Tatsuya Nakamura · Chihiro Shimizu · Mayumi Kasahara
Chiyo Nakata · Machiko Munakata · Hakuo Takahashi

Differences in antimicrobial susceptibility breakpoints for Pseudomonas aeruginosa, isolated from blood cultures, set by the Clinical and Laboratory Standards Institute (CLSI) and the Japanese Society of Chemotherapy

Received: June 22, 2006 / Accepted: November 1, 2006

Abstract A study was made of the antimicrobial susceptibility to and efficacy of various kinds of antimicrobial agents against 179 strains of Pseudomonas aeruginosa that were isolated from blood cultures at Kansai Medical University Hospital from 1990 through 2004. The annual detection rate was highest in 1994, at 22 strains (6.5%). There were 9 multidrug resistant strains of Pseudomonas aeruginosa (5.0%). Among 14 antimicrobial agents tested for measurement, ciprofloxacin (CPFX) showed the best minimum inhibitory concentration (MIC) 50 value, of 0.25 µg/ml, followed by pazufl oxacin (PZFX) and biapenem (BIPM), each at 0.5 µg/ml. When the period of 15 years was divided into three stages, the MIC50 value for each antimicrobial agent was highest in the middle stage (1995 to 1999). Assuming that the percentage of sensitive strains according to the breakpoints set by the Clinical and Laboratory Standards Institute (CLSI) represents the antimicrobial susceptibility rate, amikacin (AMK) showed the best value, of 85.5%. According to the sepsis breakpoint set by the Japanese Society of Chemotherapy (JSC), the efficacy of CPFX showed the highest rate (77.1%) of all the antimicrobial agents tested. Among β-lactams, BIPM showed the highest efficacy rate, of 67.0%. When the efficacy rates were compared with each other, the difference in efficacy rate between the breakpoint set by the CLSI and the sepsis breakpoint set by the JSC was large for β-lactams. Comparisons made based on the CLSI criteria showed no difference in cross-resistance rates between CPFX, meropenem (MEPM), and BIPM. However, when comparisons were made using the JSC sepsis breakpoint, MEPM showed a cross-resistance rate of 87.8%, while the rate for BIPM was lower, at 56.1%, with the χ² test showing a significant difference, at \( P = 0.0014 \). In accordance with the pharmacokinetics/pharmacodynamics theory that has been advocated, breakpoints which are more suitable for the clinical setting in Japan should be set so that more effective and more appropriate treatment can be carried out.

Key words Antimicrobial agents · Breakpoint · Drug susceptibility · Multidrug resistance · Infectious disease surveillance

Introduction

Pseudomonas aeruginosa is a bacterial strain which is known to cause opportunistic infections in compromised hosts and nosocomial infections mainly in intensive care units. In Japan, antimicrobial drugs such as third-generation cephems, carbapenems, fluoroquinolones, and aminoglycosides are often used to treat infectious diseases caused by P. aeruginosa. However, in recent years, P. aeruginosa has acquired various resistance mechanisms, such as β-lactamase-producing and antimicrobial efflux mechanisms. As a result, multidrug resistant P. aeruginosa, which became resistant to many drugs, appeared, the increases in the frequency of isolation of such strains in nosocomial infections have become serious social problems. Diseases caused by P. aeruginosa infection are often difficult to cure. In particular, the prognoses of patients with such infectious diseases that have developed into sepsis are considered to be bad in many cases. Of note, the so-called pharmacokinetics/pharmacodynamics (PD/PD) theory, which determines the therapeutic effect by combining pharmacokinetics with pharmacodynamics, has been advocated in recent years. As various dosing regimens have been designed in different countries, breakpoints which are more suitable for such therapeutic plans should be established. In the present study, we report the antimicrobial susceptibility of various antimicrobial agents and evaluation of their efficacies, based
on the criteria established by the Clinical and Laboratory Standards Institute (CLSI) and the sepsis breakpoint set by the Japanese Society of Chemotherapy (JSC), using P. aeruginosa strains that were isolated from blood cultures at Kansai Medical University Hospital during the period from 1990 through 2004.

