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Detection of Synergistic Antimicrobial Activities of Ceftaroline, Telavancin, Daptomycin, and Vancomycin Against Methicillin-Resistant *Staphylococcus aureus* Strains in Intensive Care Units

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading pathogen of serious infectious diseases in intensive care units. Novel antibiotic combination therapies are needed to treat serious infectious diseases caused by MRSA.
Objectives: Our objective was to evaluate the minimum inhibitory concentrations (MICs) of ceftaroline (CPT), telavancin (TLV), daptomycin (DPC), and vancomycin (VA) alone and in vitro synergistic activity of CPT-TLV, CPT-DPC, and CPT-VA combinations against MRSA isolates.
Methods: Fifty MRSA strains isolated from blood (90%) and tracheal aspirate (10%) of patients in intensive care units (ICUs) between 2013 and 2016 were included in the study. The Epsilometer test was used for determining the synergistic activities of antibiotic combinations. We evaluated the synergistic, additive, indifferent, and antagonist effects of MRSA strains by the fractional inhibitory concentration (FIC) index.
Results: Of the 50 MRSA strains tested, 100% were susceptible to TLV, DPC, and VA. CPT was detected as resistant in 3 (6%) of the isolates. CPT-TLV, CPT-DPC, and CPT-VA combinations were found to have synergistic effects in 14%, 38%, 10% and additive effects in 40%, 32%, and 22% of the isolates, respectively. No antagonism was detected in any of the combinations.
Conclusions: The combination of CPT with DPC showed the best synergy profile among all antibiotic combinations tested against MRSA isolates obtained from patients in ICUs.

Keywords: Intensive Care Units, Methicillin-Resistant *Staphylococcus aureus*, Synergy

1. Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading pathogen of serious infections in intensive care units (1, 2). Methicillin-resistant *S. aureus* infections are associated with higher morbidity and mortality rates and prolonged hospital stays (3). Although several studies suggest that infections with MRSA have declined in recent years, they are still among the top three clinically important pathogens (4, 5). Methicillin-resistant *S. aureus* strains are frequently resistant to multiple classes of antimicrobial agents including aminoglycosides, macrolides-lincosamides-streptogramins, and tetracyclines.

Until now, glycopeptides have been considered as the drugs of choice for the treatment of severe MRSA infections (6). However, resistance to vancomycin in MRSA strains has increased recently worldwide (7). Resistance to newer antimicrobial agents such as linezolid, teicoplanin, and daptomycin has also been reported in the studies (8). Alternative therapies including novel combinations are essential to treat MRSA infections. Different antibiotic combinations are frequently used for the treatment of infections caused by MRSA strains (9-14).

2. Objectives

In this study, our objective was to determine the synergistic antimicrobial activities of a newly developed

fifth-generation cephalosporin, ceftaroline (CPT), and telavancin (TLV), daptomycin (DPC), and vancomycin (VA) by the Epsilometer test (E-test) against MRSA strains isolated from patients in intensive care units (ICUs).

3. Methods

3.1. Ethics Statement

This study was supported by a Grant from Yüksek İhtisas Training and Research Hospital and approved by its Ethics Committee (Grant No: 328-5).

3.2. Isolates and Antibacterials Assay

We evaluated a total of 50 MRSA strains, isolated from patients in intensive care units between 2013 and 2016. 45 (90%) isolates were obtained from blood and 5 (10%) from tracheal aspirate. The identification of MRSA strains was performed by conventional methods. Antibiotic susceptibility tests and the minimum inhibitory concentration (MIC) values were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards (15).

