Relation of %T＞MIC of piperacillin to the clinical outcome in the treatment of Gram-negative bacterial infections

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There are few reports of direct assessment of the percent duration of the dosing interval for which the concentration of the antibiotic in the blood remains above the minimum inhibitory concentration (MIC) (time above the MIC% [%fT＞MIC]) and the clinical outcome for piperacillin (PIPC). Therefore, we investigated the relationship between the %fT＞MIC and the outcomes in patients receiving PIPC therapy. In patients treated with PIPC at Kitasato University East Hospital, the %fT ＞MIC for the antibiotic was determined retrospectively for each patient from the serum concentrations of the drug plotted over time, and the relationship between the %fT＞MIC and the therapeutic response rate was calculated by logistic regression analysis. Evaluation of the efficacy of the drug was carried out on the basis of its bacteriological effects (elimination of the bacterial pathogen). The analysis revealed that a response rate of ＞90% was achieved when the %fT＞MIC was ≥60%. Assessment of the relationship between the emergence of resistant organisms and the %fT＞MIC in the non-responders revealed that the emergence of resistant organisms can be prevented if a %fT＞MIC of 60% can be achieved, at which the drug is known to exert maximal bactericidal effect. In conclusion, this study suggested that maintaining the %fT＞MIC at a target of 60% in the dosage design of PIPC therapy would result in improved clinical outcomes.

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1. Introduction

Since the 1990s, rapid progress has been made in research on the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents, which has contributed in great measure to appropriate treatment of infections and development and marketing of novel antimicrobial agents. Proper use antimicrobial drugs on the basis of the patient background characteristics, causative organisms, site of infection, and the PK/PD characteristics of the drugs is recommended in the Antimicrobial Stewardship Guideline released jointly by the Infection Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA)[1]. It has become possible to gain a better understanding of the pharmacologic effects in relation to the changes of the serum drug concentrations over time by PK/PD analysis, and the information secured thereby is particularly important for proper use of antimicrobial agents[2–4].

Among the most useful outcomes of studies on the PK/PD is clarification of the PK/PD parameters that are correlated with the bactericidal effects of antimicrobial agents *in vivo*. The PK/PD parameters vary with the type of antimicrobial agent studied. In the case of β-lactam antibiotics, for example, it has been shown that the percent time over which the drug concentration remains over the minimum inhibitory concentration (MIC) relative to the dose interval, i.e., the time above MIC% (%T＞MIC), represents a PK/PD parameter[5]. It has also been reported that in the case of penicillin antibiotics, a bacterial growth-inhibitory effect can be achieved at doses yielding a free-form (unbound) drug %T＞MIC (%fT＞MIC) of ≥30% and a maximum bactericidal effect can be obtained at doses yielding a %fT＞MIC of ≥50%[6]. It is of importance, therefore, to set the dosage and administration schedule so as to achieve an appropriate %fT＞MIC in penicillin pharmacotherapy.

We previously assessed the dosage and administration schedule of tazobactam/piperacillin (TAZ/PIPC) from the viewpoint of PK/PD, by determining the association of the dosage and administration schedule with the %fT＞MIC[7]. The %fT＞MIC was calculated from the serum drug concentrations, although the drug concentrations in the infected tissues also appear to have a bearing on the actual therapeutic responses. Consequently, there is the possibility, if the %fT＞MIC calculated from the serum concentrations of the drug is set as an indicator of the efficacy that the drug levels in the infected tissues do not reach the MIC, and it is necessary to relate the therapeutic responses to the %fT＞MIC when this parameter is applied in the clinical practice setting. In Japan, the currently approved daily dose levels of antimicrobial agents are frequently lower than those in Europe and the United States; therefore, there are instances in which the breakpoint stated in the guidelines of the Clinical and Laboratory Standards Institute (CLSI)[8] and European Committee on Antimicrobial Susceptibility Testing (EUCAST)[9] cannot be directly utilized. The approved maximum dose of PIPC, a penicillin antibiotic, is 8.0 g/day in Japan. As of March 2015, a rise in the maximum dose of this antibiotic has been approved and it is now feasi-

ble in Japan to carry out treatment with this drug at the same dose levels as those in Europe and the United States. However, there are no reports yet of direct assessment of the therapeutic responses to PIPC in relation to its %fT＞MIC.

