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In Vitro Activity of Doripenem against *Pseudomonas aeruginosa* and *Burkholderia cepacia* Isolates from both Cystic Fibrosis and Non-Cystic Fibrosis Patients

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The in vitro activities of doripenem, imipenem, levofloxacin, piperacillin, ceftazidime, aztreonam, tobramycin, and cefepime were determined for 160 isolates of *Pseudomonas aeruginosa* (82 from cystic fibrosis [CF] patients) and 34 isolates of *Burkholderia cepacia*. Doripenem MIC_{90}s were lower than those of all other comparative agents against all isolates combined and against all *P. aeruginosa* isolates. Doripenem was as active as levofloxacin and 2- to 32-fold more active than the other comparative agents against *B. cepacia*.

Chronic lung infection, repeated exacerbations, and progressive deterioration in lung function caused by *Pseudomonas aeruginosa* and *Burkholderia cepacia* are a major cause of mortality in cystic fibrosis (CF) patients despite current antimicrobial therapy (1, 5). In approximately 25% of CF patients infected with *B. cepacia* (2) and 40 to 60% of cases with *Pseudomonas* pneumonia, the clinical course is ultimately fatal (6). Novel antibiotics may help improve patient survival and reduce healthcare resource utilization. Both the infections caused by *P. aeruginosa* and those caused by *B. cepacia* are often treated with difficulty due to emergence of resistance and lack of effective antibiotics. Doripenem is a new carbapenem currently under clinical investigation for treatment of a variety of infections in humans. This study was designed to help assess the in vitro activities of doripenem against *B. cepacia* and *P. aeruginosa* isolates from CF patients and non-CF patients.

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A total of 194 clinical strains from our frozen stock culture collection were tested. All stock isolates were stored at −70°C in defibrinated sheep blood. They included 160 stock isolates of *P. aeruginosa* (82 from CF patients and 78 from non-CF sources) and 34 isolates of *B. cepacia*. CF *Pseudomonas* isolates were collected from 1996 through 2001, and non-CF *Pseudomonas* isolates were collected from mid-1999 through mid-2002. *B. cepacia* isolates were all collected before 2001, and there are no records as to whether or not they were isolated from CF patients or other sources.

In addition, *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested for quality control purposes.

All strains were tested by the broth microdilution method recommended by the Clinical Laboratory Standards Institute (formerly NCCLS) (3). Doripenem was compared to a variety of antimicrobial compounds including imipenem, levofloxacin, piperacillin, ceftazidime, aztreonam, tobramycin, and cefepime.

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The broth microdilution method outlined in the CLSI approved standard (M7-A6, 2003) (3) was used throughout. Each compound was dissolved and diluted according to CLSI specifications. Stock solutions of each agent were prepared immediately before use. Serial twofold dilutions of from 0.25 to 512 μg/ml were prepared for each drug except cefepime, for which dilutions of from 0.25 to 128 μg/ml were prepared. The 96-well microdilution plate susceptibility test panels were prepared at the Clinical Microbiology Institute and stored in a −70°C freezer until use. CLSI breakpoints were used for all comparative agents (4). No interpretive breakpoints were available for doripenem since there are no FDA- or CLSI-approved breakpoints at this time.

All MICs obtained when testing *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were within the ranges recommended by the CLSI (M100-S13). The doripenem MICs for *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were all ≤0.25 μg/ml (five replicates of each strain).

Table 1 summarizes the MICs (in micrograms per milliliter) of doripenem and comparative drugs against all bacterial isolates tested. Results for each group represented are arranged by geometric mean MIC in ascending order. Doripenem had the lowest geometric mean MIC of all antimicrobials tested against the entire collection of organisms. The doripenem MIC at which 50% of the isolates tested were inhibited (MIC_{50}) was 4- to 32-fold lower than those of the other comparative agents, and the doripenem MIC_{90} was equal to that of levofloxacin (8 μg/ml) and 2- to 16-fold lower than those of the other agents under study.

Against 34 strains of *B. cepacia*, doripenem was 1 doubling dilution less active than levofloxacin (doripenem MIC_{50} of 2 μg/ml versus 1 μg/ml for levofloxacin) but 2- to 32-fold more active than the other antimicrobials tested (Table 1). The MIC_{90}s for doripenem and levofloxacin were both 8 μg/ml (2- to 32-fold lower than those of the other antimicrobials).

As noted earlier, doripenem was the most active agent in terms of overall in vitro potency for all isolates tested, including *P. aeruginosa* strains isolated from both CF patients ($MIC_{50/90}$, 0.25/2 μg/ml) and non-CF patients ($MIC_{50/90}$, 0.25/1 μg/ml). The *P. aeruginosa* strains from CF patients tended to be slightly more resistant to all antimicrobials than were the

TABLE 1. Percent susceptible, intermediate, and resistant (CLSI breakpoints) for doripenem versus *P. aeruginosa* and *B. cepacia*[a]