The minimum inhibitory concentration values and the synergy tests were determined by using the E-test method, which is a 'ready-to-use' reagent strip with a predefined gradient of antibiotic, according to the manufacturer's instructions (bioMerieux, France). The minimum inhibitory concentration values were assessed first for CPT, TLV, DPC, and VA alone and then, in combination (CPT-TLV, CPT-DPC, and CPT-VA) for each of the MRSA isolates. First, the bacterial suspensions were prepared to 0.5 MacFarland standard turbidity; then, the suspensions were spread onto 150-mm Mueller-Hinton agar plates. After this procedure, E-test strips (bioMerieux, France) for CPT, TLV, DPC, and VA were placed onto the plates. After the incubation of the plates for 24 h at 37°C, the MIC values were recorded.

We evaluated the synergistic effect of three different antibiotic combinations (CPT-TLV, CPT-DPC, and CPT-VA) by the E test method (bioMerieux, France) against MRSA strains isolated from patients in intensive care units. First, we applied the E test that belonged to antibiotic A to the surface of planted Mueller-Hinton agar. We marked the site at which the E-test strip was placed on the plate and incubated the plates for 1 h at 37°C. Then, we removed the strip and applied the other antibiotic's strip (antibiotic B) onto the imprint of antibiotic A. At the end, we re-incubated the plates at 37°C for 24 h and recorded the MIC levels of each combination.

3.3. FIC Evaluation

We evaluated the synergistic, additive, indifferent, and antagonist effects of MRSA strains by fractional inhibitory concentration (FIC) index for the combinations of the antibiotics according to the formula given below.

FIC index = FIC A + FIC B

FIC A = The MIC value of antibiotic A in the presence of antibiotic B / The MIC value of single antibiotic A.

FIC B = The MIC value of antibiotic B in the presence of antibiotic A / The MIC value of single antibiotic B.

If the FIC index was ≤ 0.5, we considered the combination as synergistic. We interpreted the combination as additive when the FIC index value was > 0.5 but ≤ 1. We determined the combination as indifferent when the FIC value was > 1 but ≤ 4. We considered the combination as antagonistic when the FIC index value was > 4 (16).

4. Results

Of the 50 MRSA strains tested, 100% were susceptible to TLV, DPC and VA. CPT was detected as resistant in 3 (6%) of the isolates. For CPT, we determined the MIC_{50} and MIC_{90} values as 0.5 μg/mL and 1 μg/mL, for TLV as 0.032 μg/mL and 0.064 μg/mL, for DPC as 0.38 μg/mL and 0.75 μg/mL, and for VA as 1 μg/mL and 2 μg/mL, respectively (Table 1). The FIC values and the activities of antibiotic combinations are shown in Table 2. CPT-TLV, CPT-DPC, and CPT-VA combinations were found to have synergistic effects in 14%, 38%, and 10% and additive effects in 40%, 32%, and 22% of the isolates, respectively. No antagonism was detected in any of the combinations (Table 3).

5. Discussion

Staphylococcus aureus is a serious human pathogen worldwide that causes a broad range of clinical infections (17). MRSA is a common infectious agent that causes both nosocomial and community-acquired infections and it keeps high morbidity and mortality rates (18). The combination of antibiotics acting by different mechanisms is recommended for the treatment of MRSA infections in order to ensure a synergistic action, reduce the occurrence of side-effects, and decrease the risk of resistance. These different antibiotic combinations offer a potential option in the management of the infections caused by MRSA (9-14). In our study, the E test method was used to evaluate the synergistic effects of the antibiotics against MRSA strains isolated from patients in intensive care units. Time-kill and checkerboard tests can be employed to assess the synergy of antibiotic combinations. These methods are costly in time and materials. The E test method is simple to use, time-efficient, and inexpensive. It can be used in routine clinical practice (19).