Materials and methods

Strains used

The present study included 179 strains of P. aeruginosa which were isolated from blood cultures at our hospital during the period of 15 years from January 1990 through December 2004. When multiple strains with different detection dates were isolated from one patient and the antimicrobial susceptibility of those strains was the same, they were regarded as the same strain and the first isolated strain was selected. When the antimicrobial susceptibility patterns were different, the strains were handled as different ones. Based on the antimicrobial susceptibility, the detection rates of multidrug resistant P. aeruginosa (MDRP) were studied. We defined MDRP strains as meeting all of the following minimal inhibitory concentrations (MIC): ≥16 µg/ml for imipenem (IPM), ≥32 µg/ml for amikacin (AMK), and ≥4 µg/ml for ciprofloxacin (CPFX).

Antimicrobial susceptibility testing

Minimal inhibitory concentrations (MICs) were measured in accordance with the broth microdilution method specified by the CLSI.14 The measurements were made for the following 14 drugs, using an Opt Panel (Kyokuto Pharmaceutical Industrial, Tokyo, Japan): pazufl oxacin (PZFX), CPFX, meropenem (MEPM), panipenem (PAPM), IPM, biapenem (BIPM), AMK, tobramycin (TOB), aztreonam (AZT), ceftazidime (CAZ), cefepime (CFPM), cefozopran (CZOP), sulbactam/cefoperazone (SBT/CPZ), and tazobactam/piperacillin (TAZ/PIPC). The MIC50 and MIC90 values were measured in each of 12 serial dilutions in the range of 0.015 to 32 µg/ml for the fluoroquinolones, aminoglycosides, and carbapenems and in the range of 0.06 to 128 µg/ml for the others. The period of 15 years was divided into three stages (5 years each), and the MIC50 and MIC90 values were compared between these three stages.

Evaluation of efficacies

Based on the results of the antimicrobial susceptibility testing, we assumed the percentages of strains showing susceptibility to be the antimicrobial susceptibility rates according to the breakpoints of the CLSI and the sepsis breakpoint of the JSC.15 and then evaluated the effectiveness of those breakpoints. Because no standard breakpoints were indicated for CZOP, SBT/CPZ, and Pazufl oxacin (PZFX), the value for coftazidime (CAZ) was used for CZOP; that for levofl oxacin (LVFX) was used for PZFX that for MEPM was used for PAPM and BIPM; and that for CPZ was used for SBT/CPZ as standards.

Cross-resistance of CPFX to BIPM and MEPM

The cross-resistance rates of CPFX to BIPM and MEPM were calculated using the respective breakpoints, and the χ² test was used to obtain significant differences. In comparisons with the breakpoints of the CLSI, resistance was determined as being present when the MIC values for CPFX were larger than 2 µg/ml and when the MIC values for MEPM and BIPM were greater than 8 µg/ml. In comparisons with the sepsis breakpoint of the JSC, resistance was determined as being present when the MIC values for CPFX, MEPM, and BIPM were larger than 1 µg/ml.

Results

Detection rates of P. aeruginosa from blood cultures

Table 1 shows changes in the detection rates of P. aeruginosa for the period of 15 years from 1990 through 2004. The highest detection rate was 22 strains (6.75%), in 1994. The lowest was 4 strains (1.19%) in 2000. There were nine MDRP strains (5.0%).

Antimicrobial susceptibility (Table 2)

Cephems, combinations of β-lactamase inhibitors and β-lactams, and monobactams

Among these antimicrobial agents, CZOP showed the lowest MIC50 value, of 2 µg/ml. CAZ and CFPM showed an MIC50 value of 4 µg/ml, and the value for TAZ/PIPC, SBT/CPZ, and AZT was 8 µg/ml. When the MIC50 values were

Table 1. Detection of Pseudomonas aeruginosa isolated from blood cultures (1990–2004)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of strains</td>
<td>211</td>
<td>193</td>
<td>256</td>
<td>282</td>
<td>326</td>
<td>323</td>
<td>405</td>
<td>384</td>
<td>222</td>
<td>313</td>
<td>335</td>
<td>393</td>
<td>425</td>
<td>388</td>
<td>485</td>
</tr>
<tr>
<td>P. aeruginosa; no. of isolates ( % detected)</td>
<td>9 (4.26)</td>
<td>12 (6.21)</td>
<td>14 (5.46)</td>
<td>9 (3.19)</td>
<td>22 (6.75)</td>
<td>14 (4.33)</td>
<td>8 (1.98)</td>
<td>17 (4.43)</td>
<td>7 (3.15)</td>
<td>4 (1.28)</td>
<td>4 (1.19)</td>
<td>4 (5.09)</td>
<td>20 (2.82)</td>
<td>16 (4.12)</td>
<td>26 (5.36)</td>
</tr>
</tbody>
</table>