Meanwhile, inappropriate antimicrobial drug administration that fails to provide sufficient serum drug concentrations may give rise to not only failure of treatment, but also to diminution of the antimicrobial susceptibility (emergence of resistant organisms)[10,11]. Treatment with an antimicrobial agent at its MIC, which is the lowest concentration at which it exerts its antimicrobial effect, does not necessarily eliminate all susceptible organisms, and exposure to the drug at a concentration only slightly higher than the MIC may result in a selection of resistant organisms only. The drug concentration at which the selection of resistant organisms is suppressed is termed mutant prevention concentration (MPC), and the concentration range between the MIC, at which resistant variants may be selected, and the MPC is referred to as the mutant selection window (MSW)[12]. There is, in our view, the need for a new parameter to determine the concentration at which emergence of resistant organisms would be suppressed, because it is almost impracticable to determine the MPC in the clinical setting. The mortalities associated with hospital-acquired pneumonia and ventilator-associated pneumonia are still high[13], and one report has documented the emergence of resistant organisms in approximately 10–50% of cases of hospital-acquired pneumonia treated with β-lactam antimicrobial agents[14]. It has been suggested that in an *in vitro* infection setting, the ratio of the trough concentration to the MIC (trough/MIC) of a β-lactam antimicrobial agent was associated with suppression of the emergence of resistant organisms[15], although the relationship between the extent of exposure and the emergence of resistant organisms still remains to be clarified.

Under these circumstances, we conducted this study to assess the relationship between the %fT＞MIC and the clinical efficacy and between the %fT＞MIC and emergence of drug-resistant organisms by means of PK/PD analysis in patients receiving treatment with PIPC.

2. Patients and methods

2-1. Patients

From among inpatients treated with PIPC between January 2006 and March 2014 at the Kitasato University East Hospital (this hospital, hereafter), those with bacterial isolates for which the MICs of PIPC were determined at the time of bacterial culture were included retrospectively in the efficacy evaluation. Poor responders to the antimicrobial therapy were included in the evaluation for the emergence of resistant variants. Patients in whom the duration of treatment with PIPC was ≤3 days and those who concomitantly received other antimicrobial agents were excluded from the analysis.

2-2. Methods of evaluation of the efficacy and the emergence of resistant variants

The efficacy evaluation and evaluation for the emergence of resistant variants were based on bacteriological evaluation. In the efficacy evaluation, patients in whom the post-PIPC treatment bacterial culture demonstrated disappearance of the isolate were regarded as responders, and those in whom the post-PIPC culture showed persistence of the isolate were labeled as non-responders. In the evaluation for the emergence of resistant variants, the occurrence of an isolate from a non-responder for which the MIC of PIPC increased from the initial susceptible range to the intermediate or resistant range after the start of treatment was defined as emergence of a resistant variant. The CLSI criteria were employed for the assessment of the antimicrobial susceptibility of the bacterial isolates[8]. The upper limit of detection of PIPC in the MIC assay at this hospital is 64 mg/L, so that it was impracticable to carry out the evaluation of the isolates for which the initial MIC was already 64 mg/L; therefore, such isolates were excluded from the evaluation for the emergence of resistant variants.

2-3. Calculation of %fT＞MIC

Changes in the serum PIPC concentrations over time in the subject patients were estimated from results of the population pharmacokinetics (PPK) analysis[7], and the %fT＞MIC was calculated for each bacterial isolate species from the changes of the serum concentrations over time and the MIC for each isolate, using the programming software R, version.2.11.1. The changes in the serum concentrations over time were calculated using the following formulae and also the basic information of the subjects.

$$Conc = \{Dose/(CL \cdot T_{inf})\}\{\exp(-kt^{*}) - \exp(-kt)\} \times fuB$$

$$t^{*} = \begin{cases} 0, & (t \leq T_{inf}) \\ t - T_{inf}, & (t > T_{inf}) \end{cases}$$

$k = CL/Vd$　　fuB＝fraction of unbound drug in the blood

Using a protein-binding rate of PIPC of 21.2% (cited from Interview Form), the percent fraction of unbound drug in the blood was calculated. Meanwhile, data from the PPK analysis were used for calculation of the clearance (CL) and distribution volume (Vd). Calculation of the CL requires the creatinine clearance (Ccr), which was derived from patient's basic information using the Cockcroft-Gault equation[16]. For patients with a serum creatinine (Scr) of ＜0.6 mg/dL, in whom the Ccr could be overestimated, the Scr was corrected to 0.6 mg/dL to calculate the Ccr. As the lower detection limit of PIPC in the MIC assay is 8 mg/L at this hospital, the %fT＞MIC for the organisms for which the MIC was ≤8 mg/L was calculated assuming an MIC＝8 mg/L. Similarly, for the organisms for which the MIC was ≥64 mg/L, the %fT＞MIC was calculated assuming an MIC＝64 mg/L, as the upper detection limit of PIPC in the MIC assay at our hospital is

64 mg/L.

