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Evaluation of Gepotidacin Activity when Combined with Select Antimicrobial Agents and Tested Against Bacterial Isolates Using Checkerboard Methodology

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– **This study at JMI Laboratories was supported by GlaxoSmithKline. JMI Laboratories received compensation fees for services in relation to preparing the poster.**

Introduction and Methods

– Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in clinical development for the treatment of uncomplicated UTI (acute cystitis) and urogenital gonorrhea. This study evaluated combinations of gepotidacin and other antimicrobial agents for synergistic or antagonistic activity.

Study Design

– 5 isolates from each of the following species were evaluated:
  – *S. saprophyticus*, *E. faecalis*, *E. coli*, *C. freundii*, *E. cloacae* species complex, *K. aerogenes*, *K. pneumoniae*, *P. mirabilis*, and *P. rettgeri*
– Interactions between gepotidacin and 10 marketed antibiotics were studied by checkerboard broth microdilution method.
  – azithromycin, ceftazidime, levofloxacin, nitrofurantoin, tetracycline, trimethoprim/sulfamethoxazole, aztreonam, meropenem, linezolid, and vancomycin
– Minimum and maximum fractional inhibitory concentration (ΣFIC) values were calculated for each combination.
  – ΣFICs ≤0.5 : Synergy.
  – ΣFICs >0.5 – 4 : Indifference.
  – ΣFICs >4: Antagonism.
  – Indeterminate was assigned when combination effects could not be determined.

Results and Conclusions

- Gepotidacin showed no antagonism in any combination.
- While synergy was observed for gepotidacin combined with select comparators against select species, the only combination to display consistent syngergy was gepotidacin and vancomycin and only against *S. saprophyticus*.
- When gepotidacin was combined with vancomycin against *S. saprophyticus*:
  - 4 of 5 isolates had a ΣFICmin ≤0.25 to 0.31.
  - Time-kills showed gepotidacin/vancomycin synergy for all 5 *S. saprophyticus* isolates.
- *E. faecalis* was the only organism for which no synergy was observed.

Summary of activity of gepotidacin and comparators when tested in combination

	No. of instances by interpretive category (% of total)		
Combination agent	SYNERGY	INDIFFERENCE or INDETERMINANT	ANTAGONISM
Azithromycin	2 (4.4)	43 (95.6)	0 (0.0)
Ceftazidime	5 (11.1)	40 (88.9)	0 (0.0)
Levofloxacin	1 (2.2)	44 (97.8)	0 (0.0)
Nitrofurantoin	1 (2.2)	44 (97.8)	0 (0.0)
Tetracycline	1 (2.2)	44 (97.8)	0 (0.0)
Trimethoprim/sulfamethoxazole	2 (4.4)	43 (95.6)	0 (0.0)
Aztreonam [a]	4 (11.4)	31 (88.6)	0 (0.0)
Meropenem [a]	5 (14.3)	30 (85.7)	0 (0.0)
Linezolid [b]	0 (0.0)	10 (100.0)	0 (0.0)
Vancomycin [b]	4 (40.0)	6 (60.0)	0 (0.0)

[a] Aztreonam and meropenem were only tested against Gram-negative isolates.
[b] Linezolid and vancomycin were only tested against Gram-positive isolates.

For full poster see last slide

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Introduction

Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in Phase 3 clinical development for the treatment of gonorrhea and uncomplicated urinary tract infections (uUTIs).

Gepotidacin inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism.

The objective of this study was to evaluate synergy / indifference / antagonism interactions between gepotidacin and select antimicrobial agents using reference *in vitro* broth microdilution checkerboards.

Materials and Methods

Recent clinical isolates (2019) of *Citrobacter* species, *E. cloacae* species complex, *E. coli*, *K. aerogenes*, *K. pneumoniae*, *P. mirabilis*, *P. rettgeri*, *E. faecalis*, and *S. saprophyticus* (5 isolates per species) were tested.

BMD panels were prepared according to methods described in the Clinical Microbiology Procedure Handbook, 4th Edition, 2016, Chapter 5.16.

Minimum and maximum fractional inhibitory concentration (ΣFIC) values were calculated for each combination to assess interactions.

- ΣFICs ≤0.5: Synergy
- ΣFICs >0.5 – 4: Indifference
- ΣFICs >4: Antagonism
- Indeterminate was assigned when combination effects could not be determined.

