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In Vitro Activity of Tebipenem (SPR859), Tebipenem-Pivoxil (SPR994) and Meropenem Against a Broad Spectrum of Anaerobic Bacteria

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ABSTRACT

Background: Carbapenems are potent antibacterial agents with broad spectrum activity. SPR994 is tebipenem-pivoxil, an orally available carbapenem with activity against extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae. SPR859 is the microbiologically active form of tebipenem-pivoxil prodrug SPR994. To further define the spectrum of activity, we performed susceptibility testing on a broad spectrum of 189 strains of anaerobic bacteria.
Methods: Isolates were recovered from clinical infections of patients and stored as pure cultures in 20% skim milk at -70 °C. Prior to testing, isolates were transferred to *Brucella* agar supplemented with sheep blood, vitamin K and hemin to ensure purity and good growth. Agar dilution testing was performed according to procedures described in CLSI M11-A8. On the day of the testing, isolates were suspended in *Brucella* broth to the turbidity of the 0.5 McFarland standard and applied to the drug plates for a final concentration of ~10^5 CFU/spot. The plates were incubated in the anaerobic chamber at 36° C for 44 h before examining for growth. The MIC was the concentration that resulted in no growth or a marked reduction in growth compared to the drug-free control. Meropenem (MEM) and metronidazole (MTZ) were included for comparison.
Results: MICs for SPR859 and SPR994 were similar to that of MEM. QC results were within the acceptable ranges for all strains.
Conclusion: SPR859 and SPR994 were active against a broad spectrum of anaerobic bacteria, with activity similar to MEM. Even though there may be an effect on the viability of common anaerobic bacteria in the gut, SPR859 and SPR994 were also active against *C. dificile*, similar to MEM.

INTRODUCTION

- Carbapenems are potent antibacterial agents with broad spectrum activity.
- SPR994 is tebipenem-pivoxil, an orally available carbapenem with activity against extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae.
- SPR859 is the microbiologically active form of tebipenem-pivoxil prodrug SPR994.
- Use of antibiotics have been known to impact the anaerobic bacteria in the gut and dysbiosis can lead to *Clostridium difficile* infections.
- As part of the characterization of this combination, we examined the *in vitro* activity against a selection of anaerobic bacteria.

METHODS

- Isolates were recovered from clinical infections of patients and stored as pure cultures in 20% skim milk at -70° C.
- Prior to testing, isolates were transferred to *Brucella* agar supplemented with sheep blood, vitamin K and hemin to ensure purity and good growth.
- Agar dilution testing was performed according to procedures described in CLSI M11-A8.
- Meropenem (MEM) and metronidazole (MTZ) were included for QC and comparison.

RESULTS

Table 1. Agar MIC_{90} of SPR859, SPR994, MEM, and MTZ *vs.* 191 Anaerobic Clinical Isolates

Genus or Organisms Tested	N	$MIC_{50/90}$ (mg/L)			
		SPR859	SPR994	MEM	MTZ
***Bacteroides* sp.**	25	0.5 / 2	1 / 4	0.25 / 0.5	1 / 1
***Fusobacterium* spp.**	10	≤0.015	≤0.015 / 0.06	≤0.03 / 0.125	≤0.06 / 0.25
***Porphyromonas* spp.**	10	0.03 / 0.06	0.06	≤0.03 / 0.06	0.25 / 1
***Prevotella* spp.**	30	0.125 / 0.25	0.25	0.06 / 0.125	0.5 / 2
Anaerobic Gram-positive rods	38	0.06 / 1	0.125 / 4	0.25 / 8	2 / >16
***Clostridium* spp.**	48	0.5 / 2	1 / 4	0.25 / 2	0.5 / 2
Anaerobic Gram-positive cocci	24	0.06 / 0.25	0.125 / 0.25	0.06 / 0.25	0.25 / 1

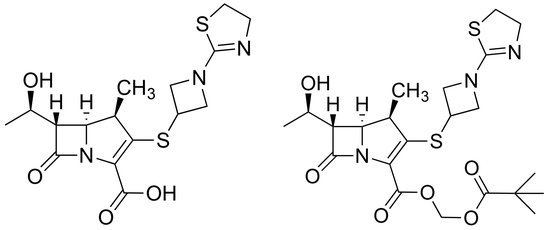
- MIC_{90} values for SPR859 and SPR994 against most strains were similar to MEM.

Table 2. Agar MIC of SPR859, SPR994 and MTZ *vs. C. dificile*

C. dificile Strain #	MIC (mg/L)		
	SPR859	SPR994	MTZ
28843	2	4	0.5
28844	2	2	0.5
28845	2	4	0.5
28846	2	4	0.25
28847	2	4	0.5
28848	2	2	0.25
28849	2	4	0.5
28850	2	4	0.5
28851	2	4	0.5
28852	2	4	0.5

- MIC values for SPR859 and SPR994 were less potent than MTZ against *C. dificile* strains tested
- MIC values for SPR859 and SPR994 were similar to MEM (as obtained in previous studies[2])

Figure 1. Structure of SPR859 and SPR994.



SPR859 / Tebipenem SPR994 / Tebipenem-pivoxil

CONCLUSIONS

- SPR859 and SPR994 were active against a broad spectrum of anaerobic bacteria, with activity similar to MEM.
- Although SPR859 and SPR994 exhibits broad spectrum activity against anaerobes, activity against *C. difficile* may prevent overgrowth in the GI tract
- Further clinical trials will determine if oral dosing would result in significant concentrations in the gut and subsequent impact on gut microflora.

REFERENCES

1. Clinical and Laboratory Standards Institute (2012) M11-A8
2. Goldstein *et al.* (2013) AAC 57(6): 2620-2630