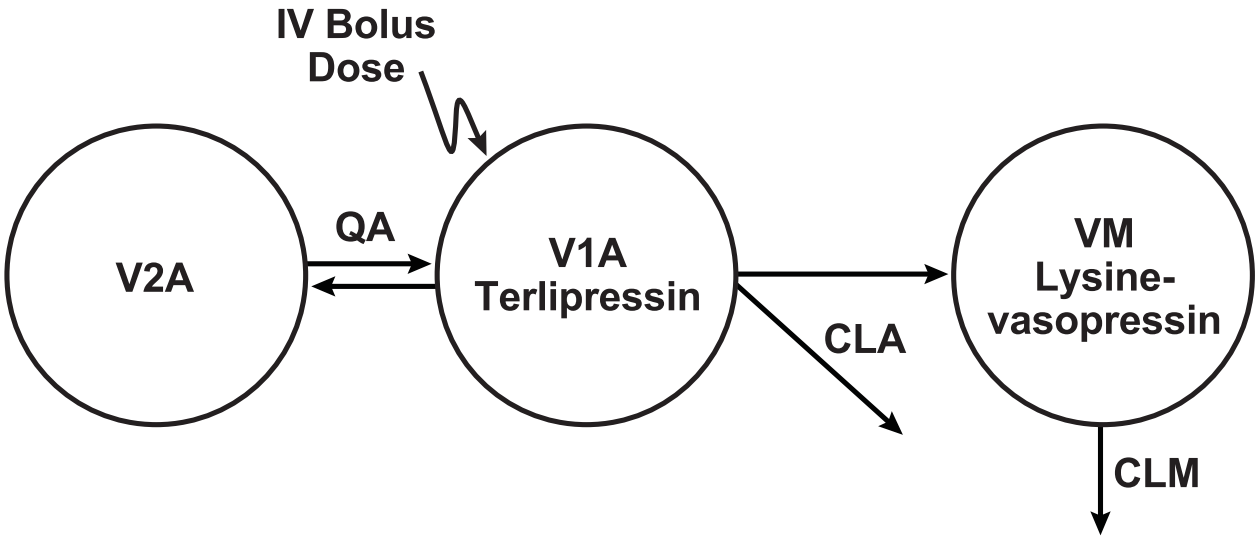

Fig. 1 Structural pharmacokinetic model for terlipressin and its active metabolite lysine-vasopressin. *CLA*, total body clearance for terlipressin; *CLM/Fm and VM/Fm*, apparent volume of central compartment and clearance for lysine-vasopressin; *IV*, intravenous; *QA*, intercompartmental flow rate; *V1A*, central volume of distribution for terlipressin; *V2A*, peripheral volume of distribution for terlipressin

parameters are presented in the footnote of Fig. 1; these included total body clearance of terlipressin (CLA), central compartment volume (V1A), intercompartment flow rate (QA), and peripheral compartment volume (V2A) for terlipressin; and the apparent clearance (CLM/Fm) and apparent central compartment volume (VM/Fm) for L-VP. The fraction of terlipressin dose that is metabolized to L-VP, Fm, is unknown and cannot be estimated. Thus, CLM/Fm and VM/Fm were estimated from the population PK analysis. Log normal distribution was assumed for between-subject variability (BSV) for PK parameters. An additive error model was used for log-transformed plasma concentrations. Different residual errors were assumed for terlipressin and L-VP.

Continuous covariates included in the model were body weight, age, renal function (described using creatinine clearance [CRCL]), hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALKP], bilirubin). Discrete covariates included age group (< 65 years versus ≥ 65 years of age), sex, race, Child-Pugh score for hepatic function, and concomitant medications. Graphical exploratory evaluation of covariate-parameter relationships was performed, followed by the stepwise method. Covariate analysis was also assisted by clinical relevance, reduction in BSV, and the improvement of the Loess fitting.

Plasma concentration values BQL were treated as the lower limit of quantitation divided by 2 (LLOQ/2). In addition, M3 was used for parameter estimation (Ahn et al. 2008; Bergstrand and Karlsson 2009). Comparison between the parameters from two methods was conducted.