Follow-up time-kill kinetic studies were carried out for or all compound combinations where synergy was observed (FICs ≤ 0.5) among 50% of isolates within a species.

Each organism was tested in media containing either compound or both at 1/2X, 1/4X, and 1X their respective MICs.

Time-kill concentration tubes were sampled and CFUs determined at time 0 hours (T0), T2, T4, T8, and T24.

Disclosures

This study at JMI Laboratories was supported by GlaxoSmithKline. JMI Laboratories received compensation fees for services in relation to preparing the poster.

No instances of antagonism were observed.

Combinations of gepotidacin with β-lactam agents resulted in the most instances of synergy among gram-negative isolates.

Among the gram-positive isolates, the only synergy observed was with gepotidacin/vancomycin against *S. saprophyticus*.

Table 1 Indifferences and synergies observed for gepotidacin plus comparator combinations

Codrug Interpretation	*Citrobacter* spp	*E. cloacae* sc	*E. coli*	*K. aerogenes*	*K. pneumoniae*	*P. mirabilis*	*P. rettgeri*	*E. faecalis*	*S. saprophyticus*
Azithromycin									
Indifference [a]	5	5	5	4	5	4	5	5	5
Synergy	0	0	0	1	0	1	0	0	0
Ceftazidime									
Indifference	4	3	5	5	5	4	4	5	5
Synergy	1	2	0	0	0	1	1	0	0
Levofloxacin									
Indifference	5	5	5	5	5	4	5	5	5
Synergy	0	0	0	0	0	1	0	0	0
Nitrofurantoin									
Indifference	5	5	5	5	5	5	4	5	5
Synergy	0	0	0	0	0	0	1	0	0
Tetracycline									
Indifference	5	5	5	5	5	5	4	5	5
Synergy	0	0	0	0	0	0	1	0	0
Trimethoprim-sulfamethoxazole									
Indifference	5	5	5	5	3	5	5	5	5
Synergy	0	0	0	0	2	0	0	0	0
Aztreonam									
Indifference	4	3	5	5	5	5	4		
Synergy	1	2	0	0	0	0	1		
Meropenem									
Indifference	4	4	4	4	5	5	4		
Synergy	1	1	1	1	0	0	1		
Linezolid									
Indifference								5	5
Synergy								0	0
Vancomycin									
Indifference								5	1
Synergy								0	4

sp, species; sc, species complex.

Gray shading represent drug/isolate combinations not tested.

[a] Indeterminant ΣFIC results inculded in these totals

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Results

Of the 360 organism/combinations tested, synergy was demonstrated in 25 (6.9%) organism/combinations (Table 1).

The prevalence of synergistic interactions varied by isolate and antimicrobial combination.

For Enterobacterales, the greatest number of synergistic combinations with gepotidacin were observed with the β-lactams:

- Meropenem (5/35; 14.3%).
- Ceftazidime (5/35; 14.3%).
- Aztreonam (4/35; 11.4%).

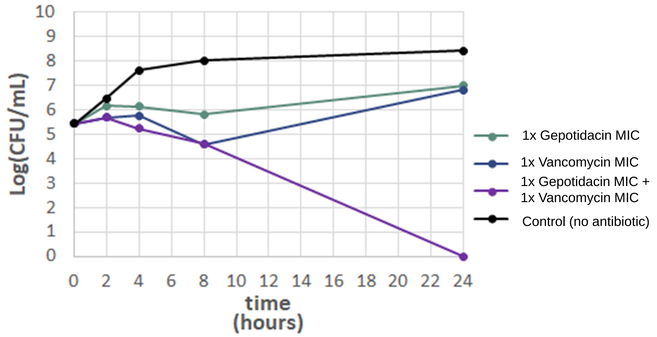
An instance of synergy was observed at least once for each gram-negative species; these instances were most seen in:

- *E. cloacae* (5/40; 12.5%).
- *P. rettgeri* (5/40; 12.5%).
- *Citrobacter species* (3/40; 7.5%).
- *P. mirabilis* (3/40; 7.5%).

Other species had observed synergy in 1 to 2 organism/combinations tested.

Among gram-positive isolates, the only synergy observed occurred with gepotidacin and vancomycin. Four of five isolates had a ΣFICmin ≤0.25 to 0.31 and time-kills showed gepotidacin/vancomycin synergy for all 5 *S. saprophyticus* isolates.

Figure 1: Time-kill curves for gepotidacin and vancomycin against *S. saprophyticus* isolate # 1129086



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