Characterization of Sulopenem Pharmacokinetics-Pharmacodynamics Using a One-Compartment *In Vitro* Infection Model

Brian D. VanScoy, B.S.
Institute for Clinical Pharmacodynamics, Inc.
242 Broadway
Schenectady, NY 12305
Telephone: (518) 631-8100
Fax: (518) 631-8199
E-mail: BVanscoy@ICPD.com

B.D. VanScoy[1], S. Jones[1], H. Conde[1], C.E. Vincent[1], S.M. Bhavnani[1], C.M. Rubino[1], S.I. Aronin[2], S. Puttagunta[2], P.G. Ambrose[1]
[1]Institute for Clinical Pharmacodynamics, Inc., Schenectady, NY; [2]Iterum Therapeutics, Old Saybrook, CT

INTRODUCTION

- Sulopenem etzadroxil, the oral prodrug of the active moiety sulopenem is a thiopenem with activity against drug-resistant pathogens known to cause uncomplicated urinary tract infections.
- Oral sulopenem is a bilayer tablet composed of sulopenem etzadroxil and probenecid, an organic anion transport inhibitor that delays renal excretion of sulopenem.
- The goal of the studies described herein was to characterize the pharmacokinetics-pharmacodynamics (PK-PD) of sulopenem against a diverse panel of Enterobacterales using a one-compartment *in vitro* model. Specific objectives included the following:
  - To carry out dose-fractionation studies in order to identify the PK-PD index most associated with efficacy of sulopenem against Enterobacterales; and
  - To carry out dose-ranging studies to determine the magnitude of the PK-PD index most associated with efficacy that is required for various levels of bacterial reduction for a panel of Enterobacterales isolates.

METHODS

Antimicrobial Agent and Challenge Isolates

- Sulopenem was provided by Iterum Therapeutics (Old Saybrook, CT).
- A panel of 10 Enterobacterales isolates were supplied from the 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 [1], susceptibility studies were completed in triplicate over a two-day period to determine the sulopenem minimum inhibitory concentration (MIC) associated with each Enterobacterales isolate in the challenge panel.

One-Compartment *In Vitro* Infection Model Dose-Fractionation Studies

- A series of 24-hour dose-fractionation studies were completed to identify the PK-PD index associated with sulopenem efficacy using a single *Escherichia coli* isolate (NCTC 13441).
- Bacteria (1 x 10^6 colony forming units [CFU]/mL) were exposed to sulopenem concentrations that mimicked human healthy volunteer free-drug plasma concentration-time profiles (protein binding of 10.7%, T_{max} = 2 hours and a $t_{1/2}$ of 1.18 hours) following oral drug administration.
- Five sulopenem total daily dose levels (representing plasma concentrations linearly scaled from the 500 mg q12h regimen) were fractionated in equal divided doses administered every 4, 8, or 12 hours (q4h, q8h, and q12h, respectively).
- Samples were collected for the evaluation of pharmacokinetic (PK) profiles via qualified liquid chromatography tandem mass-spectrometry (LC-MS/MS), and enumeration of bacterial burden over the course of the study.

One-Compartment *In Vitro* Infection Model Dose-Ranging Studies

- In the dose-ranging studies, 10 clinically relevant Enterobacterales isolates were exposed to sulopenem q12h regimens simulating the percent of time over 24 hours that sulopenem free-drug concentrations were above the MIC (free-drug %T>MIC) values ranging from 0 to 98.8%.

Pharmacokinetic-Pharmacodynamic Analysis

- A one-compartment population PK model was fit to the observed concentration-time data collected from the dose-fractionation studies in order to estimate clearance and volume of distribution.