2-4. Statistical processing

Statistical analyses were performed using the Chi-squared test for categorical variables and the Student's t-test for continuous variables. Using logistic regression analysis, the "response rate (good＝1, poor＝0)" was incorporated as a dependent variable and the %fT＞MIC as the independent variable in the efficacy evaluation. In the evaluation for the emergence of resistant variants, the "percent emergence of resistant variants (resistant＝1, not resistant＝0)" was incorporated as a dependent variable and the %fT＞MIC as the independent variable. A p-value of ≤5% was considered to denote statistical significance. All statistical calculations were performed using a software package (SPSS® version.20.0 for Windows®).

2-5. Ethical approval

This study was conducted with the approval of the Ethics Committee of Kitasato University School of Medicine (Approval Number: The Ethics Committee of Kitasato University School of Medicine and Hospital, B Ethics 09–80).

3. Results

3-1. Patients

Of the 190 patients treated with PIPC, the background characteristics of the 45 patients included in the efficacy evaluation and 22 patients evaluated for the emergence of resistant variants are summarized in Table 1. There were no significant differences in the patient background characteristics between patients included in the efficacy evaluation and patients included in the evaluation for the emergence of resistant variants.

3-2. Bacterial isolates

Details of the 56 strains of Gram-negative bacteria isolated from the patients included in the efficacy evaluation are shown in Figure 1. A breakdown of the 22 Gram-negative bacterial strains included in the evaluation for the emergence of resistant variants is given in Figure 2. The bacterial isolates subjected to the analysis did not include any that produced extended-spectrum beta lactamase (ESBL).

3-3. Relation of the efficacy and emergence of resistant organisms to the %fT＞MIC

The present study results are schematically illustrated in Figure 3. Of the 56 Gram-negative bacterial strains isolated from the patients included in the efficacy evaluation, 32 strains proved to be responsive to the treatment (mean %fT＞MIC, 38.3±14.6%). The remaining 24 strains were

Table 1. Characteristics of patients included in this study

Parameter	Evaluation of efficacy (N=45)	Evaluation of resistant (N=22)	Significant difference
Sex (male/female)	32/13	14/8	n.s.*1
Age (year)	68.5±11.0 (44.0-91.0)	65.0±10.0 (52.0-82.0)	n.s.*2
Height (cm)	159.5±9.2 (140.0-180.0)	160.1±9.9 (140.0-180.0)	n.s.*2
Weight (kg)	53.9±12.2 (35.9-92.2)	55.2±16.7 (37.5-92.2)	n.s.*2
Dose (g/day)	2.8±1.3 (1.0-8.0)	3.0±1.5 (2.0-8.0)	n.s.*2
Dosing period (day)	7.42±2.66 (4.0-14.0)	8.65±2.21 (5.0-14.0)	n.s.*2
Creatinine clearance (mL/min)	64.8±31.4 (18.7-146.7)	67.1±23.0 (37.0-140.0)	n.s.*2
%fT>MIC (%)	31.8±17.2 (0-81.6)	34.7±10.3 (18.9-58.1)	n.s.*2
Infectious disease type (Duplicate)	Pneumonia : 20 Urinary tract infection : 20 Sepsis : 5 Other : 4	Pneumonia : 11 Urinary tract infection : 9 Sepsis : 1 Other : 1	-

Mean±S.D. (range)

*1 Chi-squared test

*2 Student's t-test

n.s. : not significant

Fig. 1. Details of the 56 strains of Gram-negative bacteria isolated from the patients included in the efficacy evaluation

