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NOTE

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Comparative in-vitro activity of carbapenem antibiotics against respiratory pathogens isolated between 1999 and 2000

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Abstract We investigated the antibacterial activity of 12 antibiotics, inclusive of four carbapenems, against 167 strains of respiratory pathogens isolated between 1999 and 2000. Thirty strains of methicillin-susceptible *Staphylococcus aureus* (MSSA), 28 strains of methicillin-resistant *S. aureus* (MRSA), 11 strains of penicillin-susceptible *Streptococcus pneumoniae* (PSSP), 29 strains of penicillin-resistant *S. pneumoniae* (PRSP), 30 strains of *Pseudomonas aeruginosa*, 14 strains of *Moraxella catarrhalis*, and 25 strains of *Haemophilus influenzae* were examined. The minimum inhibitory concentration $(MICs)_{50/90}$ (μg/ml) of imipenem, panipenem, meropenem, and biapenem against the clinical isolates obtained between 1999 and 2000 were: 0.06/0.25, 0.12/0.25, 0.12/0.25, and 0.12/0.25, respectively, against MSSA; 16/32, 16/32, 16/32, and 8/32 against MRSA; ≦0.015/0.06, ≦0.015/0.03, 0.03/0.12, and ≦0.015/0.06 against PSSP; 0.12/0.25, 0.03/0.06, 0.25/0.5, and 0.12/0.25 against PRSP; 1/8, 2/8, 0.5/2, and 2/16 against *P. aeruginosa*; 0.06/0.06, 0.03/0.06, ≦0.015/0.06, and 0.06/0.12 against *M. catarrhalis*; and 1/4, 1/4, 0.12/0.25, and 2/4 against *H. influenzae*. A comparison of the antibacterial activity of the four carbapenems with that found in our previous studies showed no significant difference in the susceptibility of clinical isolates, except for a slight decrease in the susceptibility of MSSA. Carbapenems have remained effective for severe infections. The MIC data showed that imipenem and panipenem were more active than meropenem and biapenem against gram-positive bacteria, and that meropenem and biapenem were more active than imipenem and panipenem against gram-negative bacteria. As only meropenem had an MIC_{90} below the breakpoint of pneumonia against all species except MRSA, meropenem was considered to be the most potent of the four carbapenems studied.

Key words Carbapenem · Antibacterial activity · Respiratory pathogens · Antibiotic resistance · MRSA · *Pseudomonas aeruginosa*

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Of the carbapenem antibiotics available in Japan, imipenem/cilastatin (IPM/CS) and panipenem/betamipron (PAPM/BP) are combined preparations, with a dehydropeptidase/organic anion transport inhibitor and an organic anion transport inhibitor, respectively. Meropenem (MEPM), which shows low nephrotoxity, is less rapidly metabolized in the kidneys than imipenem and panipenem. Meropenem, therefore, is the first carbapenem developed as a single-component preparation without the inhibitor.[1] Because carbapenems, including biapenem (BIPM) and S-4661, which are currently under development, possess a broad antibacterial spectrum and strong antibacterial activity, exceeding those of penicillins and cephems, they have been used mainly for severe infections.[2] It has been shown that major pathogenic isolates in respiratory tract infections are *S. pneumoniae*, followed by *H. influenzae*, *P. aeruginosa*, *M. catarrhalis*, and MSSA.[3,4] Of these species, *S. pneumoniae* and *H. influenzae* have recently tended to become resistant; e.g., PRSP[5,6] and β-lactamase-negative ampicillin-resistant (BLNAR) strains of *H. influenzae*.[7] These resistant strains may cause severe respiratory tract infections. Obviously, an antibiotic with strong activity against the above five major species is the first drug of choice in the treatment of respiratory tract infections. Thus, it can be stated that carbapenems and the new third-generation cephems are suitable for the treatment of respiratory tract infections.[8,9] However, it is inevitable that clinical isolates become less susceptible to antibiotics. Thus, it is of major clinical importance to continuously monitor the susceptibility of clinical isolates to antibiotics. It has already been shown that carbapenems have retained their strong and stable antibacterial activity against clinical isolates in 1993 and 1997.[10]

In the present study, we determined the antibacterial activity of a total of 12 antibiotics, including carbapenems, ceftazidime (CAZ), and vancomycin (VCM), against respiratory pathogens isolated between 1999 and 2000. We report the results herein.

