In Vitro Activities of ME1036 (CP5609), a Novel Parenteral Carbapenem, against Methicillin-Resistant Staphylococci

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Received 27 November 2003/Returned for modification 22 January 2004/Accepted 26 April 2004

ME1036, formerly CP5609, is a novel parenteral carbapenem with a 7-acylated imidazo[5,1-b]thiazole-2-yl group directly attached to the carbapenem moiety of the C-2 position. The present study evaluated the in vitro activities of ME1036 against clinical isolates of gram-positive and gram-negative bacteria. ME1036 displayed broad activity against aerobic gram-positive and gram-negative bacteria. Unlike other marketed β-lactam antibiotics, ME1036 maintained excellent activity against multiple-drug-resistant gram-positive bacteria, such as methicillin-resistant staphylococci and penicillin-resistant Streptococcus pneumoniae (PRSP). The MICs of this compound at which 90% of isolates were inhibited were 2 μg/ml for methicillin-resistant Staphylococcus aureus (MRSA), 2 μg/ml for methicillin-resistant coagulase-negative staphylococci, and 0.031 μg/ml for PRSP. In time-kill studies with six strains of MRSA, ME1036 at four times the MIC caused a time-dependent decrease in the numbers of viable MRSA cells. The activity of ME1036 against MRSA is related to its high affinity for penicillin-binding protein 2a, for which the 50% inhibitory concentration of ME1036 was approximately 300-fold lower than that of imipenem. In conclusion, ME1036 demonstrated a broad antibacterial spectrum and high levels of activity in vitro against staphylococci, including β-lactam-resistant strains.

Until now, many β-lactams have been developed and widely used for chemotherapy for bacterial infections. However, the emergence of antibiotic-resistant strains of staphylococci, in particular, Staphylococcus aureus, has been reported in many countries. Several previous reports suggested that the prevalence of methicillin-resistant S. aureus (MRSA) has increased all over the world and that such strains are prone to cause serious outbreaks (6, 7, 15). In the United States, the prevalence of MRSA and methicillin-resistant coagulase-negative staphylococci (MR-CoNS) steadily increased in the 1990s, and in 2000 the rate of resistance of S. aureus to methicillin was 55.3% (8, 18). A nationwide survey carried out in Japan during 1992 and 1993 showed that 60.3% of 7,033 clinical isolates were resistant to methicillin, and 86% of these were isolated from inpatients (10). In addition, clinical infections caused by vancomycin-resistant S. aureus isolates carrying the vanA gene were reported from the United States in 2002 (1, 2).

In order to obtain drugs with improved activities against MRSA, our research has been directed toward the development of novel carbapenems. In the course of a research program for more potent carbapenems, a series of carbapenems possessing various 7-acylated imidazo[5,1-b]thiazole-2-yl groups were synthesized and evaluated for their antibacterial activities. Consequently, ME1036, formerly CP5609, which carries a 7-(1-carboxyethylmethylpyridinium-3-yl) carbonyl imidazo[5,1-b]thiazole-2-yl group at the C-2 position of the carbapenem skeleton (Fig. 1) was chosen for further evaluation from among more than 200 derivatives because of its potent activity against MRSA (E. Shitara, Y. Yamamoto, Y. Kano, T. Maruyama, M. Takahashi, and K. Atsumi, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-319, 2002). This report describes the in vitro activities of ME1036 against clinical isolates of gram-positive and gram-negative bacteria and details of its in vitro activity against MRSA.

MATERIALS AND METHODS

Antibacterial agents. ME1036 was synthesized at the Pharmaceutical Research Center of Meiji Seika Kaisha Ltd. (Tokyo, Japan). The following other reference antibacterial agents were purchased commercially: vancomycin (Shionogi & Co. Ltd., Osaka, Japan); imipenem (Banyu Pharmaceutical, Tokyo, Japan); meropenem (Sumitomo Pharmaceuticals, Osaka, Japan); cefoselis (Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan); gatifloxacin (Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan); teicoplanin and quinupristin-dalfopristin (Aventis Pharmaceutical Co., Tokyo); linezolid (Pharmacia, Tokyo, Japan); and penicillin G, methicillin, ampicillin, oxacillin, and ceftriaxone (Sigma Chemical Co., St. Louis, Mo.).

