In Vitro Activities of Meropenem, PD 127391, PD 131628, Ceftazidime, Chloramphenicol, Co-Trimoxazole, and Ciprofloxacin against *Pseudomonas cepacia*

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In a study of 110 *Pseudomonas cepacia* isolates from patients without cystic fibrosis, the in vitro potencies of three new compounds, meropenem, PD 127391, and PD 131628, were comparable to those of ceftazidime and ciprofloxacin and exceeded those of chloramphenicol and co-trimoxazole. The MICs of ceftazidime, ciprofloxacin, meropenem, and the PD compounds for 90% of strains tested were ≤4 µg/ml, whereas they were 32 µg/ml for chloramphenicol and co-trimoxazole. Data for 20 isolates from patients with cystic fibrosis indicated that the isolates were less susceptible to all seven antibiotics tested, with the most active compounds being meropenem and PD 127391.

Pseudomonas cepacia, a phytopathogen first described as the cause of soft rot of onions (4), is now recognized as a significant opportunistic pathogen in patients with nosocomial infections (9, 12). Patients with cystic fibrosis (CF) appear to be particularly susceptible to pulmonary colonization with this organism (2, 13, 23, 25): CF patients colonized with *P. cepacia* experience more pulmonary exacerbations and a higher mortality than do noncolonized CF patients (26).

P. cepacia is innately resistant to a wide range of antibiotics and disinfectants including polymyxin, aminoglycosides, and traditional antipseudomonal penicillins such as ticarcillin (3, 7, 15, 21). It is not surprising, therefore, that *P. cepacia* infections are generally refractory to antibiotic therapy and pose a significant challenge in the management of patients with CF (9, 10). Historically, the most effective antibiotics for the treatment of *P. cepacia* infections were trimethoprim-sulfamethoxazole and chloramphenicol, although these agents displayed limited clinical efficacy (20, 27). More recently available antibiotics, including ceftazidime, temocillin, imipenem, and ciprofloxacin, exhibit some in vitro activity against this organism (1, 17, 26). However, initial clinical experience with some of these compounds has shown variable benefits (8).

The availability of new agents with in vitro and in vivo activities against *P. cepacia* would be of considerable importance in the management of patients with CF. Thus, we examined a new carbapenem, meropenem, and two more recently developed quinolones for their activities against a large collection of *P. cepacia* isolates, including those from patients with CF.

Meropenem (ICI 194660 or SM 7338) is a new carbapenem with an exceptionally broad spectrum of antibacterial activity (14). Unlike imipenem, which is metabolized by renal dipeptidases and requires the coadministration of cilastatin, meropenem is stable to dehydropeptidase-I, and thus, it is not necessary to coadminister it with cilastatin (6, 18). PD 127391, 7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4,dihydro-4-oxo-3-quinolone-carboxylic acid, and

PD 131628, 7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, are oral quinolones that are being developed by Warner-Lambert and that may possess pharmacokinetics superior to those of clinically available 4-quinolones (5, 16). The data presented here describe the in vitro activities of these compounds against *P. cepacia* compared with those of the most active antibiotics available, ceftazidime, ciprofloxacin, chloramphenicol, and trimethoprim-sulfamethoxazole (co-trimoxazole). Most previous in vitro studies of the activity of meropenem and the two PD compounds have tested only small numbers of *P. cepacia* or used collections of pseudomonads which were not identified to the species level (5, 14, 16).

In the present study, we investigated a total of 130 *P. cepacia* isolated from CF and non-CF patients in France, the United Kingdom, and the United States. All strains were identified by standard methods (11), including use of the API 2ONE system (API System, La Balme les Grottes, France) and determination of their ability to grow on a selective medium (7). The strains included in the study were further characterized by bacteriocin typing (11, 22); multiple isolates from individual patients or epidemics belonging to the same bacteriocin type were excluded from the study. The antibiotics used in the study were obtained through the indicated sources: meropenem (ICI 194660, SM 7338), ICI Pharmaceuticals, Macclesfield, United Kingdom; PD 127391 (CI 960), PD 131628 (CI 990), and chloramphenicol, Clinical Research Northern Europe, Parke-Davis Warner-Lambert, Eastleigh, United Kingdom; ceftazidime, Glaxo Pharmaceuticals Ltd., Greenford, United Kingdom; ciprofloxacin, Bayer UK Ltd., Newbury, United Kingdom; and co-trimoxazole, Wellcome, Bromley, United Kingdom. Determination of MICs was done by the guidelines of the National Committee for Clinical Laboratory Standards (19). Bacterial antibiotic susceptibility tests were performed by an agar dilution method on Mueller-Hinton agar (Oxoid Ltd., Basingstoke, United Kingdom), with an initial inoculum of approximately 10^4 CFU per spot, by using a multipoint inoculator (model A400; Denley Instruments Ltd., Sussex, United Kingdom). The MIC was determined as the lowest