We used the following antibiotics in this evaluation: imipenem (Banyu Pharmaceutical, Tokyo, Japan), panipenem (Sankyo, Tokyo, Japan), meropenem (Sumitomo Pharmaceuticals, Osaka, Japan), biapenem (Lederle Japan, Tokyo, Japan), ceftazidime (GlaxoSmithKline, Tokyo, Japan), cefozopran (CZOP; Takeda Chemical Industries, Osaka, Japan), cefepime (CFPM; Bristol Pharmaceuticals, Tokyo, Japan), flomoxef (FMOX; Shionogi, Osaka, Japan), piperacillin (PIPC; Toyama Chemical, Tokyo, Japan), clindamycin (CLDM; Pharmacia, Tokyo, Japan), vancomycin (Shionogi), and arbekacin (ABK; Meiji Seika, Tokyo, Japan).

From May 1999 to April 2000, a total of 167 bacterial strains were isolated from respiratory tract specimens of patients with respiratory infections at our institute and at Sendai Kosei Hospital. The strains were comprised of five major respiratory pathogens; 30 strains of methicillin-susceptible *Staphylococcus aureus* (MSSA), 28 strains of methicillin-resistant *S. aureus* (MRSA), 11 strains of penicillin-susceptible *Streptococcus pneumoniae* (PSSP), 29 strains of penicillin-resistant *S. pneumoniae* (PRSP), 30 strains of *Pseudomonas aeruginosa*, 14 strains of *Moraxella catarrhalis*, and 25 strains of *Haemophilus influenzae*.

To examine antibacterial activity against clinical isolates, we determined minimal inhibitory concentrations (MICs), by the broth microdilution method, according to the approved standards of the Japanese Society of Chemotherapy,[11] as described previously.[10]

Table 1 summarizes the MIC data for each antibiotic against the clinical isolates obtained between 1999 and 2000. Of the four carbapenems examined, imipenem was slightly more active than the other agents against MSSA.

Table 1. Comparison of MIC range, MIC_{50}, and MIC_{90} of imipenem, panipenem, meropenem, biapenem, ceftazidime, cefozopran, cefepime, flomoxef, piperacillin, clindamycin, vancomycin, and arbekacin against five major species of respiratory pathogens isolated between 1999 and 2000

Organism (no. tested)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Staphylococcus aureus (MSSA)[a] (*n* = 30)	Imipenem	≦0.03–0.5	0.06	0.25
	Panipenem	≦0.03–0.5	0.12	0.25
	Meropenem	0.06–0.5	0.12	0.25
	Biapenem	0.06–1	0.12	0.25
	Ceftazidime	2–32	8	16
	Cefozopran	0.5–2	1	2
	Cefepime	1–16	8	16
	Flomoxef	0.25–8	2	8
	Piperacillin	1–64	4	32
	Clindamycin	0.12–1	0.25	0.5
	Vancomycin	0.5–2	1	1
	Arbekacin	0.25–2	2	2
Staphylococcus aureus (MRSA)[b] (*n* = 28)	Imipenem	4–>64	16	32
	Panipenem	4–>64	16	32
	Meropenem	1–32	16	32
	Biapenem	1–>64	8	32
	Ceftazidime	8–>64	>64	>64
	Cefozopran	0.5–64	16	32
	Cefepime	4–>64	>64	>64
	Flomoxef	8–>64	64	>64
	Piperacillin	64–>64	>64	>64
	Clindamycin	>64	>64	>64
	Vancomycin	1–2	1	2
	Arbekacin	0.5–16	2	8
Streptococcus pneumoniae (PSSP)[C] (*n* = 11)	Imipenem	≦0.015–0.06	≦0.015	0.06
	Panipenem	≦0.015–0.03	≦0.015	0.03
	Meropenem	≦0.015–0.25	0.03	0.12
	Biapenem	≦0.015–0.12	≦0.015	0.06
	Ceftazidime	0.12–2	0.5	2
	Cefozopran	0.03–1	0.12	0.5
	Cefepime	≦0.015–0.5	0.06	0.25
	Flomoxef	0.06–1	0.12	0.5
	Piperacillin	0.03–2	0.25	1
	Clindamycin	0.06–0.12	0.12	0.12
	Vancomycin	0.12–0.25	0.25	0.25
	Arbekacin	8–32	16	32