Bacterial strains and plasmids. Clinical isolates collected in Japan were tested. The collection of organisms included 127 isolates of S. aureus (100 isolates were methicillin resistant), 53 coagulase-negative staphylococcal isolates (methicillin resistant), 138 Streptococcus pneumoniae isolates (45 isolates were penicillin resistant), 26 Streptococcus pyogenes isolates, 26 Streptococcus agalactiae isolates, 27 Enterococcus fecalis isolates, 27 Enterococcus faecium isolates, 27 Escherichia coli isolates, 26 Klebsiella pneumoniae isolates, 27 Enterobacter cloacae isolates, 27 Citrobacter freundii isolates, 27 Serratia marcescens isolates, 27 Pseudomonas aeruginosa isolates, 130 Haemophilus influenzae isolates (81 isolates, including 7 β-lactamase-positive isolates), 27 Moraxella catarrhalis isolates, and 52 Neisseria gonorrhoeae isolates. The clinical isolates of MRSA, S. pneumoniae, and H. influenzae were collected from various hospitals in Japan from 2000 to 2001. The other clinical isolates were collected from various hospitals in Japan over a 10-year period. The MRSA and MR-CoNS isolates were identified by PCR detection of the mecA gene (12).

An isogenic set of three S. aureus strains was used in this study: heterogeneous methicillin-resistant strain MF535, isolated from a Japanese hospital in 1992; homogeneous methicillin-resistant mutant MF535HR, which is a highly resistant mutant derived from MF535 grown on Muller-Hinton (MH) agar (Difo Laboratories, Detroit, MI) containing 400 μg of methicillin per ml; and methicillin-resistant staphylococci (MRSA) have increased all over the world and that such strains are prone to cause serious outbreaks (6, 7, 15). In the United States, the prevalence of MRSA and methicillin-resistant coagulase-negative staphylococci (MR-CoNS) steadily increased in the 1990s, and in 2000 the rate of resistance of S. aureus to methicillin was 55.3% (8, 18). A nationwide survey carried out in Japan during 1992 and 1993 showed that 60.3% of 7,033 clinical isolates were resistant to methicillin, and 86% of these were isolated from inpatients (10). In addition, clinical infections caused by vancomycin-resistant S. aureus isolates carrying the vanA gene were reported from the United States in 2002 (1, 2).

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sustainable mutant MF535 Δmec, which is a spontaneous mecA deletion mutant derived from MF535, Phasmid pMS18, which allows expression of β-lactamase, was kindly provided by T. Okubo from the Laboratory of Drug Resistance in Bacteria, Gunma University School of Medicine, and was transducted with phage S2 into the three strains described above. β-Lactamase production was determined by an iodometric assay (16).

**Susceptibility testing.** MICs were determined by the agar dilution method in MH agar, unless otherwise specified. Two percent sodium chloride was added to MH agar, as required. MH agar supplemented with 5% sheep blood was used for staphylococcal and HA agar with hematin (15 μg/ml) and NAD (15 μg/ml) was used for H. influenzae. Approximately 10^6 CFU per spot was inoculated onto agar plates containing twofold serial dilutions of antibacterial agents. After incubation for 18 to 20 h at 35°C, the MIC was defined as the lowest drug concentration that prevented visible growth. MICs for MRSA test strains were inoculated onto MH agar plates containing twofold serial dilutions of antibacterial agents. After incubation for 18 to 20 h at 35°C, the MIC was defined as the lowest drug concentration that prevented visible growth. MICs for N. gonorrhoeae were determined by an agar dilution method with GC medium (Becton Dickinson, Sparks, Md.) containing growth supplements, as recommended by the NCCLS (17).