Population PK/PD models

Sequential PK/PD analysis was performed to develop the population PK/PD model. Predicted individual terlipressin and L-VP concentrations at the same time points as the PD measurements were used in the PD model development. Both linear and nonlinear PK/PD models for MAP or HR were tested. A log-normal distribution for BSV of the baseline MAP or HR was assumed. Normal distribution was assumed to describe BSV in the slope in the linear model or maximum change in HR (Imax) in the Imax model. An additive error model was assumed.

Model evaluation

Model evaluation was conducted using standard diagnostic tools such as goodness-of-fit criteria, diagnostic plots, and a prediction-corrected visual predictive check (VPC) (Holford 2005). Model stability and performance were also evaluated using the bootstrap method.

Simulation to evaluate dosing regimen

Model-based simulations were conducted to evaluate the impact of identified covariates on the exposure of terlipressin and L-VP, and their potential impact on the dosing regimen such as weight-based or flat dose of terlipressin.

Results

The population PK analysis included 69 adult patients with HRS who had 227 measurable terlipressin and 246 measurable L-VP plasma samples collected from study 1 and study 2 altogether. In studies 1 and 2, 16.5% of total terlipressin PK samples were BQL and 10.2% of total L-VP PK samples were BQL.

Demographics and selected characteristics at baseline for the study population are shown in Table 1. Two patients (2.9%) had missing CRCL, weight, and Child-Pugh score data, and one had missing race information. The majority of the patient population was White (84%), male (58%), and younger than 65 years of age (87%). The median (minimum, maximum) body weight was 86 (43, 170) kg. The missing CRCL, weight, and Child-Pugh score values were imputed as the median of the study population, and the patient with missing race data was classified as White. As per the nature of HRS, all patients from studies 1 and 2 exhibited renal impairment (CRCL < 60 mL/min), and a majority (77%) had severe hepatic impairment, with a Child-Pugh score ≥ 10.

Because the BQL data points for both terlipressin and L-VP were > 10%, the M3 method to handle BQL data was also applied to the parameter estimation in addition to handling BQL as LLOQ/2. Results of the two methods of handling BQL were in good agreement. For example, the difference in parameter estimates including error models of the two methods ranged from −0.4 to 7.6%. The difference in estimated BSV from the two methods was less than 5.5% except for the central compartment volume of terlipressin, which was 35%. Optimization using M3 took longer computational time. Therefore, the method of setting BQL as LLOQ/2 was used in subsequent analyses. Diagnostic plots of the PK base model derived by setting BQL=LLOQ/2 are shown in Supplementary Fig. S1.

Covariate analysis

Graphical exploratory evaluation of covariate-parameter relationships from the base population PK model is presented in Supplementary Fig. S2. It appeared that only body weight and CRCL had a consistent trend with the PK parameters of terlipressin and L-VP.

During the stepwise forward selection step, body weight (WT), sex, and renal function were added to the clearance of terlipressin (CLA) and L-VP; sex and Child-Pugh score were added to the central compartment of terlipressin and L-VP. Stepwise backward elimination revealed that body weight on CLA was the only significant covariate (Table 2). The body weight effect on CLA can be described as below:

$$\mathrm{CLA} = 27.4 \times (\mathrm{WT}/86)^{0.549}\ \mathrm{L/h}$$

Table 2 Population pharmacokinetic parameters of terlipressin and L-VP in patients with HRS (final PK model)

Parameters	Estimate (RSE%)[a]	95% CI[b]
CLA (L/h)	27.4 (8.7)	24.8–31.1
WT on CLA[c]	0.549 (36.2)	0.413–0.850
V1A (L)	6.31 (23.3)	4.87–9.33
QA[d] (L/h)	35.6 (16.7)	24.0–43.1
V2A[d] (L)	18.4 (8.6)	15.6–22.1
CLM/F_m (L/h)	318 (11.5)	283–363
VM/F_m (L)	1370 (18.8)	1190–1520
BSV of CLA (CV%)	34.8 (39.4)	24.7–50.3
BSV of V1A (CV%)	61.9 (121.9)	35.5–113.1
BSV of CLM/F_m (CV%)	65.8 (33.5)	54.2–73.1
BSV of VM/F_m (CV%)	67.7 (34.9)	53.3–81.9
Residual errors (CV%)		
Terlipressin—study 1	70.0 (14.1)	59.5–76.2
L-VP—study 1	47.2 (5.6)	37.1–59.4
Terlipressin—study 2	39.7 (6.5)	28.2–51.6
L-VP—study 2	26.9 (18.4)	20.9–30.3