METHODS

Pharmacokinetic-Pharmacodynamic Analysis (Continued)

- The population mean fitted values for CL and V were then used to estimate the relevant PK exposure measures, free-drug area under the concentration time curve over 24 hours (free-drug $AUC_{0\text{-}24}$), maximum free-drug concentration (free-drug C_{max}), and free-drug %T>MIC.
- Data from the dose-fractionation were evaluated using Hill-type models and non-linear least squares regression. Relationships between change in $\log_{10}$ CFU/mL from baseline at 24 hours and each of the following sulopenem PK-PD indices were characterized:
  - Free-drug C_{max} to MIC ratio (C_{max}:MIC ratio), %T>MIC, and ratio of the area under the concentration time curve to MIC (AUC:MIC ratio).
- Hill-type models and non-linear least squares regression were also used to evaluate the data from the dose-ranging studies. Using the sulopenem PK-PD index most associated with efficacy based on the results of the dose-fractionation studies, the magnitude of this PK-PD index associated with various levels of bacterial reduction based on data from the dose-ranging studies was also determined.

RESULTS

In Vitro Susceptibility Testing

- Known resistance mechanisms, sequence types and sulopenem MIC values for isolates evaluated in the one-compartment *in vitro* infection model are provided in **Table 1**.
  - Sulopenem MIC values ranged from 0.03 to 0.125 mg/L for the *E. coli* isolates and 0.25 to 0.5 mg/L for the *K. pneumoniae* isolates evaluated.

Table 1. Sulopenem MIC values, known resistance mechanisms and sequence types for the isolates evaluated in the one-compartment *in vitro* infection model dose-fractionation and dose-ranging studies

Isolate	Known resistance mechanisms (Sequence Type)	Sulopenem MIC (mg/L)
E. coli NCTC 13441[a]	CTX-M-15, (ST-131)	0.125
E. coli 1031823	CTX-M-14, TEM-1 (ST-131, O25b)	0.06
E. coli 13319	CTX-M-15, TEM-1	0.125
E. coli 845741	CTX-M-15, OXA-1, SHV-12, (ST-131, O25b)	0.06
E. coli 992004	CTX-M-27, TEM-1 (ST-131, O25b)	0.06
E. coli 992013	CTX-M-27, TEM-1 (ST-131, O25b)	0.03
K. pneumoniae 934954	CTX-M-15, OXA-1, SHV-28, TEM-1	0.25
K. pneumoniae 2674	CTX-M-15	0.5
K. pneumoniae 53578	SHV-12, TEM-1	0.25
K. pneumoniae 865-604	CTX-M-15, OXA1/30, SHV-1	0.5

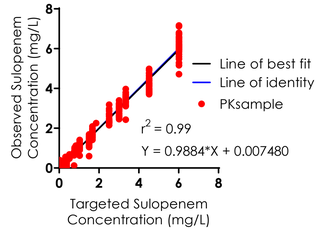
a. Isolate utilized for the dose-fractionation studies.

One-Compartment *In Vitro* Infection Model Studies

- As evidenced by the agreement between targeted and observed sulopenem concentrations shown in **Figure 1**, the targeted free-drug plasma concentration-time profiles were well simulated in the *in vitro* model and the fitted concentration-time profiles from the population PK models captured the observed PK data adequately (data not shown).

RESULTS

Figure 1. Relationship between all targeted and observed sulopenem concentrations simulated in the one-compartment *in vitro* infection model



One-Compartment *In Vitro* Infection Model Dose-Fractionation Studies

- The data from the dose-fractionation studies was pooled and the relationships between change in $\log_{10}$ CFU/mL from baseline at 24 hours and the sulopenem free-drug AUC:MIC ratio, C_{max}:MIC ratio and %T>MIC were evaluated.
- As observed by the high r^2 = 0.90, indicating the least scatter of data about the fitted line, free-drug %T>MIC best describes the PK-PD of sulopenem (**Figure 2**).