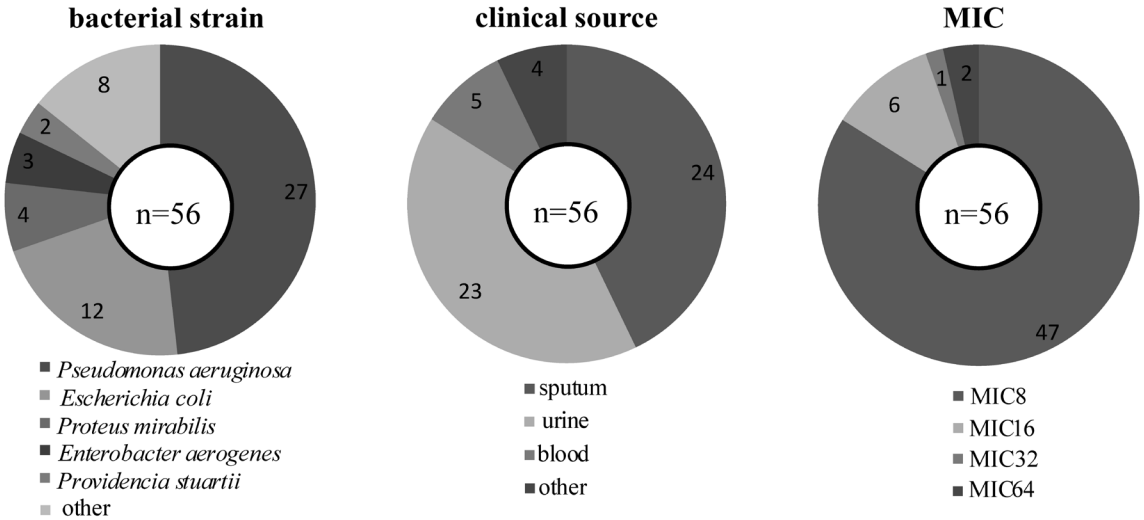


Fig. 2. Details of 22 strains of Gram-negative bacteria isolated from the patients included in the evaluation for the emergence of resistant variants

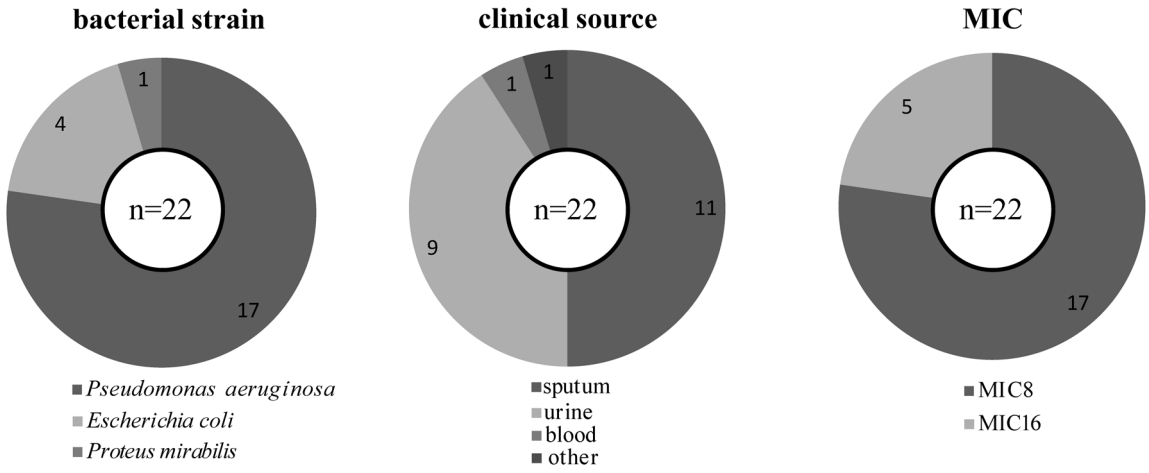


Fig. 3. The present study results are schematically illustrated

From among inpatients treated with PIPC, those with bacterial isolates for which the MICs of PIPC were determined at the time of bacterial culture were included retrospectively in the efficacy evaluation. Poor responders to the antimicrobial therapy were included in the evaluation for the emergence of resistant variants. In the evaluation for the emergence of resistant variants, the occurrence of an isolate from a non-responder for which the MIC of PIPC increased from the initial susceptible range to the intermediate or resistant range after the start of treatment was defined as emergence of a resistant variant. The CLSI criteria were employed for the assessment of the antimicrobial susceptibility of the bacterial isolates.