Table 1. Continued

Organism (no. tested)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Streptococcus pneumoniae (PRSP)[d] (*n* = 29)	Imipenem	≦0.015–0.5	0.12	0.25
	Panipenem	≦0.015–0.25	0.03	0.06
	Meropenem	≦0.015–1	0.25	0.5
	Biapenem	≦0.015–1	0.12	0.25
	Ceftazidime	0.25–16	8	16
	Cefozopran	0.03–2	1	2
	Cefepime	0.06–2	1	1
	Flomoxef	0.12–8	1	4
	Piperacillin	0.06–4	2	4
	Clindamycin	0.06–32	8	32
	Vancomycin	0.12–0.25	0.25	0.25
	Arbekacin	16–>32	32	>32
Pseudomonas aeruginosa (*n* = 30)	Imipenem	0.5–16	1	8
	Panipenem	0.5–16	2	8
	Meropenem	0.06–4	0.5	2
	Biapenem	0.12–32	2	16
	Ceftazidime	0.25–16	2	4
	Cefozopran	0.25–32	1	8
	Cefepime	0.25–64	2	8
	Flomoxef	32–>64	>64	>64
	Piperacillin	1–64	8	32
	Clindamycin	32–>64	>64	>64
	Vancomycin	16–>64	>64	>64
	Arbekacin	0.25–8	0.5	2
Moraxella catarrhalis (*n* = 14)	Imipenem	≦0.015–0.12	0.06	0.06
	Panipenem	≦0.015–0.12	0.03	0.06
	Meropenem	≦0.015–0.06	≦0.015	0.06
	Biapenem	≦0.015–0.25	0.06	0.12
	Ceftazidime	0.03–0.5	0.12	0.5
	Cefozopran	0.12–4	2	4
	Cefepime	0.06–2	0.5	2
	Flomoxef	≦0.015–1	0.25	1
	Piperacillin	0.25–8	1	8
	Clindamycin	1–16	4	8
	Vancomycin	8–>32	32	>32
	Arbekacin	1–16	2	8
Haemophilus influenzae (*n* = 25)	Imipenem	0.12–4	1	4
	Panipenem	0.06–4	1	4
	Meropenem	0.03–0.5	0.12	0.25
	Biapenem	0.06–8	2	4
	Ceftazidime	0.06–0.5	0.12	0.5
	Cefozopran	0.06–2	0.25	1
	Cefepime	0.03–1	0.25	0.5
	Flomoxef	0.5–16	4	8
	Piperacillin	≦0.015–1	0.12	0.5
	Clindamycin	1–32	4	16
	Vancomycin	4–>32	>32	>32
	Arbekacin	1–8	8	8

MIC, Minimum inhibitory concentration
[a] Methicillin-susceptible *Staphylococcus aureus*
[b] Methicillin-resistant *Staphylococcus aureus*
[c] Penicillin-susceptible *Streptococcus pneumoniae* (MIC of benzylpenicillin, <0.12 μg/ml)
[d] Penicillin-resistant *Streptococcus pneumoniae* (MIC of benzylpenicillin, ≧0.12 μg/ml)

Against MRSA, biapenem was slightly more active than the other agents. Against PSSP and PRSP, panipenem was more active than the other agents. Against *M. catarrhalis*, meropenem was slightly more active than the other agents. Against *P. aeruginosa* and *H. influenzae*, meropenem was more active than the other agents. It is to be noted that MIC_{90} of meropenem against *H. influenzae* was lower than those of the other carbapenems by a factor of 16. The β-lactamase activity of *H. influenzae* was not examined in this study. Because BLNAR strains of *H. influenzae* have re-

Table 2. Changes in MIC_{50} and MIC_{90} of imipenem, panipenem, meropenem, and biapenem against five major species of respiratory pathogens isolated in 1993,[2] 1997,[2] and between 1999 and 2000