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TABLE 1. MICs of seven antimicrobial agents for 110 non-CF
and 20 CF isolates of *P. cepacia*

Antimicrobial agent	Source	MIC (μg/ml)		
		Range	50%	90%
Chlorampenicol	Non-CF	1–128	16	32
	CF	2–>128	16	64
Co-trimoxazole	Non-CF	0.5–>128	4	32
	CF	4–>128	32	128
Ceftazidime	Non-CF	0.06–>128	2	4
	CF	1–>128	8	32
Ciprofloxacin	Non-CF	<0.06–128	1	2
	CF	0.25–128	8	128
Meropenem	Non-CF	<0.06–16	2	4
	CF	1–16	2	16
PD 127391	Non-CF	<0.06–16	0.5	1
	CF	0.12–32	4	16
PD 131628	Non-CF	<0.06–64	0.5	1
	CF	0.12–128	4	64

concentration of antibiotic that inhibited growth of the test organism after 48 h of incubation at 37°C.

Details of the in vitro activities of PD 127391 and PD 131628 against 110 non-CF isolates of *P. cepacia* are given in Table 1. The activities of PD 127391 and PD 131628 were compared with those of other relevant antibacterial agents. On the basis of the MICs for 50% (MIC_{50}s) and 90% (MIC_{90}s) of isolates tested, both of the new PD quinolone compounds showed in vitro activities slightly better than those of ciprofloxacin and ceftazidime and were considerably more active than either co-trimoxazole or chloramphenicol. On the basis of similar parameters, meropenem was less active than the PD compounds at the MIC_{50}s and MIC_{90}s. For none of the isolates tested were the MICs of meropenem or PD 127391 greater than 16 μg/ml, while for some of the isolates, MICs of the other antimicrobial agents tested, with the exception of PD 131628, were 128 μg/ml or greater. On the basis of the published activity of imipenem (24), meropenem and the PD compounds were more active at the MIC_{50}s and MIC_{90}s.

None of the presently available antimicrobial agents has proved to be effective in the treatment of *P. cepacia* colonization in patients with CF, although combination therapy with temocillin and an aminoglycoside has been reported to have some clinical effect even against aminoglycoside-resistant isolates (27). Hence, the development of new agents with in vitro and in vivo activities against *P. cepacia* would be an important advance in the management of patients with CF. The isolates from patients with CF examined in the present study were less susceptible than isolates from patients without CF, perhaps reflecting the frequent use of antibiotics in patients with CF. Nevertheless, on the basis of their in vitro activities, the carbapenem meropenem and the new quinolone PD 127391 provide alternative agents with in vitro activities against *P. cepacia* that surpass those of the five other compounds. If the upper limit of susceptibility for meropenem is taken as 8 μg/ml (14), with an MIC_{50} of 2 μg/ml and an MIC range of 1 to 16 μg/ml, most isolates of *P. cepacia* from patients with CF examined in the present study

were susceptible. If the upper limit of susceptibility for the PD compounds is put at 2 to 4 μg/ml, as suggested for similar compounds (28), PD 127391, with an MIC_{50} of 4 μg/ml and an MIC range of 0.12 to 32 μg/ml, appears marginally better than PD 131628 and the existing quinolone standard ciprofloxacin.

It is a cause of concern that two strains of *P. cepacia* that exhibited resistance to all seven antibiotics tested were isolated from two patients with CF in Wales and Scotland. Further investigation of the prevalence of such multiresistant strains is needed to assess future problems in the management of patients with CF. The MIC data indicate that, with the exception of the two isolates from patients with CF in Wales and Scotland, meropenem and the PD compounds are highly active against isolates of *P. cepacia* that are resistant to the four other antibacterial agents investigated.

We conclude that the overall activities of meropenem and the PD compounds in in vitro susceptibility tests against a comprehensive collection of *P. cepacia* isolates indicate that these are promising new agents and that further studies of their pharmacokinetics and clinical efficacies in patients with CF are needed.

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