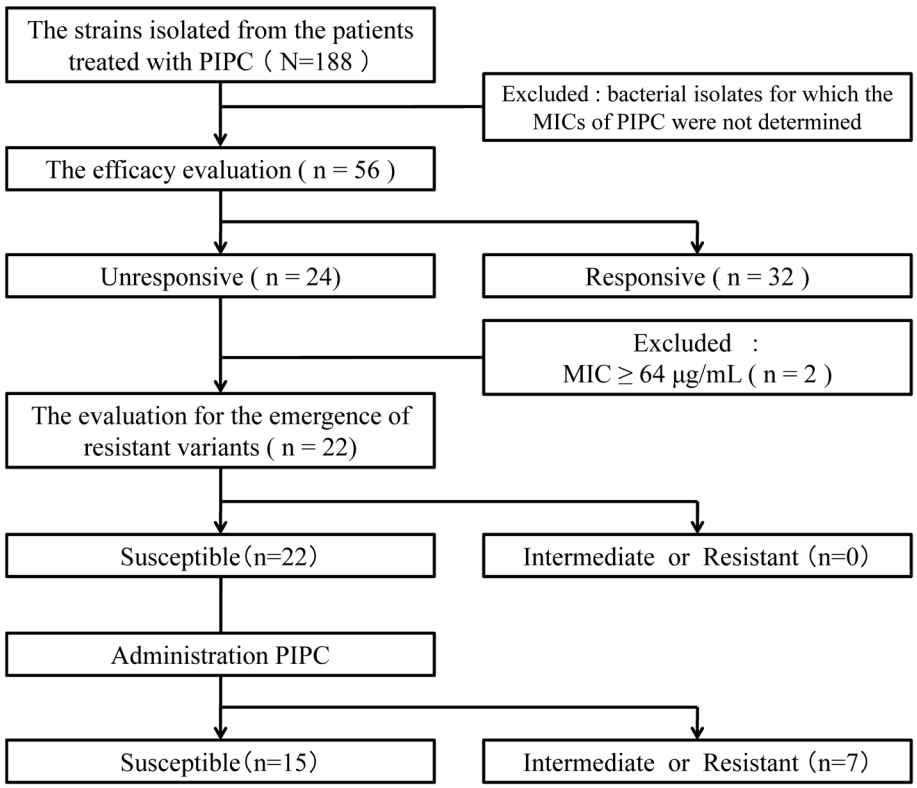
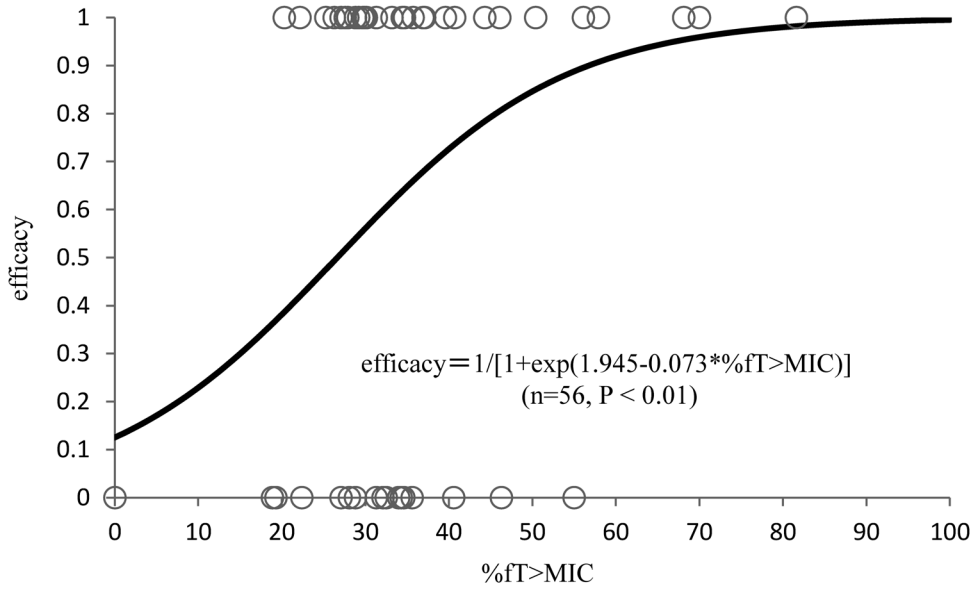


Fig. 4. Logistic regression analysis to determine the relationship between the efficacy and %fT＞MIC

