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Post-Antibiotic and Sub-Inhibitory Minimum Inhibitory Concentration Effects of Sulopenem

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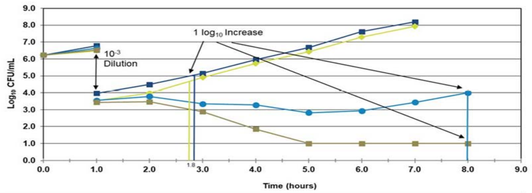
ABSTRACT

Background: Sulopenem is an oral and intravenous thiopenem antibacterial being developed for the treatment of urinary tract and intra-abdominal infections caused by multidrug-resistant pathogens. Carbapenems are known to have an *in vitro* post-antibiotic effect (PAE) and sub-inhibitory minimum inhibitory concentration (MIC) effects (PAE-SME). The objective of this study was to evaluate the *in vitro* PAE and PAE-SME of sulopenem.
Materials/methods: *In vitro* time-kill assays against 4 *Escherichia coli* and 2 *Klebsiella pneumoniae* isolates were used to determine PAE and PAE-SME of sulopenem and ertapenem. Reference broth microdilution susceptibility testing was conducted according to Clinical and Laboratory Standards Institute (CLSI; M07, 2018) guidelines using cation-adjusted Mueller-Hinton broth. Quality control ranges for *E. coli* ATCC 25922 and interpretive criteria for sulopenem and ertapenem were as published in CLSI M100 (2018).
For PAE testing, the isolates were exposed to sulopenem or ertapenem at 1x, 5x, and 10x the modal MIC value for a period of 1 hour (h). For PAE-SME testing, only the initial 5x antibacterial concentration was used, followed by removal of the antibacterial via dilution (1:1000) and reintroducing sub-inhibitory (¼x MIC and ½x MIC) concentrations.
Results: A prolonged PAE-SME of >5.2 h was obtained for sulopenem against all the isolates tested following a 1h exposure to sulopenem at 5x the MIC followed by sub-inhibitory concentration testing at ½x the sulopenem MIC. PAE-SMEs (0.9 h to >5.2 h) were obtained using ¼x the sulopenem MIC. No significant PAEs were obtained with either sulopenem or ertapenem against the isolates when tested at up to 10x the MIC.
Figure. *E. coli* #937254 PAE-SME after 1h exposure to sulopenem at 5x MIC followed by sub-MIC exposures (sulopenem MIC, 0.12 µg/mL).



	M – C = PAE-SME
Sulopenem 5x MIC + 1/4x MIC (0.03 µg/mL)	7.0 – 1.8 = >5.2 h
Sulopenem 5x MIC + 1/2x MIC (0.06 µg/mL)	7.0 – 1.8 = >5.2 h

Conclusions: Sulopenem, as described for other penems, exhibited a sub-MIC effect after brief exposure of bacteria to concentrations at multiples above the MIC, reflecting a potential concentration effect. Inclusion of a sub-MIC effect may be worth considering in any PK/PD modeling designed to guide dose selection.

INTRODUCTION

- The Post Antibiotic Effect (PAE) refers to the persistent suppression of bacterial growth after a brief exposure of bacteria to an antibiotic.
- A PAE sub-MIC effect (PAE-SME) refers to suppression of growth after brief antibiotic exposures at or above the MIC followed by subsequent exposure at concentrations lower than the MIC.
- PAE and PAE-SME may be additional factors that contribute to the antimicrobial effect of an antibiotic during the dosing interval.
- Sulopenem is a thiopenem antibiotic with an intravenous and oral formulation being developed for the treatment of urinary tract and intra-abdominal infections caused by multi-drug resistant Enterobacteriaceae.

METHODS

- *In vitro* time-kill assays against 4 *Escherichia coli* and 2 *Klebsiella pneumoniae* isolates were used to determine PAE and PAE-SME of sulopenem and ertapenem.
- Reference broth microdilution susceptibility testing was conducted according to Clinical and Laboratory Standards Institute (CLSI; M07, 2018) guidelines using cation-adjusted Mueller-Hinton broth.
- Quality control ranges for *E. coli* ATCC 25922 and interpretive criteria for sulopenem and ertapenem were as published in CLSI M100 (2018).
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RESULTS

Figure 1 *Escherichia coli* ATCC 25922 PAE after 1-hr exposure to sulopenem at 1x, 5x, and 10x MIC

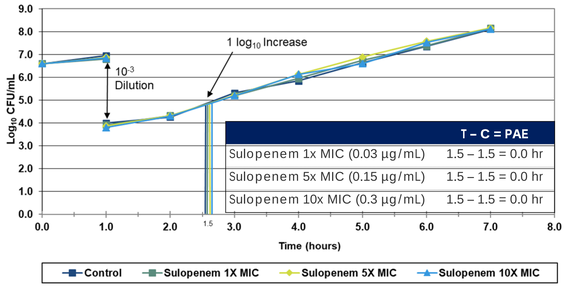
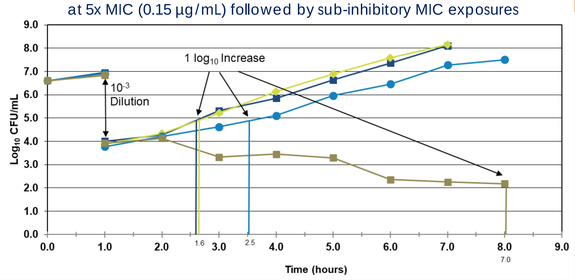


Figure 2 *Escherichia coli* ATCC 25922 PAE-SME after 1-hr exposure to sulopenem at 5x MIC (0.15 µg/mL) followed by sub-inhibitory MIC exposures



