Characterization of Tebipenem Pivoxil Hydrobromide Pharmacokinetics-Pharmacodynamics in a Neutropenic Murine Acute Pyelonephritis Model

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INTRODUCTION

- Tebipenem pivoxil hydrobromide (tebipenem hydrobromide [HBr]), an orally (PO) bioavailable prodrug of tebipenem, is a carbapenem with broad-spectrum activity against Gram-positive and -negative bacteria that is being developed for the treatment of patients with complicated urinary tract infections, including acute pyelonephritis.
- Data from a previously-completed one-compartment *in vitro* infection model demonstrated that the ratio of free-drug plasma area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) adjusted for dosing interval tau (τ) [AUC:MIC ratio•1/τ] was the pharmacokinetic-pharmacodynamic (PK-PD) index most associated with tebipenem HBr efficacy [1].
- As described herein, studies were undertaken to characterize the magnitude of tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ associated with efficacy for Enterobacterales using a neutropenic murine acute pyelonephritis model.

OBJECTIVES

- The objectives of the series of *in vivo* studies undertaken were the following:
  - To evaluate the pharmacokinetics of tebipenem in mice with acute pyelonephritis following oral administration of SPR994;
  - To carry out dose-ranging studies to evaluate the inter-isolate variability associated with the efficacy of tebipenem and;
  - To evaluate the relationship between change in $\log_{10}$ colony forming units (CFU)/g of kidney tissue from baseline and free-drug plasma AUC:MIC ratio•1/τ and using this relationship, calculate the magnitude of AUC:MIC ratio•1/τ associated with achieving various bacterial reduction endpoints.

METHODS

Antimicrobial Agent and Challenge Isolates

- Tebipenem was provided by Spero Therapeutics (Cambridge, MA).
- A panel of seven Enterobacterales isolates was supplied from the American Type Culture Collection (ATCC), National Collection of Type Cultures (NCTC) and JMI Laboratories (North Liberty, IA).

In Vitro Susceptibility Testing

- In accordance with Clinical Laboratory Standards Institute (CLSI) guidelines [2], susceptibility studies were completed in triplicate over a two-day period to determine the tebipenem, meropenem, ertapenem, levofloxacin and fosfomycin minimum inhibitory concentration (MIC) values associated with each Enterobacterales isolate in the challenge isolate panel.

METHODS

Neutropenic Murine Acute Pyelonephritis Model

- All animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals [3] and all animal procedures described herein were completed following ICPD protocols approved by an Institutional Animal Care and Use Committee (IACUC).
- Female Outbred Swiss Webster mice weighing 23 to 27 g were made neutropenic following two intraperitoneal injections of cyclophosphamide (150 mg/kg on Day -4, and 100 mg/kg on Day -1).
- On Day 0, all animals were anesthetized and inoculated with bacteria suspensions via intrarenal injection to achieve an initial burden of 1.0 x 10^4 CFU/g per kidney.
- At the point of sacrifice, both kidneys were harvested, pooled, homogenized, and serially diluted for enumeration of bacterial burden.

Single-Dose Pharmacokinetic Study

- A single-dose pharmacokinetic (PK) study was completed in neutropenic mice infected with 1.0 x 10^4 CFU/kidney of *Escherichia coli* NCTC 13441.
- Plasma samples were collected at 0.25, 0.5, 1, 2, 4, 6, and 8 hours post-treatment initiation of four different tebipenem HBr regimens (1, 15, 45, and 100 mg/kg) administered as a single dose.

Multiple Isolate Dose-Ranging Studies

- Dose-ranging studies to evaluate tebipenem efficacy were completed using the panel of seven Enterobacterales isolates (tebipenem MIC values of 0.015 to 0.5 mg/L).
- Mice were infected with 10^4 CFU/g per kidney via intrarenal injection. Two hours post-infection, 8 total daily tebipenem HBr doses (0.3 to 135 mg/kg) were fractionated into regimens administered every 8 hours.