The glycopeptide VA was proposed as the best alternative for the treatment of MRSA strains. However, a number of studies established a relationship between elevated

Table 1. Mic Range, MIC_{50}, and MIC_{90} Values and Susceptibility Rates in Clinically Isolated MRSA Strains in ICUs

Antibiotic	MIC (μg/mL)			Susceptibility Rate (%)	
	MIC Range	MIC_{50}	MIC_{90}	Susceptible	Resistant
CPT	0.19 - 2	0.50	1.0	94	6
TLV	0.016 - 0.125	0.032	0.064	100	0
DPC	0.094 - 1	0.38	0.75	100	0
VA	0.38 - 2	1.0	2.0	100	0

Abbreviations: CPT, ceftaroline; DPC, daptomycin; ICUs, intensive care units; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; TLV, telavancin; VA, vancomycin.

VA MICs and treatment failures in patients infected with MRSA strains (20-23). According to Thati et al. (20), the MIC for 335 out of 358 isolates (93.57%) for VA was $\leq$ 2 μg/mL and the MIC values indicated that 1.9% of the MRSA isolates were resistant to vancomycin. Chadha et al. investigated the susceptibility to VA in 163 clinical isolates of MRSA by using E-test methodology and determined the susceptibility rate as 99%. For VA, 56% of the isolates had MICs of $\leq$ 1.0 μg/mL and 43% had MICs of $\geq$ 1.5 μg/mL (24). Rybak et al. investigated the susceptibility to VA in 50 MRSA isolates. MIC_{50} and MIC_{90} values were 0.50 μg/mL and 1 μg/mL, respectively, and the MIC range was 0.25 - 2.0μg/mL for VA (25). Sader et al. investigated the susceptibility to VA in 9875 MRSA isolates. The $MIC_{50/90}$ values were 1/1 μg/mL for VA. The susceptibility rate to VA was > 99.9% (26). In the present study, we determined all the strains as susceptible to vancomycin. MIC_{50} and MIC_{90} values for VA were 1 μg/mL and 2 μg/mL, respectively. The MIC range was 0.38 - 2.0 μg/mL.

Telavancin, which is derived from vancomycin, has a potent bactericidal activity against Gram-positive bacteria, including MSSA, MRSA, VISA, and MDR (multi-drug resistant) streptococci and enterococci (27, 28). Smith et al. determined the MICs for TLV by broth microdilution method in 70 DNS *S. aureus* and 100 VISA strains. The MIC_{50} and MIC_{90} values were 0.06 - 0.125 for both DNS *S. aureus* and VISA strains (29). Mendes et al. determined the $MIC_{50/90}$ values as 0.03/0.06 μg/mL for TLV against 4651 MRSA strains (27). In the present study, we determined the MIC_{50} and MIC_{90} values for TLV as 0.032 μg/mL and 0.064 μg/mL, respectively. The MIC range was 0.016 - 0.125 μg/mL.

Ceftaroline is a novel fifth-generation cephalosporin that demonstrates in vitro activity against Gram-positive and Gram-negative pathogens. It also demonstrates a potent activity against resistant strains of *S. aureus* (30). Chadha et al. investigated the susceptibility to CPT in 163 clinical isolates of MRSA by using E-test methodology and determined the susceptibility rate as 99%. MIC_{50} value was 0.5 μg/mL and MIC_{90} value was 1 μg/mL for CPT (24). Sader et al. determined the $MIC_{50/90}$ values as 0.5/1 μg/mL for CPT against 9875 MRSA strains. The susceptibility rate was 97.2% for CPT (26). Bilmen et al. investigated 60 MRSA isolates. The $MIC_{50/90}$ values were found to be 0.5/1 μg/mL and the MIC range was 0.125 - 2 μg/mL for CPT (31). Gaikwad et al. determined $MIC_{50/90}$ values as 0.38/0.75 μg/mL and the MIC range as 0.25 - 4 μg/mL against 30 MRSA strains for CPT (32). In the present study, 3 (6%) of the strains were resistant to CPT. The $MIC_{50/90}$ values were 0.5/1 μg/mL and the MIC range was 0.19 - 2 μg/mL for CPT.