BSV, between-subject variability; *CI*, confidence interval; *CLA*, clearance of terlipressin; *CLM/F_m*, apparent clearance for L-VP; *CV%*, coefficient of variation; *HRS*, hepatorenal syndrome; *L-VP*, lysine-vasopressin *PK*, pharmacokinetic; *QA*, intercompartmental flow; *RSE*, relative standard error; *V1A and V2A*, volume of central compartment and peripheral compartment for terlipressin, respectively; *VM/F_m*, apparent volume of L-VP; *WT*, body weight

[a] Parameter precision (RSE%) is expressed as CV%

[b] 95% CI estimated from bootstrap of 1110 replicated samples

[c] $\mathrm{CLA} = 27.4 * (\mathrm{WT}/86)^{0.549}$

[d] BSV was fixed as 0

For patients with a body weight of 86 kg, the median weight in our population, the typical value of CLA was 27.4 L/h. Given the body weight range of the two studies, from 43 kg to 170 kg, CLA varied from 18.7 L/h to 39.8 L/h, respectively. The typical value of the central compartment volume for terlipressin was 6.31 L. The mean CLM/Fm and VM/Fm for L-VP were 318 L/h and 1370 L, respectively. A large degree of BSV was derived from the analysis, with the BSV in V1A, CLM/Fm, and VM/Fm above 60%.

Evaluation of the population PK model

Diagnostic plots for the final population PK model shown in Fig. 2 suggested that the final population PK model was adequate in describing plasma concentration-time profiles in patients with HRS.

Based on the bootstrap results shown in Supplementary Table S1, the parameter estimates of the final population PK model were comparable to the median values of 1110 resampled bootstrapping runs. All of the parameter estimates for the final population PK model fell within the 95% confidence intervals (CIs) obtained from the

