ID week 2022
Thursday, Oct. 20
Poster # 626

Hartford HealthCare
Hartford Hospital

Tebipenem Pharmacokinetics and Soft-Tissue Distribution in Diabetic Patients with Lower Extremity Infections using *In Vivo* Microdialysis

Yasmeen Abouelhassan,[1] Andrew J. Fratoni,[1] Ashley K. Shepard,[2] David P. Nicolau,[1,3] and Tomefa E. Asempa[1]

[1]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT; [2]Hartford Healthcare Medical Group, Podiatric Surgery, Hartford, CT; [3]Division of Infectious Diseases, Hartford Hospital, Hartford, CT

Tomefa E. Asempa, PharmD
Center for Anti-Infective Research & Development, Hartford Hospital
80 Seymour Street
Hartford, CT 06102
Telephone: (860) 972-1109
Fax: (860) 545-3992
Tomefa.Asempa@hhchealth.org

ABSTRACT (Revised)

Objective: Administration of the oral carbapenem, tebipenem along with its broad spectrum of activity against anaerobic, Gram-positive and Gram-negative pathogens including extended-spectrum β-lactamase-producing Enterobacterales, offers clinicians a potential new option and route to treat a range of infections. Lower extremity infections in diabetic patients are associated with high rates of hospitalization and amputation. Given the microvascular dysfunction and poor peripheral circulation in this population, the aim of this study was to assess tebipenem soft tissue pharmacokinetics (PK) and interstitial fluid distribution among diabetic patients with lower extremity infections using in vivo microdialysis.

Methods: This was a single-center, open-label, observational PK study in diabetic patients with foot infections who were enrolled and received tebipenem pivoxil HBr (600 mg) orally q8 hrs for a total of 3 doses. A microdialysis catheter was inserted within 4-8 cm of the wound margin to allow for dialysate sampling. Ten concurrent plasma and dialysate samples over an 8 hr period starting immediately prior to the last dose of tebipenem were obtained. Protein binding was determined by ultracentrifugation at 1 hr post-third dose. Plasma and dialysate samples were assayed via a validated LC/MS/MS assay. Non-compartmental analyses for free plasma and soft-tissue concentration were used to obtain PK parameters.

Results: Six diabetic patients with an age of 58 ± 8 years and a hemoglobin A1C of 10.0 ± 1.9% were consented. All patients had an active complicated skin and soft tissue infection as defined by PEDIS Grade 2 or 3. Mean ± standard deviation (SD) plasma protein binding was 54% ± 5%. Mean ± SD tebipenem PK parameters in plasma were: maximum free concentration (fC_{max}), 3.40 ± 2.86 mg/L; time to C_{max} (T_{max}), 2.83 ± 1.47 hr; half-life ($t_{1/2}$), 2.02 ± 1.32 hr and free area under the concentration-time curve ($fAUC_{p\ (0\text{-}8)}$): 10.01 ± 4.81 mg.h/L. Mean ± SD parameters in tissue were: C_{max}, 2.73 ± 1.44 mg/L; T_{max}, 3.00 ± 1.26 h; $t_{1/2}$ 1.79 ± 1.15 hr; and $AUC_{t\ (0\text{-}8)}$, 8.60 ± 2.88 mg.h/L.

Conclusion: This study demonstrates that tebipenem has excellent distribution into interstitial fluid and lower extremity tissue of diabetic patients with ongoing foot infections.

INTRODUCTION

- Tebipenem pivoxil HBr (TBP-PI-HBr) is a first-in-class oral carbapenem.[1]
- Tebipenem's oral dosing and broad spectrum of activity are of great interest for the management of a range of inpatient and outpatient infections.
- Wound infections of the lower extremities are frequent in diabetic patients and associated with hospitalization and amputation.[2]

OBJECTIVE

- We assessed plasma and soft-tissue PK exposure of tebipenem in six patients with ongoing diabetic foot infection (DFI) using *in vivo* microdialysis.