**Affinity for PBPs.** The affinities of ME1036, imipenem, cefoxitin, and oxacillin for penicillin-binding proteins (PBPs) were analyzed by a competitive assay with [3H]benzylpenicillin binding by 50% (IC50) compared with that of the control in the absence of the antibiotics tested. The MICs of ME1036 for E. coli, K. pneumoniae, and S. marcescens ranged from 2 to 4 μg/ml. Although the MIC50 of ME1036 for these species were equal to those of imipenem, the MIC50s were four- or eightfold greater than those of imipenem. ME1036 was inactive against P. aeruginosa.

**Antibacterial activities.** The MIC ranges, the MICs at which 50% of the isolates were inhibited (MIC50s), and the MIC90s are shown in Table 1. The MIC50 of ME1036, vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin, imipenem, and gentamicin for 100 clinical isolates of MRSA were 2, 1, 2, 2, 0.5, 64, and 64 μg/ml, respectively. The activity of ME1036 against MR-CoNS was 32-fold more potent than that of imipenem, the strains were inhibited by ≥2 μg of ME1036 per ml. ME1036 (MIC90, 0.016 μg/ml) was slightly more active than imipenem against methicillin-susceptible S. aureus (MSSA).

ME1036 was highly active against S. pneumoniae, including penicillin-resistant strains. The MIC90 of ME1036 was at least 16-fold greater than those of meropenem and ceftriaxone. ME1036 was active against E. faecalis isolates, with an MIC50 of 0.5 μg/ml. ME1036 was inactive against ampicillin-resistant E. faecium.

ME1036 was active against a variety of gram-negative bacteria but was not active against P. aeruginosa. The MIC50 of ME1036 for E. coli and K. pneumoniae were 0.125 and 0.063 μg/ml, respectively, which were comparable to those of imipenem. The MIC50 of ME1036 for C. freundii, E. cloacae, and S. marcescens were determined by an agar dilution method with GC medium (Becton Dickinson, Sparks, Md.) containing growth supplements, as recommended by the NCCLS (17).

**Development of resistance.** Six MRSA strains grown on MH agar plates were inoculated into 5 ml of MH broth. Overnight cultures of those bacterial suspensions grown at 35°C were diluted to about 10^6 CFU/ml with 5 ml of fresh MH broth. After a 2-h preincubation at 35°C, the antibiotic was added at concentrations equivalent to 1/64, 1/4, or 4 times the MIC. The surviving bacteria were counted after 0, 2, 4, and 6 h of incubation at 35°C by subculturing 50-μl serial dilutions (at least 10-fold, to minimize drug carryover) of samples on MH plates. The colonies were counted after incubation for 24 h at 35°C.

**MIC determinations with a high inoculum.** To determine the minimal concentration capable of inhibiting the highly resistant subpopulation of MRSA isolates, determinations of the MICs with a high inoculum of MRSA were carried out as follows: Each strain was grown overnight in 5 ml of MH broth at 35°C for 10 min, after which [3H]penicillin was added to the mixture. After 10 min of incubation, excess unbound benzylpenicillin was added to stop the reaction. Sarkosyl-soluble membrane fractions were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and fluorography. The affinities of the antibiotics for PBPs were expressed in terms of the concentration required to inhibit [3H]benzylpenicillin binding by 50% (IC50) compared with that of the control in the absence of the antibiotics tested.

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### TABLE 1. Antibacterial activities of ME1036 and reference compounds for clinical isolates of bacteria

<table>
<thead>
<tr>
<th>Bacteria (no. of strains) and compound</th>
<th>Bacteria (no. of strains) and compound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MIC (µg/ml)</strong></td>
<td><strong>MIC (µg/ml)</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>50%</strong></td>
<td><strong>90%</strong></td>
</tr>
</tbody>
</table>

**Streptococcus pneumoniae**

- Penicillin susceptible (68)
  - ME1036
    - Vancomycin: ≤0.001–0.004 µg/ml
    - Ceftriaxone: 0.016–0.063 µg/ml
  - Meropenem: 0.008–0.063 µg/ml
  - Penicillin G: 0.016–0.063 µg/ml
  - Vancomycin: 0.25–0.5 µg/ml
  - Levofloxacin: 0.25–2 µg/ml