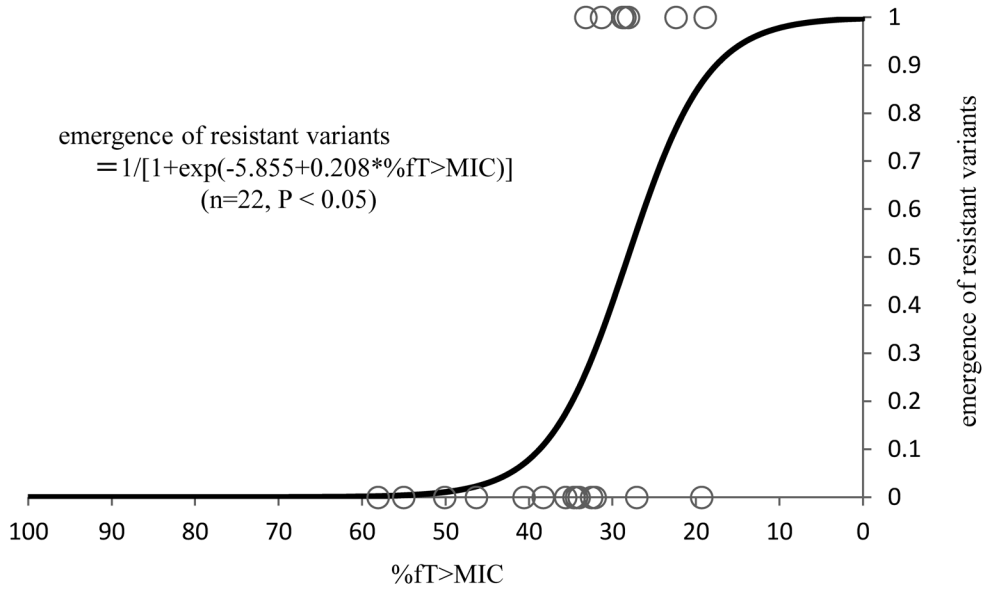


unresponsive to treatment (mean %fT＞MIC, 23.1±16.9%). Results of logistic regression analysis to determine the relationship between the efficacy and %fT＞MIC are presented in Figure 4. A model formula of therapeutic response rate＝1/[1＋exp(1.945－0.073*%fT＞MIC)] was estimated (P＜0.01), and the %fT＞MIC required for achieving a therapeutic response rate of 90% was calculated as 56.7%. Of the 24 strains rated as unresponsive to the treatment in the efficacy evaluation, 22 were subjected to the evaluation for the emergence of resistant variants. Of these 22 Gram-negative strains, no resistant variants were found for 15 of the strains (%fT＞MIC, 38.2 ±10.4%); on the other hand, resistant variants emerged for 7 of the strains (%fT＞MIC, 27.3± 5.0%). Results of logistic regression analysis to determine the relationship between the emergence of resistant variants and the %fT＞MIC are presented in Figure 5. A model formula of therapeutic response rate＝1/[1＋exp(－5.855＋0.208*%fT＞MIC)] was estimated (P＜0.05), and the %fT＞MIC required for achieving a non-emergence rate of resistant variants of 90% was calculated as 38.7%. As a results of sub-analysis for each disease, although there is no significant, there was a tendency like that sufficient efficacy rate of 90% can be obtained with %fT＞MIC＝ 47.2% for urinary tract infection (P＝0.051) and %T＞MIC＝82.6% for pneumonia (P＝0.176).

4. Discussion

Severe infections are associated with increased mortality rates, prolongation of hospitalization, and increase in medical expenses[17,18]. Gram-negative bacterial infections, in particular, are

Fig. 5. Logistic regression analysis to determine the relationship between the emergence of resistant variants and the %fT＞MIC



difficult to treat and are associated with high mortality rates[19]. Furthermore, changes in the PK profiles of drugs may also occur in patients with infections[20]. Increased exposure to drugs due to changes in the PK of a drug increases the possibility of adverse drug reactions to the drug, whilst decreased exposure to drugs increases the chances of failure of treatment or of emergence of drug-resistant organisms[21]. Therefore, selection of a dosing schedule appropriate for each patient is of crucial importance. The trend of increasing resistant organisms is a major global public health concern, and apprehensions over the emergence of resistant organisms are especially relevant at medical facilities. Multidrug-resistant organisms have a bearing on the morbidity rate and duration of hospitalization, and may ultimately account, at least in part, for an increase in the mortality rate. Therefore, effective methods are being sought to prevent transmission of resistant organisms from infected patients to other patients, including by administration of appropriate antimicrobial agents at appropriate doses for appropriate periods[22,23].