MATERIALS & METHODS

- Single-center, open-label, observational pharmacokinetic study.
- Six eligible patients with ongoing DFI were enrolled per inclusion/ exclusion criteria.
- Subjects received 3 doses of 2 TBP-PI-HBr 300 mg orally (total dose of 600 mg) q8 hrs.
- A microdialysis probe (63 MD catheter, MDialysis Inc. N. Chelmsford, MA, USA) was inserted in the infected foot of the patient, within 4-8 cm of the wound margin, to allow for interstitial fluid sampling (Figure 1).
- After catheter insertion, the probe was flushed and then perfused with 0.9% sodium chloride for injection solution (rate: 2 µL/min). Samples were collected in microvials over 0.5-1 hour.
- A total of 10 plasma and 10 dialysate samples were collected starting before the third dose and continued for 8 hours.
- After dialysate sampling concluded, the catheter was calibrated by retrodialysis technique.
- Plasma protein binding was assessed in triplicate using Centrifree® Ultrafiltration devices.
- Plasma, dialysate, and ultrafiltrate samples were analyzed by a validated LC/MS/MS assay.
- Non-compartmental pharmacokinetic analyses of plasma and tissue concentrations were conducted using Phoenix WinNonlin (version 6.4, Pharsight Corporation, Mountain View, CA).

Inclusion Criteria	Exclusion Criteria
1. Male or female with a negative serum pregnancy test	1. Less than 18 years
2. Documented type I or type II diabetes	2. Hypersensitivity or allergy to tebipenem, β- lactams or lidocaine derivatives
3. Receiving insulin or anti-hyperglycemic agent	3. Currently receiving probenecid or valproic acid
4. Suspected complicated skin infection	4. CrCl < 30 mL/min
5. Willing to participate in the study	5. Likely to require multiple surgical interventions during study period which could affect placement of microD catheter
	6. Males who are not surgically sterilized and females of child-bearing potential must agree to use 2 highly effective methods of contraception from screening, during trial and for 90 days after last dose of tebipenem

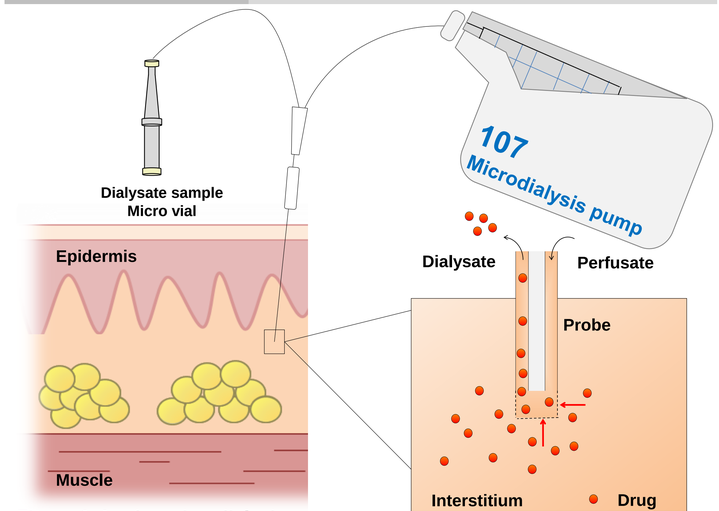


Figure 1. ***In vivo*** **microdialysis**

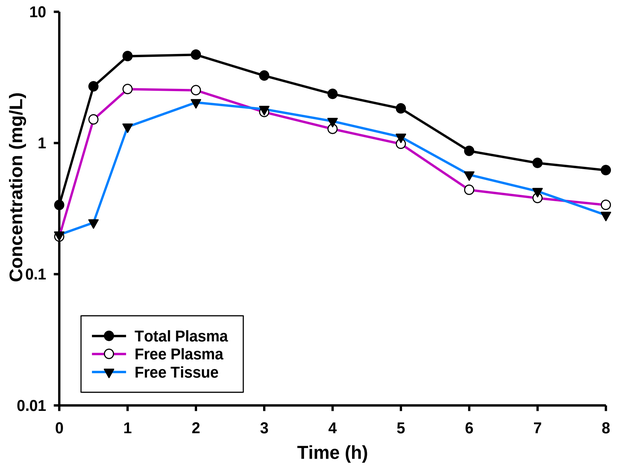
RESULTS

Table 1. Characteristics of study participants (n=6)