Figure 2. Relationships between change in $\log_{10}$ CFU/mL from baseline at 24 hours and each of sulopenem free-drug AUC:MIC ratio, C_{max}:MIC ratio, and %T>MIC based on data for *E. coli* NCTC 13441 evaluated in dose-fractionation studies conducted using a one-compartment *in vitro* infection model

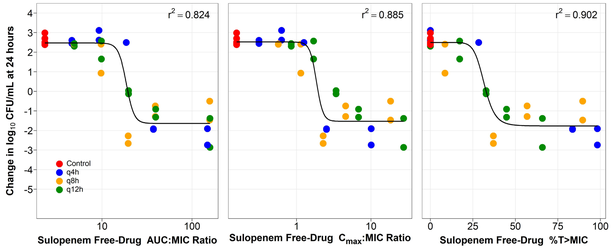


Table 2. Summary of sulopenem free-drug %T>MIC associated with various levels of bacterial reduction endpoints determined from the Hill-type models evaluating the relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and free-drug %T>MIC for the isolates evaluated in the dose-ranging studies

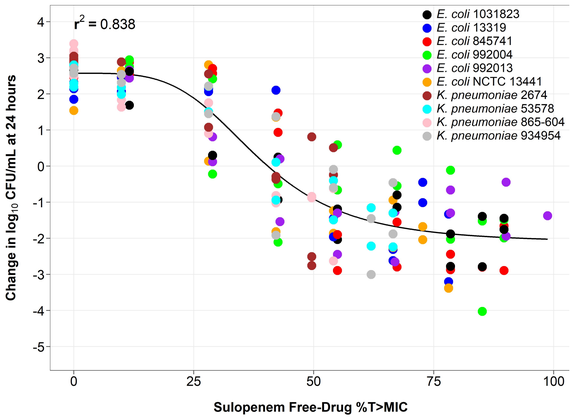
Enterobacterales Isolate	Sulopenem Free-Drug %T>MIC			
	r^2	Net bacterial stasis	1-$\log_{10}$ CFU reduction	2-$\log_{10}$ CFU reduction
E. coli 13319	0.93	48.2	50.2	N/A
E. coli NCTC 13441	0.87	41.3	52.6	65.8
E. coli 845741	0.97	43.3	43.9	45.0
E. coli 992004	0.76	42.2	62.7	N/A
E. coli 992013	0.91	32.0	42.7	N/A
E. coli 1031823	0.94	33.7	50.2	93.2
K. pneumoniae 865-604	0.94	36.8	48.3	59.4
K. pneumoniae 2674	0.79	36.0	N/A	N/A
K. pneumoniae 53578	0.94	40.4	49.4	N/A
K. pneumoniae 934954	0.83	42.2	53.7	N/A
Pooled Enterobacterales	0.84	40.4	51.3	93.5
Mean		39.6	50.4	65.9
Median		40.9	50.2	62.6

RESULTS

One-Compartment *In Vitro* Infection Model Dose-Ranging Studies

- The relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and sulopenem free-drug %T>MIC based on data from the dose-ranging studies is shown in **Figure 3**.
- As shown in **Table 2**, the median free-drug %T>MIC associated with achieving net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline, which was determined from the Hill-type models evaluating the PK-PD relationships for each of the 10 Enterobacterales isolates, was 40.9, 50.2, and 62.6%, respectively.

Figure 3. Relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and sulopenem free-drug %T>MIC based on data from a panel of 10 Enterobacterales isolates evaluated in the dose-ranging studies conducted using a one-compartment *in vitro* infection model



CONCLUSIONS

- The 24-hour dose-fractionation studies that were completed using a one-compartment *in vitro* infection model allowed for the evaluation of the PK-PD for sulopenem.
  - The relationship between change in bacterial burden from baseline over 24 hours and sulopenem free-drug %T>MIC best described the activity of sulopenem.
- The median free-drug %T>MIC associated with achieving net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline based on data from the dose-ranging studies was 40.9, 50.2, and 62.6, respectively.

REFERENCES

1. Clinical Laboratory Standards Institute. Methods for Dilutional Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 11th edition. CLSI standard M07; Wayne, PA; 2018.

ACKNOWLEDGEMENTS

This project was completed with support from Iterum Therapeutics, Old Saybrook, CT.