In the present study, logistic regression analysis revealed a significant relationship of the %fT＞MIC to the efficacy (bacteriological effect). The therapeutic response rate and the incidence of emergence of resistant variants were calculated for each level of %fT＞MIC, using the computed model formula (Table 2). Analysis using the model formula revealed that the therapeutic response rate was as high as 50% or more at %fT＞MIC＝30%, at which PIPC is known to exert a growth-inhibitory effect on Gram-negative bacteria, and that the therapeutic response rate was ≥80% at %fT＞MIC＝50%, at which the drug is known to exert its maximal bactericidal effect. It follows that maintaining the %fT＞MIC at 30% would yield therapeutic response rates of

Table 2. Relationship between the therapeutic response rate and the incidence of emergence of resistant variants

%fT>MIC	Therapeutic response rate (%)	Incidence of emergence of resistant variants (%)
10	22.4	97.8
20	36.7	84.5
30	53.9	40.5
40	70.2	7.8
50	82.6	1.1
60	90.5	0.1
70	95.0	<0.1
80	97.5	<0.1
90	98.7	<0.1
100	99.4	<0.1

≥50%; while it was inferred from the results of analysis of the relationship between the emergence of resistant variants and the %fT＞MIC, that the %fT＞MIC at which 50% of the infecting organisms might acquire resistance in case of failure of antimicrobial drug therapy was 28.2%. The present study represents a new research attempt to assess the clinical outcome by focusing on the therapeutic response rate and the incidence of emergence of resistant variants with reference to the %fT＞MIC, using clinical data. The results of our analysis showed that not only the therapeutic response rate, but also the incidence of emergence of resistant variants became worse at a bacteriostatic level of the %fT＞MIC, suggesting the importance of selecting a dosing method taking into account bactericidal levels of the %fT＞MIC. By designing the dosage aimed at attaining a %fT＞MIC of 60%, a therapeutic response rate of 90.5% and incidence of emergence of resistant variants of 0.1% can be obtained, enabling sufficient efficacy and sufficient prevention of emergence of resistant organisms.

With a view to interpreting the secured data by linking the dosing method to the clinical responses, probability of target attainment (therapeutic response rate and incidence of resistant variants) in various dosing programs was calculated for each level of renal function as well as for each graded MIC level (8 mg/L, 16 mg/L, and 32 mg/L), with the drip infusion time set at 0.5 hour; the results are summarized in Tables 3-1, 3-2, and 3-3. The breakpoint for PIPC is set at 16 mg/L according to the CLSI and EUCAST criteria, whereby MIC＝16 mg/L is interpreted as implying the organism is susceptible[8,9]. At MIC＝16 mg/L, it is considered that a therapeutic response rate of ≥90% can be attained by adopting a PIPC dose level of ≥12 g/day, even when the Ccr＝100 mL/min (Table 3-2). At MIC＝32 mg/L, on the other hand, there is the possibility that a sufficient therapeutic response rate may not be obtained, depending on the severity of renal dys-

Table 3-1. Probability of target attainment in various dosing programs for each level of renal function (MIC＝8 mg/L)

MIC=8mg/L Tinf=0.5hr	Probability of target attainment					
	Therapeutic response rate (%)	Incidence of resistant variants (%)	Therapeutic response rate (%)	Incidence of resistant variants (%)	Therapeutic response rate (%)	Incidence of resistant variants (%)
	Ccr = 20mL/min		Ccr = 60mL/min		Ccr = 100mL/min	
1.0g q 12h	77.7	3.8	58.3	34.4	46.0	68.4
1.0g q 8h	94.5	<0.1	81.4	2.0	67.5	14.5
1.0g q 6h	98.8	<0.1	93.2	0.1	83.5	1.3
2.0g q 8h	98.9	<0.1	93.4	0.1	83.8	1.2
2.0g q 6h	99.5	<0.1	98.5	<0.1	94.5	<0.1
3.0g q 8h	99.5	<0.1	96.6	<0.1	89.8	0.3
3.0g q 6h	99.5	<0.1	99.4	<0.1	97.2	<0.1

Table 3-2. Probability of target attainment in various dosing programs for each level of renal function (MIC＝16 mg/L)