Analysis of Tebipenem Pharmacokinetics-Pharmacodynamics

- Plasma concentrations were determined using liquid chromatography –tandem mass spectrometry.
- All observed concentration-time data from the murine pyelonephritis plasma PK study was analyzed using non-compartmental methods to estimate the free-drug plasma AUC over 24 hours.
- A Hill-type model and non-linear least squares regression were used to evaluate the relationship between change in $\log_{10}$ CFU/g of kidney tissue from baseline at 24 hours and free-drug plasma AUC:MIC ratio•1/τ.
  - The magnitude of free-drug plasma AUC:MIC ratio•1/τ associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU/g reductions from baseline at 24 hours was determined.

RESULTS

In Vitro Susceptibility Testing

- Results of *in vitro* susceptibility testing and known resistance mechanisms for the isolates evaluated using the neutropenic murine acute pyelonephritis model are provided in **Table 1**.

Table 1. Results of *in vitro* susceptibility testing and summary of known resistance mechanisms for seven Enterobacteriaceae isolates evaluated using a neutropenic murine acute pyelonephritis model

Isolate	Known Resistance Mechanisms	Modal MIC Value (mg/L)				
		Tebipenem	Meropenem	Ertapenem	Levofloxacin	Fosfomycin[a]
E. coli NCTC 13441	CTX-M-15 (ST-131)	0.015	0.03	0.03	>8	1
E. coli 845741	CTX-M-15, OXA-1, SHV-12, (ST-131)	0.03	0.03	0.03	>8	1
E. coli 992013	CTX-M-27, TEM-1 (ST-131)	0.015	0.03	0.008	>8	0.5
E. coli 998822	CTX-M-15, OXA-1, OXA-30 (ST-131)	0.03	0.03	0.015	>8	256
E. coli ATCC BAA-2523	OXA-48	0.5	0.5	2	0.25	2
K. pneumoniae ATCC 43816	Wild type reference strain	0.015	0.03	0.015	0.06	8
K. pneumoniae 934954	CTX-M-15, OXA-1, SHV-28, TEM-1	0.125	0.25	0.5	>8	16

a. Fosfomycin MIC values determined using agar dilution methodologies as per CLSI protocols [2].

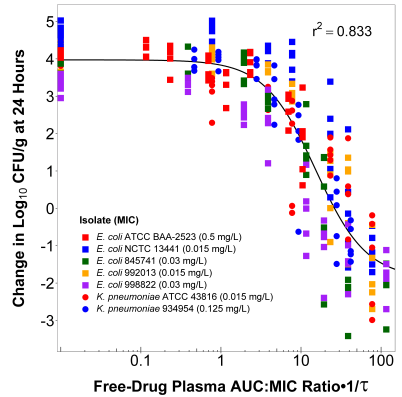
Analysis of Tebipenem Pharmacokinetics-Pharmacodynamics

- The relationship between change in $\log_{10}$ CFU/g of kidney tissue from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ described the data well as evidenced by an r^2 value of 0.833 (**Figure 1**).
  - The magnitude of free-drug plasma AUC:MIC ratio•1/τ associated with net bacterial stasis and a 1-$\log_{10}$ CFU/g reduction from baseline at 24 hours was 26.2 and 54.1, respectively.
  - A 2-$\log_{10}$ CFU/g reduction from baseline was not achieved.

CONCLUSIONS

- The data from dose-ranging studies using conducted a neutropenic murine acute pyelonephritis model were well described by the relationship between change in $\log_{10}$ CFU/g of kidney tissue from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ.
- The magnitude of tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ associated with net bacterial stasis and a 1-$\log_{10}$ CFU/g reduction from baseline at 24 hours was 26.2 and 54.1, respectively.
- These data will be useful to support tebipenem HBr dose selection for clinical studies in patients with acute pyelonephritis.

Figure 1. Relationship between change in $\log_{10}$ CFU/g of kidney tissue from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•1/τ based on data from a panel of seven Enterobacterales isolates evaluated in the dose-ranging studies conducted using a neutropenic murine acute pyelonephritis model



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