Organism	Antimicrobial	MIC_{50}	MIC_{90}	Minimum	Maximum	Geometric mean	Mode	% S	% I	% R
All strains (n = 194)	Doripenem	0.25	8	0.25	256	0.59	0.25	NA	NA	NA
	Imipenem	1	16	0.25	256	1.37	1	83.00	4.60	12.40
	Levofloxacin	1	8	0.25	128	1.43	0.5	69.10	10.80	20.10
	Piperacillin	8	128	0.25	>512	9.43	4	SS	SS	SS
	Ceftazidime	2	16	0.25	>512	2.98	2	88.70	3.60	7.70
	Aztreonam	8	64	0.25	>512	7.19	8	66.0	12.40	21.60
	Tobramycin	1	64	0.25	>512	1.78	0.5	78.90	1.00	20.10
	Cefepime	4	32	0.25	256	4.1	2	78.90	9.80	11.30
B. cepacia (n = 34)										
	Doripenem	2	8	0.25	128	2.35	8	NA	NA	NA
	Imipenem	4	16	0.25	128	3.69	16	50.00	20.60	29.40
	Levofloxacin	1	8	0.25	8	1.2	0.25	76.50	11.80	11.80
	Piperacillin	32	128	2	>512	19.22	2	41.20	38.20	20.60
	Ceftazidime	4	16	0.25	>512	2.83	4	82.40	14.70	2.90
	Aztreonam	32	256	0.25	512	21.72	64	29.40	14.70	55.90
	Tobramycin	64	128	0.25	256	18.45	64	23.50	0.00	76.50
	Cefepime	16	128	0.25	256	8.68	0.25	47.10	14.70	38.20
P. aeruginosa (CF isolates; n = 82)										
	Doripenem	0.25	2	0.25	256	0.52	0.25	NA	NA	NA
	Imipenem	1	16	0.25	256	1.28	1	86.60	1.20	12.20
	Levofloxacin	1	16	0.25	128	1.75	0.5	63.40	11.00	25.60
	Piperacillin	8	256	0.25	>512	10.85	4	86.60	NA	13.40
	Ceftazidime	2	32	0.25	256	3.47	2	84.10	2.40	13.40
	Aztreonam	8	64	0.25	>512	7.8	8	63.40	14.60	22.00
	Tobramycin	0.5	8	0.25	512	1.04	0.5	89.00	2.40	8.50
	Cefepime	2	16	0.25	64	3.52	2	84.10	7.30	8.50
P. aeruginosa (non-CF isolates; n = 78)										
	Doripenem	0.25	1	0.25	16	0.36	0.25	NA	NA	NA
	Imipenem	1	2	0.25	32	0.95	1	93.60	1.30	5.10
	Levofloxacin	1	8	0.25	64	1.25	0.5	71.80	10.30	17.90
	Piperacillin	8	16	0.25	512	5.97	4	96.20	NA	3.80
	Ceftazidime	2	8	0.25	64	2.61	2	96.20	0.00	3.80
	Aztreonam	8	16	0.25	64	4.07	8	84.60	9.00	6.40
	Tobramycin	1	2	0.25	>512	0.97	0.5	92.30	0.00	7.70
	Cefepime	2	16	0.25	32	3.47	2	87.20	10.30	2.60

[a] Abbreviations: S, susceptible; I, intermediate; R, resistant; NA, not applicable (no approved ranges); SS, species specific. MIC_{50}, MIC_{90}, minimum, maximum, geometric mean, and mode are all in micrograms per milliliter.

non-CF isolates. The greatest differences in percent resistance between CF strains and non-CF strains were observed with aztreonam (22% versus 6.4%), piperacillin (13.4% versus 3.8%), and ceftazidime (13.4% versus 3.8%, respectively). The geometric mean doripenem MIC for CF isolates was 0.52 μg/ml versus 0.36 μg/ml for non-CF strains (Table 1). In both instances, the doripenem geometric mean MICs were substantially lower than those of any other antimicrobial compound tested.

Table 2 shows the MIC data for doripenem versus imipenem on 16 *P. aeruginosa* strains that were either resistant or intermediate to imipenem. Eleven of these strains were from CF patients, and five were from non-CF patients. Eight of the 16 strains (50%) had doripenem MICs that were 2- to 16-fold lower than the imipenem MICs for these strains.

In conclusion, the in vitro activity of doripenem against clinical strains of *B. cepacia* and *P. aeruginosa* was greater than that of all other antimicrobials tested. Doripenem was active against most *B. cepacia* strains (MIC_{50}, 2 μg/ml, and MIC_{90}, 8 μg/ml). Tobramycin was the least effective among those tested, with 76% of isolates being resistant. Strains of *P. aeruginosa* isolated from CF patients tended to be slightly more resistant

TABLE 2. Doripenem versus imipenem-resistant and -intermediate *P. aeruginosa* isolates[a]

Strain no.	Isolate type	Doripenem MIC	Imipenem MIC, I or R
N1873	CF isolate	4	16R
N2408	CF isolate	2	16R
N3794	CF isolate	4	16R
N4082	CF isolate	2	16R
N6687	CF isolate	1	16R
N7086	Non-CF isolate	1	16R
N7087	Non-CF isolate	2	16R
N4972	CF isolate	2	8I
N7982	Non-CF isolate	4	8I
N3791	CF isolate	16	64R
N4077	CF isolate	8	16R
N4079	CF isolate	256	256R
N5395	CF isolate	16	16R
N6693	CF isolate	16	16R
N7093	Non-CF isolate	16	32R
N7095	Non-CF isolate	16	16R

[a] MICs are in micrograms per milliliter. I, intermediate; R, resistant.

to all antimicrobials than were strains recovered from non-CF patients. Of the 16 strains of *P. aeruginosa* that were resistant or intermediate to imipenem, 50% had doripemen MICs that were 2- to 16-fold lower than those of imipenem. If successfully developed, doripenem may be a useful agent against *P. aeruginosa* and *B. cepacia* infections.

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