MIC=16mg/L Tinf=0.5hr	Probability of target attainment					
	Therapeutic response rate (%)	Incidence of resistant variants (%)	Therapeutic response rate (%)	Incidence of resistant variants (%)	Therapeutic response rate (%)	Incidence of resistant variants (%)
	Ccr = 20mL/min		Ccr = 60mL/min		Ccr = 100mL/min	
1.0g q 12h	53.1	49.0	38.6	83.7	31.2	92.8
1.0g q 8h	76.1	4.8	56.8	38.4	44.7	71.4
1.0g q 6h	89.9	0.3	73.4	7.0	59.1	32.5
2.0g q 8h	94.5	<0.1	81.4	2.0	67.5	14.5
2.0g q 6h	98.8	<0.1	93.2	0.1	83.5	1.3
3.0g q 8h	97.9	<0.1	89.8	0.3	78.2	3.5
3.0g q 6h	99.5	<0.1	97.2	<0.1	91.3	0.2

function, even at a PIPC dose of 12 g/day (Table 3-3). These present findings provide evidence to support the definition of intermediate resistance by the CLSI. At MIC＝16 mg/L, therefore, treatment with PIPC is quite feasible and the breakpoint set in the CLSI and EUCAST criteria is considered to be valid.

Table 3-3. Probability of target attainment in various dosing programs for each level of renal function (MIC＝32 mg/L)

MIC=32mg/L Tinf=0.5hr	Probability of target attainment					
	Therapeutic response rate (%)	Incidence of resistant variants (%)	Therapeutic response rate (%)	Incidence of resistant variants (%)	Therapeutic response rate (%)	Incidence of resistant variants (%)
	Ccr = 20mL/min		Ccr = 60mL/min		Ccr = 100mL/min	
1.0g q 12h	25.9	96.5	20.8	98.4	18.6	98.9
1.0g q 8h	35.3	88.5	26.3	96.3	22.3	97.9
1.0g q 6h	46.0	68.4	32.6	91.6	26.7	96.1
2.0g q 8h	76.1	4.8	56.8	38.4	44.7	71.4
2.0g q 6h	89.9	0.3	73.4	7.0	59.1	32.5
3.0g q 8h	89.5	0.3	72.9	7.5	58.7	33.4
3.0g q 6h	97.1	<0.1	87.7	0.5	75.3	5.4

A limitation of this study was that cases with MIC ≤8 mg/L were considered as cases with MIC＝8 mg/L for calculation of the %fT＞MIC, because the lower limit of detection of the MIC assay for PIPC at our hospital is 8 mg/L. According to a surveillance reported by Tsuji *et al.*, the percentage of *Pseudomonas aeruginosa* isolates for which the MIC of PIPC is ＜8 mg/L is 44.4%, suggesting the presence of clinical isolates of *P. aeruginosa* for which the MIC of PIPC is less than 8 mg/L[24]. Finally, there is the possibility that the MICs were overestimated in our present analysis, resulting in underestimation of the %fT＞MIC. It would be reasonable to assume that PIPC was effective against those isolates for which the MIC of the drug was ＜8 mg/L. Considering that the %fT＞MIC values may have been underestimated in this study, it is possible that the %fT＞MIC actually required to achieve a therapeutic response rate of 90% may be smaller than that estimated in this study. Further, the %fT＞MIC was calculated from the changes in the serum drug concentrations over time, which were based on a renal function parameter (Ccr). However, it can be assumed that the changes in the serum drug concentrations over time and the therapeutic response would vary with the drug distribution to the sites of infection and the severity of the infection. No assessments by the site/severity of the disorder were performed, nor were any assessments made taking into account the drug distribution into the infected tissues in the present analysis. Furthermore, the bacterial isolates that were evaluated for the emergence of resistant variants were from the same patients and belonged to the same strains, however, no genetic assessment of the strains' identity was performed. This limitation was related to the retrospective nature of the study, and further prospective studies in a larger number of clinical cases are needed.

A rise in the maximum dose of PIPC was approved in March 2015 in Japan, enabling clinical use of this drug at doses comparable to those used in Europe and the United States. It is considered deeply significant for appropriate therapy in the future, that associations were demonstrated in the present analysis, carried out based on the PK/PD theory, between the response/suppression of emergence of resistant variants and the dosage and administration schedule of antimicrobial drugs.

Conflict of interest

None declared.

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