- Penicillin intermediate (25)
  - ME1036
    - Vancomycin: 0.5–1 µg/ml
    - Levofloxacin: 0.5–2 µg/ml

- Penicillin resistant (45)
  - ME1036
    - Vancomycin: 0.25–0.5 µg/ml

**Streptococcus pyogenes**

- ME1036
  - Vancomycin: 0.5–1 µg/ml
  - Levofloxacin: 0.5–2 µg/ml

- Streptococcus agalactiae (26)
  - ME1036
    - Vancomycin: 0.5–1 µg/ml
  - Levofloxacin: 0.5–5 µg/ml

- Enterococcus faecalis (27)
  - ME1036
    - Vancomycin: 0.125–0.5 µg/ml

**Streptococcus pyogenes**

- ME1036
  - Vancomycin: 0.5–1 µg/ml
  - Levofloxacin: 0.5–2 µg/ml

**Streptococcus pneumoniae**

- MRSA (100)
  - ME1036
    - Vancomycin: 0.5–2 µg/ml
    - Ceftriaxone: 0.5–1 µg/ml
  - Imipenem: 0.063–0.125 µg/ml
  - Meropenem: 0.008–0.016 µg/ml
  - Ceftriaxone: 0.063–0.125 µg/ml
  - Vancomycin: 0.25 µg/ml
  - Levofloxacin: 0.063 µg/ml

**MR-CoNS (53)**

- ME1036
  - Vancomycin: 0.5–2 µg/ml
  - Ceftriaxone: 0.5–1 µg/ml
  - Meropenem: 0.008–0.063 µg/ml
  - Ceftriaxone: 0.016–0.063 µg/ml
  - Vancomycin: 0.25–0.5 µg/ml
  - Levofloxacin: 0.25–2 µg/ml

**Escherichia coli (27)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.5 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Klebsiella pneumoniae (26)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Citrobacter freundii (27)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Enterobacter cloacae (27)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Serratia marcescens (27)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Pseudomonas aeruginosa (27)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Haemophilus influenzae (130)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Monoxella catarrhalis (27)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml

**Neisseria gonorrhoeae (52)**

- ME1036
  - Vancomycin: 0.25 µg/ml
  - Ceftriaxone: 0.63 µg/ml
  - Levofloxacin: 0.63 µg/ml
of MRSA strains. The growth of all MRSA strains tested was inhibited by ME1036 at one-fourth the MIC of but not by vancomycin at one-fourth the MIC.

**MIC determinations with a high inoculum.** The minimal concentrations at which ME1036 and reference antibiotics inhibited the growth of bacterial cells, including the highly resistant subpopulation, are shown in Fig. 3. No subpopulation resistant to ME1036 was detected at a concentration of 16 \( \mu \text{g/ml} \) or higher. The geometric mean MIC with a high inoculum (geomeanMIC-HI) of ME1036 was 4.4 \( \mu \text{g/ml} \). In contrast, highly resistant subpopulations were found by selection with imipenem and oxacillin, and the geomeanMIC-HIs of imipenem and oxacillin were 142 and 1,245 \( \mu \text{g/ml} \), respectively. The geomeanMIC-HI of cefoselis was halfway between those of ME1036 and imipenem. However, most colonies that grew on plates containing a concentration greater than the MIC (inocula of \( 10^4 \) CFU/spot) were extremely small, and their growth was very slow. Figure 4 shows the correlation between the binding affinity for PBP 2a and the geomeanMIC-HIs of ME1036 and reference \( \beta \)-lactams. The decrease in affinity for PBP 2a appeared to increase the geomeanMIC-HI.

**Development of resistance.** One MSSA isolate and four MRSA isolates were serially passaged in medium containing increasing concentrations of ME1036, namely, MSSA strain MF535 \( \Delta \text{mec} \), low-level methicillin-resistant strains N315 (14) and MF535, and high-level methicillin-resistant strains CR1434 and MF685 (Fig. 5). The MICs of ME1036 and imipenem for MSSA strain MF535 \( \Delta \text{mec} \) did not increase after 14 passages. The MRSA strains tested in this study rapidly acquired resistance to imipenem, and the final MIC was 32 \( \mu \text{g/ml} \) or higher. In contrast, the increase in the ME1036 MIC was less than four times for these MRSA strains; in particular, the MIC for pre-MRSA strain N315 did not increase during this test. The final MICs of ME1036 for all MRSA strains tested were 4 \( \mu \text{g/ml} \) or lower.

