The Pharmacokinetics of Terlipressin Administered as a Continuous Infusion in Six Cirrhotic Patients with Refractory Ascites

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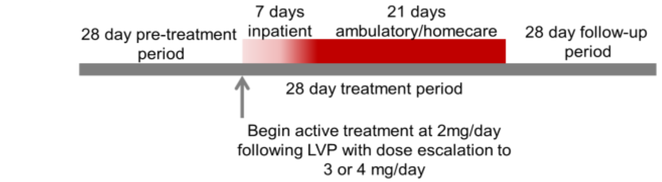
PREMISE

- Terlipressin is cleaved, *in vivo*, to 8-lysine vasopressin
- (8-LVP), a potent agonist of human V1 receptors.
- Approved in Europe for treatment of life-threatening complications of cirrhosis: Bleeding esophageal varices and hepatorenal syndrome type 1 administered by intermittent intravenous (IV) bolus.
- Terlipressin continuous IV infusion may be safer and more effective and allow for treatment of other complications of cirrhosis (e.g., control of portal hypertension, prevention of HRS, reduction of ascites) in the outpatient setting.
- Pharmacokinetics (PK) of terlipressin and 8-LVP during administration by continuous IV infusion is not known.

METHODS

- Six cirrhotic patients with refractory ascites were enrolled
- Open-label single arm trial designed to evaluate the safety and tolerability and explore the efficacy in refractory ascites of terlipressin administered as a continuous infusion for 28 days.



- Serial plasma samples were collected throughout treatment
- Plasma assayed for terlipressin and 8-LVP by LC-MS/MS. (LLOQ 0.25 and 0.05 ng/mL, respectively)
- Plasma concentration data were fit for each individual by non-linear regression analysis.
- Pharmacokinetic model: $C_{terlipressin} = \frac{k_0}{CL}\left(1 - e^{-\frac{CL}{V} \times t}\right)$

Where $C_{terlipressin}$ = terlipressin plasma concentration, t = time, k_o = terlipressin infusion rate, CL = clearance, V = volume of distribution

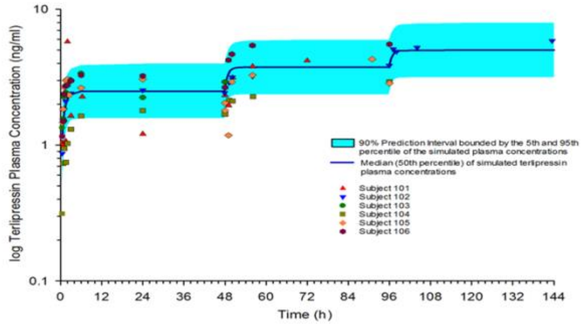
RESULTS

Patient Baseline Characteristics

	Patient Number					
	101	102	103	104	105	106
Age (years)	60	64	36	61	61	63
Weight (kg)	85.1	89.8	71.2	120.7	75.6	84
Sex	Male	Male	Male	Male	Male	Male
Race	Black	Hispanic	White	White	Black	White
Cirrhosis etiology	HepC/Alc	HepC	Alc	Alc	Alc	HepC/Alc
CTP (Class)	10 (C)	8 (B)	11 (C)	7 (B)	8 (B)	11 (C)
MELD-Na score	16	12	22	13	9	18
SCr, mg/dL	1.6	1.1	2	1.2	0.8	1.1
LVP interval[1], days	7	17	6	14	20	21

1= pre-infusion

Observed and Simulated Terlipressin Plasma Concentrations from Population PK Modelling



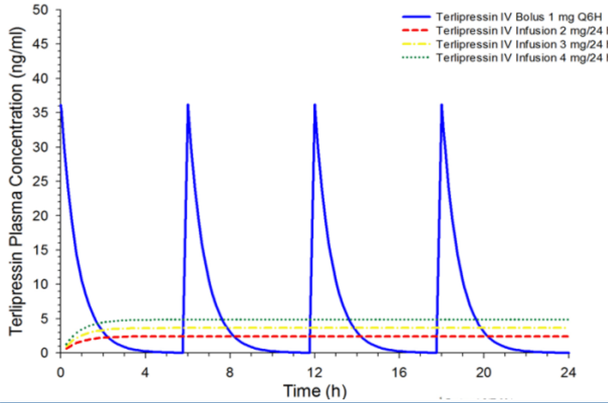
PK Parameters and Efficacy

	Patient Number					
	101	102	103	104	105	106
Infusion (max), mg/day	3	4	2	3	3	3
Treatment days	28	14	24	28	9	28
CL (mL/min/kg)	6.0	5.1	5.7	5.7	6.9	4.1
V (L/kg)	0.29	0.3	0.27	0.68	0.18	0.27
$T_{1/2}$ (min)	33.4	40.8	32.8	83.1	18.3	45.3
C_{ss} Ter, ng/mL	3.99	5.55	2.91	2.6	3.27	5.48
C_{ss} 8-LVP, ng/mL	0.058	0.108	0.138	0.072	0.11	0.131
Change in LVP interval[a]	0%	+70%	+116%	+414%	+215%	-10%
Change in SCr (mg/dL)[b]	-0.4	0	-1.0	-0.4[c]	-0.4[d]	0

a = Prior to treatment vs during treatment; b = D14 of treatment unless noted otherwise; c = D15; d = D7

Pharmacokinetic parameters: Steady-state average plasma concentration = $C_{ss\text{-}ave}$ Elimination rate constant (k) = CL/V, Elimination half-life ($t_{1/2}$) = 0.693/k.

Simulated terlipressin plasma concentrations following IV bolus of 1 mg every 6 hours and IV continuous infusions of 2 mg, 3 mg, or 4 mg per day[1]



CONCLUSIONS

- One-compartment model with zero-order input and first-order elimination best described terlipressin plasma concentrations during continuous intravenous infusion.
- Terlipressin plasma concentrations closely agreed with values predicted by the pharmacokinetic model.
- Steady state 8-lysine vasopressin plasma concentrations were lower than both peak and average plasma concentrations reported from previous studies following IV bolus administration.[2]
- Administration of terlipressin as a continuous infusion prevents high, potentially harmful, peak concentrations associated with intermittent IV bolus dosing.

DISCLOSURES: Penelope Markham and Patrick Yeramian – BioVie Employees; James Fischer and Denise Smith – BioVie Consultants; Jasmohan Bajaj has received consulting fees from BioVie

REFERENCES:

1 Continuous infusion data: current study

2 https://www.tga.gov.au/sites/default/files/auspar-terlipressin-130827-cer.pdf