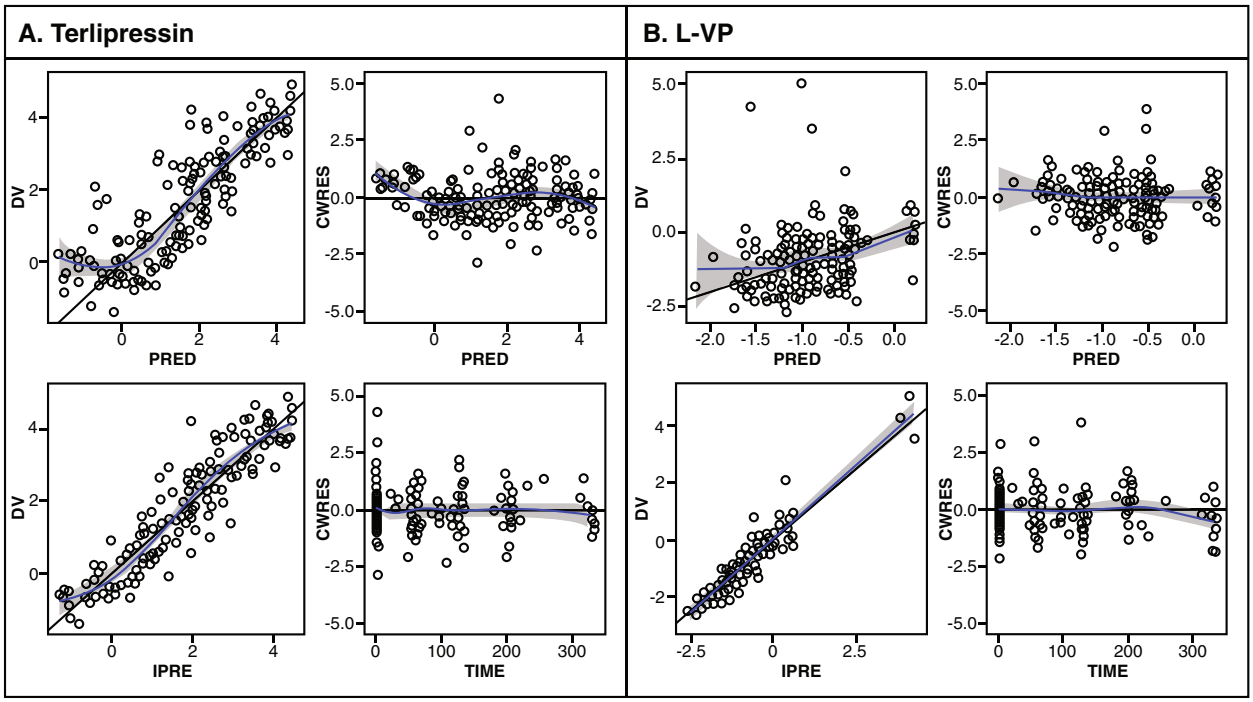

Fig. 2 Goodness-of-fit diagnostic plots of the final model of terlipressin. *CWRES*, conditional weighted residual value; *DV*, observed concentration; *IPRE*, individual predicted value; *L-VP*, lysine-vasopressin; *PRED*, typical value. Log transformed observed data used for model development

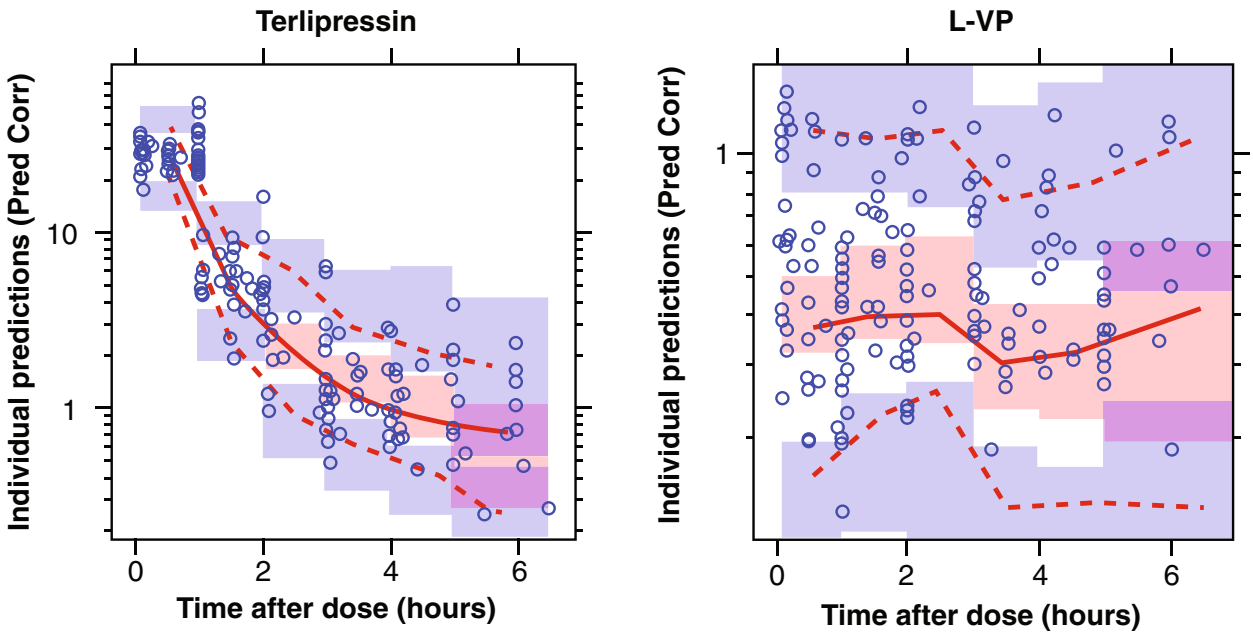

Fig. 3 Visual predictive check: model-predicted and observed plasma concentrations of terlipressin and L-VP in patients with HRS. Blue circle markers represent observed PK data; solid red line represents the median observed values; solid red areas indicate the model-predicted 90% confidence interval for the median. The 2.5th and 97.5th percentiles of observed data are presented with dashed red lines, and the blue solid areas represent the model-predicted 90% confidence intervals for the corresponding percentiles. *HRS*, hepatorenal syndrome; *L-VP*, lysine-vasopressin; *PK*, pharmacokinetic

bootstrap, the results of the bootstrap runs demonstrated sufficient stability of the final PK model.