### TABLE 2. Antibacterial activities of ME1036 and other \( \beta \)-lactam antibiotics against *S. aureus* MF535 and its derivatives

<table>
<thead>
<tr>
<th>Strain</th>
<th>( \beta )-Lactamase</th>
<th>2% NaCl</th>
<th>MIC (( \mu \text{g/ml} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MF535 ( \Delta \text{mec} )</td>
<td></td>
<td>ME1036</td>
</tr>
<tr>
<td>MF535</td>
<td>–</td>
<td>–</td>
<td>0.031</td>
</tr>
<tr>
<td>MF535 ( \Delta \text{mec} )</td>
<td>+</td>
<td>+</td>
<td>0.031</td>
</tr>
<tr>
<td>MF535HR</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>MF535HR ( \Delta \text{mec} )</td>
<td>+</td>
<td>+</td>
<td>0.031</td>
</tr>
<tr>
<td>MF535/pMS18</td>
<td>+</td>
<td>–</td>
<td>0.125</td>
</tr>
<tr>
<td>MF535HR/pMS18</td>
<td>+</td>
<td>+</td>
<td>0.25</td>
</tr>
</tbody>
</table>

### TABLE 3. Binding affinities of ME1036 for staphylococcal PBPs

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibiotic</th>
<th>IC( _{50} ) (( \mu \text{g/ml} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBP 1</td>
<td>PBP 2</td>
</tr>
<tr>
<td>MF535HR (MRSA)</td>
<td>ME1036</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Imipenem</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Oxacillin</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Cefoselis</td>
<td>–</td>
</tr>
<tr>
<td>MF535 ( \Delta \text{mec} ) (MSSA)</td>
<td>ME1036</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Imipenem</td>
<td>0.017</td>
</tr>
</tbody>
</table>

\( ^{a} \) not determined.  
\( ^{b} \) NA, not applicable.

### FIG. 2. Bactericidal activities of ME1036 (A) and vancomycin (B) against six clinical isolates of MRSA. For all six strains tested, the MICs of both ME1036 and vancomycin were 1 \( \mu \text{g/ml} \). Viable cell counts (log_{10} CFU per milliliter) are indicated as the geometric means ± standard deviations calculated from each test. Symbols: –, control; ●, 4 times the MIC (4 \( \mu \text{g/ml} \)); ▲, 1/4 times the MIC (0.25 \( \mu \text{g/ml} \)); ■, 1/64 times the MIC (0.016 \( \mu \text{g/ml} \)).
DISCUSSION

We found that the introduction of an imidazo[5,1-b]thiazole group at the C-3 position of the cephem nucleus (13) or at the C-2 position of the carbapenem nucleus resulted in compounds with potent activities against MRSA. From our research on the optimization of carbapenems, ME1036 was selected as a promising candidate for further development. In the study described in this paper, we determined the MICs of ME1036 for various bacterial pathogens and the in vitro activities of ME1036 against MRSA. One of the remarkable features of the activity of ME1036 was its excellent in vitro activity against *S. pneumoniae*, including penicillin-resistant strains. Although the activity of ME1036 against penicillin-resistant *S. pneumoniae* strains was 16-fold less than the activity against penicillin-susceptible strains, ME1036 inhibited all 138 *S. pneumoniae* isolates at 0.031 μg/ml. On the basis of the MIC, ME1036 may be one of the most potent β-lactam antibiotics against *S. pneumoniae*.