Daptomycin is a semisynthetic lipopeptide that shows bactericidal activity against drug-resistant Gram-positive bacteria including MRSA. Daptomycin is being increasingly used in the treatment of complex MRSA infections (33). Chadha et al. investigated the susceptibility to DPC in 163 clinical isolates of MRSA by using E-test methodology and determined the susceptibility rate as 99%. For DPC, 99% of the isolates had MICs of $\leq$ 1.0 μg/mL (24). Rybak et al. investigated the susceptibility to DPC in 50 MRSA isolates. The MIC_{50} and MIC_{90} values were 0.13 μg/mL and the MIC range was 0.06 - 0.5 μg/mL for DPC (25). Smith et al. determined the $MIC_{50/90}$ values as 2/4 μg/mL in 70 DNS *S. aureus* strains and 1/1 μg/mL in 100 VISA strains (29). Mendes et al. determined the $MIC_{50/90}$ values as 0.25/0.5μg/mL in 4651 MRSA strains (27). Sader et al. determined the $MIC_{50/90}$ values as 0.25/0.5 μg/mL in 9875 MRSA strains for DPC (26). In the present study, all the strains were susceptible to DPC. The MIC_{50} and MIC_{90} values were 0.38 μg/mL and 0.75 μg/mL, respectively, and the MIC range was 0.094 - 1.0 μg/mL for DPC.

Recent studies have suggested an enhanced activity for DPC against MRSA when combined with CPT (12, 34, 35). Similarly, in the present study, the combination of CPT with DPC showed the best synergy profile (38% synergistic and 32% additive) among all antibiotic combinations tested against MRSA isolates obtained from patients in ICUs. There are several limitations in this study that should be noted. There is no gold standard for synergy testing. Different methodologies can be used to assess synergy between antibiotics like checkerboard assay or time-kill analysis. These methods are difficult, expensive, and time-consuming for routine antimicrobial synergy testing. Therefore, we preferred the E test method. E-test is

Table 2. The FIC Values and the Activities of Antibiotic Combinations Against 50 Clinically Isolated MRSA Strains in ICUs

No	CPT-TLV		CPT-DPC		CPT-VA	
	FIC	Activity	FIC	Activity	FIC	Activity
1	0.78	ADD	3.082	ID	1.166	ID
2	1.085	ID	0.422	S	0.751	ADD
3	2.419	ID	1.776	ID	2.26	ID
4	0.487	S	0.508	ADD	2.186	ID
5	2.824	ID	0.802	ADD	1.625	ID
6	1.085	ID	0.699	ADD	1.166	ID
7	0.868	ADD	2.032	ID	2.5	ID
8	1.128	ID	2.788	ID	2.09	ID
9	1.085	ID	0.416	S	0.999	ADD
10	1.064	ID	0.36	S	1.0	ADD
11	2.064	ID	0.4	S	0.568	ADD
12	1.128	ID	0.845	ADD	1.166	ID
13	0.974	ADD	0.428	S	3.76	ID
14	1.455	ID	1.361	ID	1.25	ID
15	0.828	ADD	0.365	S	1.13	ID
16	1.125	ID	0.499	S	1.666	ID
17	0.968	ADD	0.824	ADD	1.38	ID
18	0.823	ADD	0.888	ADD	1.58	ID
19	0.756	ADD	1.064	ID	2.0	ID
20	1.531	ID	1.128	ID	2.25	ID
21	0.42	S	1.747	ID	2.157	ID
22	0.423	S	0.26	S	0.594	ADD
23	0.965	ADD	0.747	ADD	1.494	ID
24	1.166	ID	1.172	ID	1.166	ID
25	1.256	ID	0.456	S	1.76	ID
26	0.778	ADD	0.418	S	1.32	ID
27	1.047	ID	0.375	S	0.5	S
28	0.536	ADD	0.427	S	0.565	ADD
29	0.574	ADD	0.755	ADD	1.125	ID
30	0.595	ADD	0.919	ADD	1.333	ID
31	0.484	S	0.458	S	0.5	S
32	0.737	ADD	0.661	ADD	0.91	ADD
33	0.803	ADD	0.494	S	1.666	ID
34	0.742	ADD	0.633	ADD	0.916	ADD
35	0.536	ADD	0.44	S	1.13	ID
36	0.382	S	0.419	S	1.666	ID
37	0.688	ADD	0.622	ADD	1.126	ID
38	0.803	ADD	0.413	S	1.661	ID
39	0.808	ADD	1.5	ID	1.128	ID
40	0.444	S	0.381	S	0.5	S
41	1.247	ID	0.874	ADD	1.0	ID
42	0.418	S	0.75	ADD	0.458	S
43	1.724	ID	2.256	ID	1.25	ID
44	1.054	ID	0.496	S	0.874	ADD
45	2.419	ID	1.0	ADD	1.51	ID
46	0.782	ADD	2.247	ID	0.254	S
47	1.047	ID	2.785	ID	0.94	ADD
48	1.062	ID	0.835	ADD	0.833	ADD
49	1.724	ID	1.256	ID	2.835	ID
50	1.188	ID	2.02	ID	2.26	ID