Organism[a]	Antibiotic	MIC_{50}(μg/ml)			MIC_{90}(μg/ml)		
		1993[2]	1997[2]	1999–2000	1993[2]	1997[2]	1999–2000
MSSA[b]	Imipenem	≦0.06	≦0.03	0.06	≦0.06	≦0.03	0.25
	Panipenem	≦0.06	≦0.03	0.12	≦0.06	0.06	0.25
	Meropenem	≦0.06	0.06	0.12	0.12	0.12	0.25
	Biapenem	≦0.06	0.06	0.12	0.12	0.12	0.25
MRSA[c]	Imipenem	32	8	16	64	32	32
	Panipenem	16	4	16	64	16	32
	Meropenem	16	16	16	64	32	32
	Biapenem	32	8	8	64	32	32
PSSP[d]	Imipenem	–	≦0.03	≦0.015	–	0.06	0.06
	Panipenem	–	≦0.03	≦0.015	–	≦0.03	0.03
	Meropenem	–	≦0.03	0.03	–	0.12	0.12
	Biapenem	–	≦0.03	≦0.015	–	0.06	0.06
PRSP[e]	Imipenem	–	0.06	0.12	–	0.12	0.25
	Panipenem	–	≦0.03	0.03	–	0.06	0.06
	Meropenem	–	0.25	0.25	–	1	0.5
	Biapenem	–	0.12	0.12	–	0.25	0.25
Pseudomonas aeruginosa	Imipenem	2	1	1	4	8	8
	Panipenem	16	4	2	16	16	8
	Meropenem	1	0.25	0.5	4	2	2
	Biapenem	1	0.5	2	4	4	16
Moraxella catarrhalis	Imipenem	≦0.06	≦0.03	0.06	≦0.06	0.06	0.06
	Panipenem	≦0.06	≦0.03	0.03	≦0.06	≦0.03	0.06
	Meropenem	≦0.06	≦0.03	≦0.015	≦0.06	≦0.03	0.06
	Biapenem	≦0.06	≦0.03	0.06	≦0.06	0.06	0.12
Haemophilus influenzae	Imipenem	1	0.5	1	2	2	4
	Panipenem	0.5	0.5	1	1	2	4
	Meropenem	1	0.12	0.12	4	0.25	0.25
	Biapenem	1	0.5	2	4	8	4

[a] Number of strains tested; 20 strains each of MSSA, MRSA, *P. aeruginosa*, *M. catarrhalis*, and *H. influenzae* in 1993; 38 strains of MSSA, 32 strains of MRSA, 22 strains of PSSP, 10 strains of PRSP, 53 strains of *P. aeruginosa*, 19 strains of *M. catarrhalis*, and 26 strains of *H. influenzae* in 1997; and 30 strains of MSSA, 28 strains of MRSA, 11 strains of PSSP, 29 strains of PRSP, 30 strains of *P. aeruginosa*, 14 strains of *M. catarrhalis*, and 25 strains of *H. influenzae* between 1999 and 2000
[b] Methicillin-susceptible *Staphylococcus aureus*
[c] Methicillin-resistant *Staphylococcus aureus*
[d] Penicillin-susceptible *Streptococcus pneumoniae* (MIC of benzylpenicillin, <0.12 μg/ml)
[e] Penicillin-resistant *Streptococcus pneumoniae* (MIC of benzylpenicillin, ≧0.12 μg/ml)

cently tended to increase in number, we will evaluate the antibacterial activity of meropenem against the BLNAR strains in our next study.

Table 2 compares the MIC_{50s} and MIC_{90s} of the four carbapenems between 1999 and 2000 with those reported in 1993 and 1997. Among the five bacterial species examined in this study, we observed a slight decrease in the susceptibility of MSSA. There was almost no decrease in the antibacterial activity of the carbapenems against the other species. Thus, it can be noted that carbapenems have retained their position as the drug of first choice for severe infections. However, *P. aeruginosa* showed an elevated level of resistance to biapenem, a drug that is currently under development. This seemingly paradoxical phenomenon requires further studies.

The breakpoints of the four carbapenems tested, as stated by the Japanese Society of Chemotherapy, are 2 μg/ml for pneumonia and 1 μg/ml for chronic respiratory tract infections.[12,13] All carbapenems tested each had an MIC_{50} and an MIC_{90} exceeding 2 μg/ml, the breakpoint in pneumonia, against MRSA. Imipenem, panipenem, and biapenem each had an MIC_{90} exceeding 2 μg/ml against *P. aeruginosa* and *H. influenzae*. On the other hand, meropenem was active against *P. aeruginosa* and *H. influenzae*. As meropenem was also active against gram-positive bacteria, except for MRSA, meropenem was considered to be the most potent of the four carbapenems studied.

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