Figure 3 presents prediction-corrected VPC plots of terlipressin and L-VP for the final population PK model. In general, the dashed and solid red lines (observations) for both terlipressin and L-VP run within their designated blocks (model-predicted 90% CI), indicating that the final population PK model had good predictability.

PK/PD model

HR and MAP measurements were available from 40 patients in study 2. Increasing MAP and decreasing HR were associated with the increase of L-VP concentration (data not shown). The Imax model was selected as the final PK/PD model for MAP based on its lower Akaike Information Criterion (AIC) value compared with the linear model. A summary of PK/PD parameter estimates of the MAP Imax model is presented in Table 3. The estimated L-VP potency (concentration of L-VP that produces 50% of the maximal response [IC_{50}]) was 0.26 ng/mL (95% CI = 0.008 to 1.28). The maximum increase in MAP Imax due to L-VP exposure was 16.2 mm Hg (95% CI = 9.0 to 37.8).

Similarly, the Imax model was selected as the final PK/PD model for HR based on its lower AIC value. Model parameters are presented in Table 4. The estimated potency (IC_{50}) was 0.25 ng/mL (95% CI = 0.056 to 1.06). The Imax due to L-VP exposure was −10.6 bpm (95% CI = −24.0 to −5.8).

The model-predicted relationship between L-VP plasma concentrations and MAP and HR measurements is illustrated in Supplementary Fig. S3.

Simulation to evaluate dosing algorithm

Although body weight has no direct impact on the exposure of L-VP, the impact of body weight on terlipressin might alter the exposure of L-VP. To assess this hypothesis, model-based simulations were conducted. Figure 4 presents the relationship between body weight and the exposure (average concentration within one dosing interval) of terlipressin and L-VP. Results presented in Fig. 4 demonstrated that the changes in terlipressin exposure with body weight had no noticeable effect on L-VP exposure. Because L-VP is the primary pharmacologically active moiety, no body weight-based dosing regimen of terlipressin would be necessary in patients with HRS.

Table 3 Parameter estimates of the MAP Imax model

Parameter[a]	Estimate (RSE%)[b]	95% CI[c]
B0 (mm Hg)	75.8 (2.2)	72.5–79.3
Imax (mm Hg)	16.2 (32.9)	9.0–37.8
IC_{50} (ng/mL)	0.260 (85.4)	0.008–1.280
BSV of B0 (CV%)	11.4 (25.6)	8.2–13.9
Additive error of MAP (mm Hg)	6.9 (11.6)	5.4–8.6

BSV, between-subject variability; *CI*, confidence interval; *CV%*, coefficient of variation; *IC_{50}*, concentration of lysine-vasopressin that produces 50% of the maximal response; *Imax*, maximum change in HR; *L-VP*, lysine-vasopressin; *MAP*, mean arterial pressure; *RSE*, relative standard error

[a] MAP = B0 + Imax *L-VP/(IC_{50} + L-VP)

[b] Parameter precision (RSE%) is expressed as CV%

[c] 95% CI estimated by bootstrap method

Table 4 Parameter estimates of the HR Imax model

Parameter[a]	Estimate (RSE%)[b]	95% CI
B0 (bpm)	79 (2.7)	75–84
Imax (bpm)	−10.6 (32.9)	−24.0 to −5.8
IC_{50} (ng/mL)	0.251 (65.7)	0.056–1.06
BSV of B0 (CV%)	14.0 (22.5)	10.7–16.9
BSV of Imax (bpm)	4.5 (177.5)	0.03–15.56
Additive error of HR (bpm)	5.2 (12.8)	4.1–6.3

BSV, between-subject variability; *CI*, confidence interval; *CV%*, coefficient of variation; *HR*, heart rate; *IC_{50}*, concentration of L-VP that produces 50% of the maximal response; *Imax*, maximum change in HR; *L-VP*, lysine-vasopressin; *RSE*, relative standard error

[a] HR = B0 + Imax * L-VP/(IC_{50} + L-VP)