	M – C = PAE-SME
Sulopenem 5x MIC + 1/4x MIC (0.008 µg/mL)	2.5 – 1.6 = 0.9 hr
Sulopenem 5x MIC + 1/2x MIC (0.016 µg/mL)	7 – 1.6 = >5.4 hr

RESULTS

Figure 3 *Klebsiella pneumoniae* #396798 PAE after 1-hr exposure to sulopenem at 1x, 5x, and 10x MIC

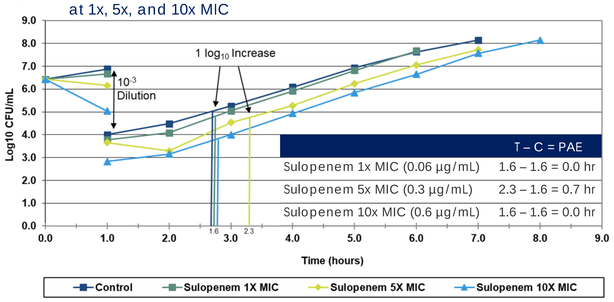
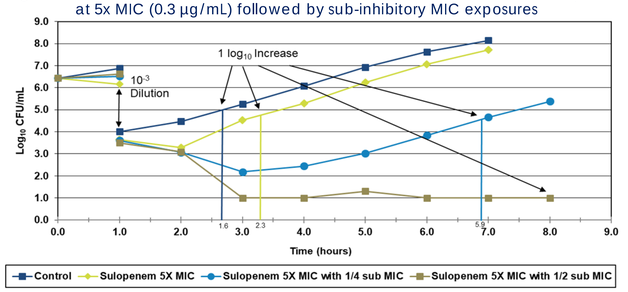


Figure 4. *Klebsiella pneumoniae* #396798 PAE-SME after 1-hr exposure to sulopenem at 5x MIC (0.3 µg/mL) followed by sub-inhibitory MIC exposures



	M – C = PAE-SME
Sulopenem 5x MIC + 1/4x MIC (0.016 µg/mL)	5.9 – 1.6 = 4.3 hr
Sulopenem 5x MIC + 1/2x MIC (0.03 µg/mL)	7.0 – 1.6 = >5.4 hr

Table 1. Sulopenem and ertapenem MIC values tested against the organisms included in this study

Organism	No. of occurrences at MIC (µg/mL) of:								
Antimicrobial (no. of tests)	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	> 0.5
***Escherichia coli* ATCC 25922**									
Sulopenem (3)			0	**3**					
Ertapenem (3)	0	**3**							
***E. coli* ATCC 35218**									
Sulopenem (3)			0	**3**					
Ertapenem (3)	0	**3**							
***E. coli* NCTC 13353**									
Sulopenem (3)				0	**3**				
Ertapenem (3)					0	**3**			
***E. coli* #937054**									
Sulopenem (3)					0	**3**			
Ertapenem (3)						0	**3**		
***K. pneumoniae* ATCC 700603**									
Sulopenem (3)						**2**		1	
Ertapenem (3)				0	**3**				
***K. pneumoniae* #396798**									
Sulopenem (3)				0	**3**				
Ertapenem (3)						0	**3**		

Figure 5. *Klebsiella pneumoniae* #396798 PAE after 1-hr exposure to ertapenem at 1x, 5x, and 10x MIC

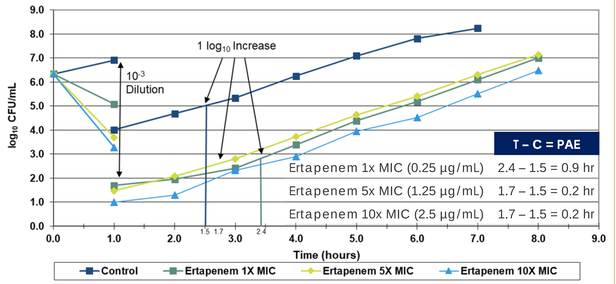
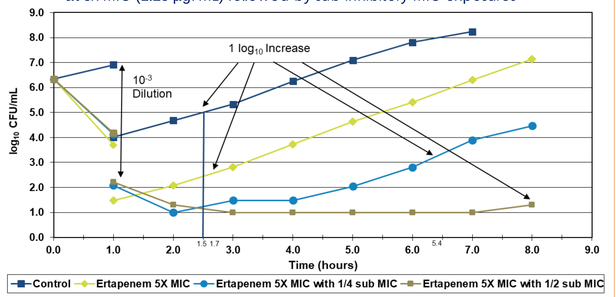


Figure 6. *Klebsiella pneumoniae* #396798 PAE-SME after 1-hr exposure to ertapenem at 5x MIC (1.25 µg/mL) followed by sub-inhibitory MIC exposures



	M – C = PAE-SME
Ertapenem 5x MIC + 1/4x MIC (0.06 µg/mL)	5.4 – 1.7 = 3.7 hr
Ertapenem 5x MIC + 1/2x MIC (0.12 µg/mL)	7.0 – 1.7 = >5.3 hr

CONCLUSIONS

- Sulopenem and ertapenem, as described for other penems, exhibited a post antibiotic subMIC effect
- This PAE-SME implies a potential concentration effect
- Sulopenem may be active for a longer period of the dosing interval than is defined by the Time over MIC
- The PAE-SME may be worth considering in any PK/PD modeling designed to guide dose selection

29th European Congress of Clinical Microbiology and Infectious Diseases; April 13–16, 2019; Amsterdam, Netherlands

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