Age, mean (SD)	58 (8)
Male, n (%)	5 (83%)
Height (cm), mean (SD)	179 (12)
Weight (kg), mean (SD)	99 (18)
BMI (kg/m^2), mean (SD)	31 (5)
Albumin (g/dL), mean (SD)	3 (0.4)
Hemoglobin A1C (%), mean (SD)	10.0 (1.9)
PEDIS infection Grade	3
Creatinine Clearance (mL/min), mean (SD)	93 (21)

- **Tebipenem Protein binding was 54 ± 5 %**
- **Tebipenem distributed well into tissue ($AUC_{t(0\text{-}8)}$ 8.60 mg.h/L vs $fAUC_{P(0\text{-}8)}$ 10.01)**
- **Prior study of tebipenem in healthy volunteers demonstrated high tissue distribution ($AUC_{t(0\text{-}8)}$ 5.99 mg.h/L vs $fAUC_{P(0\text{-}8)}$ 5.61 mg.h/L)[3]**
- **Overall exposure in patients with DFI was higher than healthy volunteers, conferring a benefit to the infected population**

Figure 2. Tebipenem plasma and tissue concentrations of patients with ongoing diabetic foot infection



Abbreviations

C_{max}: Maximum concentration
CV: Coefficient of variation
Vd: Volume of distribution
AUC: Area under the concentration-time curve
SD: Standard deviation
T_{max}: Time to C_{max}
CL: Clearance
$T_{1/2}$: Half-life
F: Bioavailability

Table 2. Plasma and tissue pharmacokinetic parameters of tebipenem from a cohort of infected patient with DFI after the third dose of tebipenem pivoxil HBr administered 600 mg every 8 hours orally

Compartment	C_{max} (mg/L)			T_{max} (h)			$T_{1/2}$ (h)			$AUC_{0\text{-}8}$ (mg•h/L)			CL/F (L/h)			Vd/F (L)		
	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
Total Plasma	6.20	4.74	76	2.83	1.47	52	2.02	1.32	66	18.54	7.72	42	36.19	11.64	32	109.16	85.72	79
Free Plasma	3.40	2.86	84	--	--	--	--	--	--	10.01	4.81	48	--	--	--	--	--	--
Tissue	2.73	1.44	53	3.00	1.26	42	1.79	1.15	64	8.60	2.88	33	--	--	--	--	--	--

CONCLUSIONS

- Microdialysis is a powerful tool for determination of antibacterial pharmacokinetics in tissues.
- Tebipenem pivoxil HBr dose of 600 mg orally every 8 hours was well tolerated in patients with DFI with no reported serious adverse events.
- This study demonstrated excellent tebipenem distribution in the interstitial fluid of patients with DFI as demonstrated by comparable $AUC_{0\text{-}24}$ in free plasma and tissue.

ACKNOWLEDGMENTS

Funding provided by Spero Therapeutics (Cambridge, MA) from the investigator-initiated research program. We acknowledge Lee Steere for his assistance with the conduct of this study.

REFERENCES

1. Jain A, et al: Tebipenem, the first oral carbapenem antibiotic. *Expert Rev Anti Infect Ther*. **2018**;16(7):513-522.
2. Lipsky BA, et al: 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. **2012**; 54(12):e132-73.
3. Abouelhassan Y, et al. Pharmacokinetics and Soft-Tissue Distribution of Tebipenem in Healthy Volunteers using in vivo Microdialysis. Oral Abstract. Session AAR-05. *ASM Microbe* **2022**, Washington DC.