[b] Parameter precision (RSE%) is expressed as CV%

Discussion

Patients with HRS are expected to have advanced, progressive liver and renal disease. Therefore, to identify the effect of severe hepatic and renal dysfunction on terlipressin PK is important. Covariate analysis in the population PK modeling suggested that hepatic dysfunction measured by baseline values for ALT, AST, total bilirubin, ALKP, and Child-Pugh scores did not appear to have any significant effect on the PK of terlipressin and L-VP. This is likely due to the fact that the liver is not involved in the conversion of terlipressin to L-VP. That renal dysfunction had no statistically significant impact is in good agreement with reported clinical results that less than 1% of administered terlipressin is excreted in urine, and less than 0.1% is excreted as L-VP in urine (Forsling et al. 1980). As such, no dose adjustment of terlipressin was recommended for patients with HRS and varying degrees of hepatic or renal dysfunction.

Age effect on the PK of terlipressin and L-VP was tested either as a continuous covariate or a categorical covariate. Neither approach showed that age or race were statistically significant covariates. Of the 69 patients evaluated, 9 (13%) were elderly (aged ≥ 65 years) and most patients were White (83.8%). Therefore, the conclusion derived from the covariate analysis that neither age nor race had any significant effect on the PK of terlipressin had its limitations.

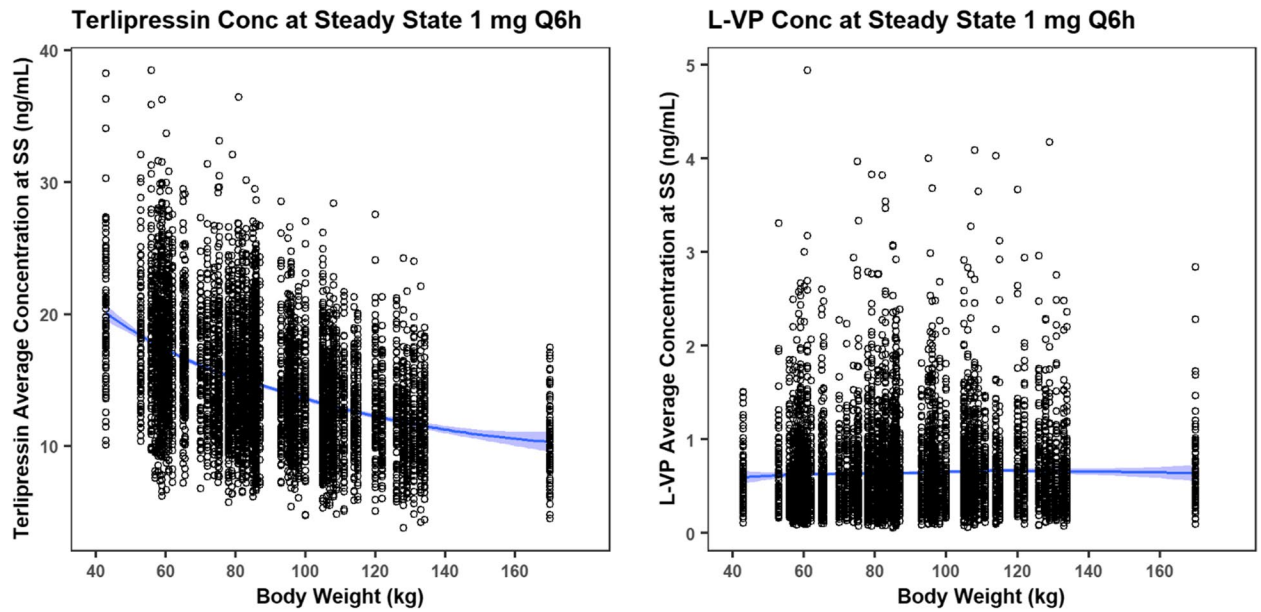

Fig. 4 Simulated terlipressin and L-VP plasma concentrations at steady state following terlipressin 1 mg administered every 6 h in patients with HRS with different body weights. The solid blue line indicates the Loess fitting and the shaded area indicates the 90% confidence interval. *Conc*, concentration; *HRS*, hepatorenal syndrome; *L-VP*, lysine-vasopressin; *Q6h*, every 6 h; *SS*, steady-state.