In addition to the potent activity against gram-positive bacteria, ME1036 was also active against members of the family *Enterobacteriaceae*. The in vitro activities of ME1036 against *E. coli* and *K. pneumoniae* were equal to those of imipenem. The activities of ME1036 against strains producing extended-spectrum β-lactamases have not yet been clarified, and further evaluations of the activities of ME1036 against extended-spectrum β-lactamase-producing strains will be needed. The MIC₉₀s of ME1036 for *C. freundii* and *E. cloacae* were lower than those of ceftriaxone but higher than those of the other carbapenems tested. The ME1036 MICs (range, 0.5 to 4 μg/ml) for the ceftriaxone-nonsusceptible strains (ceftriaxone MICs, >8 μg/ml) were higher than those (range, 0.063 to 1 μg/ml) for the ceftriaxone-susceptible strains. ME1036 may be slightly less stable than imipenem and meropenem in the presence of the AmpC β-lactamase.

Like most other carbapenems, ME1036 was inactive against *E. faecium*, since most isolates of *E. faecium* are ampicillin resistant. ME1036 had no activity against *P. aeruginosa*, which is one of the remarkable features of carbapenem antibiotics. We observed that the binding affinities of ME1036 for PBPs from *P. aeruginosa* were almost equal to those of imipenem (data not shown). ME1036 might not reach the targets due to low permeability or the presence of efflux pumps, β-lactamas, and other factors in *P. aeruginosa*.

We investigated the antibacterial activities of ME1036 against an isogenic set of MRSA strains with different levels of resistance to methicillin to clarify the details of the anti-MRSA activity of ME1036. The MIC of ME1036 for the homogeneous MRSA strain was eight times higher than that for the heterogeneous MRSA strain (determined by comparison of the MICs for MF535HR with those for MF535). The MIC of imipenem for homogeneous strain MF535HR was 128 times higher than that for heterogeneous strain MF535. It has been reported that many auxiliary genes are involved in the expression of high-level, homogeneous resistance to methicillin in MRSA (5). We think that these auxiliary genes have little influence on the activity of ME1036. In fact, ME1036 showed excellent activity against clinical isolates of MRSA and MR-CoNS.
The bactericidal activity of ME1036 at a concentration four times the MIC for MRSA strains was similar to that of vancomycin. ME1036 inhibited the growth of MRSA at one-fourth the MIC. We think that binding to PBP 2a may be involved in this growth inhibition, because this phenomenon was also observed in the case of imipenem (data not shown), and ME1036 and imipenem bound sufficiently to PBP 2a at that concentration.

By determination of the MIC-HIs for MRSA, it was found that no subpopulation was highly resistant to ME1036. We think that the geomeanMIC-HIs of β-lactams may depend on their binding affinities to PBP 2a in MRSA (Fig. 4). Therefore, β-lactams with high affinities for PBP 2a, such as ME1036, may be able to inhibit the growth of MRSA even if the highly resistant subpopulation is present at a high ratio. The reason why the highly resistant subpopulations were selected by imipenem even during passages with low inocula may involve its MIC-HI and affinity for PBP 2a.

We showed that ME1036 has a broad spectrum of antibacterial activity and has potent in vitro activities against methicillin-resistant staphylococci; these results are in agreement with its affinity for PBP 2a. Although several new anti-MRSA cephalosporins and carbapenems, such as BAL9141 (11), RWJ-54428 (3), L-695,256 (4), and SM-232724 (20), have been reported, it appears that there are no significant differences in their in vitro activities among these compounds, including ME1036, against MRSA. ME1036, however, is unique in that it also has potent in vitro activities against penicillin-resistant S. pneumoniae, E. faecalis, H. influenzae, and members of the family Enterobacteriaceae. This novel carbapenem is considered worthy of further evaluations.

ACKNOWLEDGMENTS

We thank Matsuhashi Inoue and Kimiko Ubukata from Kitasato University for kindly providing us with clinical isolates of MRSA, S. pneumoniae, and H. influenzae. We also thank Kenichi Hiramatsu from Juntendo University for supplying reference MRSA strains, such as N315, and we also thank Toyoji Ōkubo from Gunma University for

supplying plasmid pMS18 and phage S2. We thank Erumi Murase for technical assistance.

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