RESULTS

Methods: In vitro time-kill assays against 4 Escherichia coli and 2 Klebsiella pneumoniae isolates were used to determine PAE and PAE-SMEs 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 established in CLSI M100 (2018).

For PAE testing, the isolates were exposed to sulopenem or ertapenem at 1x, 5x, and 10x MIC values for a period of 1 hour (h). For PAE-SME testing, only the first 5x antibiotic concentration was used, followed by removal of the antibacterial via dilution (1:1000) and reintroducing sub-inhibitory (1x MIC) concentrations.

In vitro susceptibility testing at ½x the sulopenem MIC. PAE-SMEs (0.9 ± 0.12 µg/mL) were obtained using 1/10x the sulopenem MIC (0.12 µg/mL) followed by sub-inhibitory MIC exposures (0.12 µg/mL).

Results: A prolonged PAE of >5.2 h was obtained for sulopenem against all isolates tested following a 1h exposure to sulopenem at 5x the MIC followed by sub-MIC exposures (0.06 µg/mL).

For PAE-SME testing, only the first 5x antibacterial concentration was used, followed by removal of the antibacterial via dilution (1:1000) and reintroducing sub-inhibitory (1x MIC) concentrations. Inclusion of a sub-MIC effect was considered for other penems, exhibiting a sub-MIC effect after brief exposure of bacteria to concentrations at multiples above the MIC.

Conclusions: 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.