Two different methods to handle BQL were implemented. Parameter estimates using the two methods are in good agreement. Keizer and colleagues (Keizer et al. 2015) have reported similar outcomes between different methods in handling BQL. In particular, for a population PK model with IV administration, when the percentage data below LLOQ is less than 20%, setting BQL = LLOQ/2 has a similar performance to that of the M3 method.

PK/PD modeling

Increased MAP after administration of terlipressin in patients with HRS has been reported in the literature (Boyer et al. 2016; Sanyal et al. 2008), and this effect results in improved renal function and has provided the therapeutic rationale for terlipressin treatment in this setting. Our studies confirmed the reported effect of MAP increasing with terlipressin treatment.

Both linear and nonlinear models were explored to characterize the correlations between terlipressin and L-VP concentrations and MAP as well as HR. These exploratory investigations suggested that a mixed model with linear correlation for MAP increase attributed to terlipressin and an Imax model attributed to L-VP are appropriate. However, because of the fast decline in terlipressin concentration (half-life is 0.9 h), the early time concentration and MAP data points were not sufficient to differentiate the response contributed by terlipressin from L-VP. A simplified model assuming that the increase in MAP primarily related to L-VP described the observed MAP data equally well following the administration of terlipressin.

Conclusion

Plasma terlipressin concentrations in patients with HRS were well characterized by a two-compartment PK model while the L-VP plasma concentrations were well characterized by a one-compartment PK model. None of the covariates examined were found to have a significant effect on the PK of terlipressin and L-VP, except for body weight on clearance of terlipressin. Results from the model-based simulations suggested that although terlipressin exposure decreases with increasing body weight, the change in L-VP levels with body weight is negligible. Because L-VP is the primary pharmacologically active moiety, no body weight-based dosage adjustment of terlipressin would be necessary when treating patients with HRS. The PK/PD relationship of L-VP to MAP was well characterized by an Imax model, with a maximum estimated increase in MAP of 16.2 mm Hg and a decrease in HR of 10.6 bpm.

Abbreviations

AIC: Akaike Information Criterion; ALKP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; bpm: Beats per minute;

BQL: Below quantitation limit; BSV: Between-subject variability; CI: Confidence interval; CIV: Continuous intravenous infusion; CLA: Total body clearance of terlipressin; CLM/F_m: Apparent clearance for L-VP; Conc: Concentration; CRCL: Creatinine clearance; CV%: Coefficient of variation; CWRES: Conditional weighted residual value; DV: Observed concentration; HR: Heart rate; HRS: Hepatorenal syndrome; IC_{50}: 50% of the maximal response; Imax: Maximum change in HR; IPRE: Individual predicted value; IV: Intravenous; LLOQ: Lower limit of quantitation; LLOQ/2: Lower limit of quantitation divided by 2; L-VP: Lysine-vasopressin; M3: Method 3; MAP: Mean arterial pressure; NA: Not applicable; PD: Pharmacodynamic; PK: Pharmacokinetic; PRED: Typical value; Q6h: Every 6 h; QA: Intercompartmental flow; RSE: Relative standard error; RUE1: Residual unexplained variability in study 1; RUE2: Residual unexplained variability in study 2; SCr: Serum creatinine; SS: Steady-state; VM/F_m: Apparent volume of L-VP; VPC: Visual predictive check; WT: Body weight.

Supplementary Information

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Additional file

Additional file 1. (DOCX 370 kb)

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Authors' contributions
Khurram Jamil reviewed each draft and provided comments on the analyses. Xiaofeng Wang provided interpretation of data, reviewed each draft, provided input on the discussion, and contributed written content. The authors read and approved the final manuscript.

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Availability of data and materials
Discussion of statistical endpoints and analysis are included in the manuscript. Summary aggregate (basic) results (including information on adverse events) and the study protocol will be available on clinicaltrials.gov (OT-0401, NCT00089570; REVERSE, NCT01143246) when required by regulation. Requests for additional information should be directed to the trial sponsor company at medinfo@mnk.com.

Declarations

Competing interests
Xiaofeng Wang reports that she is a former employee of Mallinckrodt Pharmaceuticals and that she does not hold shares in Mallinckrodt Pharmaceuticals. Khurram Jamil reports that he is an employee of Mallinckrodt Pharmaceuticals and that he does not hold shares in Mallinckrodt Pharmaceuticals.

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