Abbreviations: ADD, additive; ANT, antagonistic; CPT, ceftaroline; DPC, daptomycin; FIC, fractional inhibitory concentration; ICUs, intensive care units; ID, indifferent; MRSA, methicillin resistant *Staphylococcus aureus*; S, synergistic; TLV, telavancin; VA, vancomycin.

much easier to perform, less labor intensive, and less time consuming and may be suitable for routine laboratory testing. These features of the E-test method encouraged us to determine synergistic effects by E-test. Further studies

Table 3. Synergy Test Results of CPT-TLV, CPT-DPC, and CPT-VA Combinations Against MRSA Isolates[a]

Combination	Synergistic Effect	Additive Effect	Indifferent Effect	Antagonistic Effect
CPT-TLV	7 (14)	20 (40)	23 (46)	0 (0)
CPT-DPC	19 (38)	16 (32)	15 (30)	0 (0)
CPT-VA	5 (10)	11 (22)	34 (68)	0 (0)

Abbreviations: CPT, ceftaroline; DPC, daptomycin; MRSA, methicillin resistant *Staphylococcus aureus*; TLV, telavancin; VA, vancomycin.
[a]Data are presented as No. (%) of bacterial strains.

to compare the E-test technique with the checkerboard or time-kill methodologies for the determination of synergy between these antibiotics will strengthen the results of the study. In addition, *in vitro* studies have limited value in the prediction of in vivo synergy. The ability of in vitro combination testing to determine clinical synergy is unknown. The clinical benefits of these antibiotic combinations in vivo must be done before being used therapeutically.

5.1. Conclusions

In the present study, the antimicrobial activities of CPT, which is a newly developed fifth-generation cephalosporin, and TLV, DPC, and VA combinations, have been studied with the aim of developing new therapeutic options for infections caused by MRSA strains isolated from patients in ICUs. The combination of CPT with DPC showed the best synergy profile (38% synergistic and 32% additive) among all antibiotic combinations. All these data will help clinicians to determine the appropriate antibiotic combinations against infections caused by MRSA strains.

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Footnotes

Authors' Contribution: Study concept and design: Laser Şanal; acquisition of data: Laser Şanal; analysis and interpretation of data: Laser Şanal, Reyhan Öztürk, and Süha Sen; drafting of the manuscript: Laser Şanal and Salih Cesur; critical revision of the manuscript for important intellectual content: Laser Şanal and Neziha Yılmaz; administrative, technical, and material support: Laser Şanal and Hatice Uludağ Altun; study supervision: Laser Şanal and Neziha Yılmaz. Dr. Laser Şanal developed the original idea and the protocol, abstracted and analyzed the data, wrote the manuscript, and is the guarantor.

Ethical Considerations: There was no need for ethical approval for our study.

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