Evaluation of arbekacin anti-MRSA agents for adult in Japan

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There are a limited number of reports that compare the clinical efficacy of anti-MRSA agents such as arbekacin (ABK), vancomycin (VCM), teicoplanin (TEIC) and linezolid (LZD). There is a tendency for these four agents to show variation in the inflammatory response parameters, in C-reactive protein (CRP) and in white blood cell count (WBC), depending on the administration period. There was no significant difference among the agents in analysis of variance (ANOVA) in the group of days 1–3 ($p=0.0536$) but there was some significant difference in the group of days 4–7, as well as days 8–14 ($p<0.001$, $p<0.01$) in relative variation rate of CRP. Furthermore, we compared in more detail the groups of LZD, VCM and ABK, with a significant decrease of CRP, each of which showed more decrease in comparison with the group of TEIC in the period days 4–7 ($p<0.01$). We took 1-hr serum level after days 3–4, with the ABK treatment as the peak concentration (C_{peak}). Having made nonlinear logistic regression analysis of CRP and C_{peak}/MIC, we concluded that the decrease rate estimable by early inflammatory effect could be decreased to some 40%, assuming that C_{peak}/MIC shows the high value within 4 days after ABK treatment.

Introduction

The anti-MRSA agents currently available in Japan are: arbekacin (ABK) of the antibacterial agent aminoglycoside, and both vancomycin (VCM) and teicoplanin (TEIC) of the agent glycopeptide. Also, linezolid (LZD) of the agent oxazolidinone was considered appropriate to add as one of the anti-MRSA agents. Recently, daptomycin (DAP) is a newly-approved antibacterial

agent, the first lipopeptide agent to be released onto the market in Japan. The antibacterial power against MRSA using ABK, VCM, TEIC and LZD, showed an equivalent value of MIC_{90}[1–3]. The quick sterilizing efficacy using these 4 drugs against MRSA, *in vitro*, resulted in ABK significantly reducing bacterial count, VCM less significantly, LZD less than VCM, and TEIC less than VCM[1]. It is important to clinically decrease patients' inflammatory parameters quickly, in order to support their QOL and treatment fees. There have been limited reports on this point, and analysis is difficult until various influencing factors have been excluded. We previously calculated the relative variation rate of reduction of CRP related to the drug administration period, using a commonly available simple measuring method. We also evaluated the clinical efficacy of these four drugs as well as the medical economic problem[4]. This time we extended the examination period and added WBC in the examination items prior to evaluation. Examination of the details indicated that the results of using the anti-MRSA agents varied, depending on the part infected and in which department of the hospital the patient belonged. Therefore, in order to avoid distortion, we examined the following points by grouping the clinical effects of each administration period: calculation of the relative variation rate of CRP and WBC in the anti-MRSA drug administration period and evaluation of the cases with ABK, using pharmacokinetic-pharmacodynamic (PK-PD) parameters. The early CRP reduction rate was evaluated by nonlinear logistic regression analysis.

Materials and Methods

We examined all patients who had received ABK, LZD, TEIC and VCM of the injectable anti-MRSA agents at Kitasato University Hospital from April 2006 to August 2007. Patients treated with TEIC were included in the survey only when they had received a loading dose of the same drug.

Evaluation on relative variation rate of CRP and WBC

Patients matching any of the following criteria were excluded from the objects of this study:

(1) pediatric patients
(2) patients taking anticancer drugs within one month after the dose of the anti-MRSA agents
(3) patients taking steroids within one month after the dose of the anti-MRSA drugs
(4) patients taking anti-fungal agents during dosage of the anti-MRSA treatment
(5) patients not undergoing a hematological test within 3 days before or after the dose of the anti-MRSA drugs
(6) patients with hemorrhagic shock or DIC
(7) patients with a hematogenic tissue tumor
(8) patients taking the anti-MRSA drugs for less than 3 days
(9) patients whose decrease rate of CRP value after taking the anti-MRSA drugs was under 30%

Calculation of the relative change in CRP and WBC

The starting day of anti-MRSA treatment was regarded as day 0. The day of the laboratory test was regarded as day 0, provided it was performed after the initiation of treatment and within 48 hours. The following days were counted as days 1 and 2.

Relative change in CRP on day N was calculated using equation 1 shown below.

$$\text{Relative change in CRP}(\%) = \frac{\text{CRP day N} - \text{CRP day 0}}{\text{CRP day 0}} \times 100 \qquad \text{(Equation 1)}$$

The dosing period was divided into three periods: days 1–3, days 4–7 and days 8–14. For each period, the mean relative change in CRP in response to each anti-MRSA agent was calculated. In addition, homogeneity of the data for each of the three groups relative to the data for the entire population studied was evaluated by ANOVA. If this analysis revealed significant inter-group differences, pairwise comparison and statistical tests were performed. WBC was also analyzed in the same way. In the days 1–3 group, the percentage of reduction in CRP relative to its baseline value was calculated against each agent.

PK-PD analysis through nonlinear logistic regression analysis of ABK

The drug concentration within an hour after a dose of ABK was considered peak concentration (C_{peak}) and PK-PD was analyzed by examining the values of primary MIC and CRP. For safety evaluation purposes, the drug concentration immediately prior to the dose was regarded as C_{trough}. Ccr was calculated using blood urea nitrogen (BUN), serum creatinine (Scr) and Cockcroft-Gault equation analysis[5]. These three indicate renal function. When Scr was below 0.4 μg/mL, which is the detectable limit of ABK, the drug concentration was regarded as 0.4 μg/mL.

Criteria for judgment of infection

Such cases were deemed to be infectious when bacteria were isolated from the aseptic parts, *e.g.*, blood, and when bacteria at a level over 10^6 CFU/mL were isolated from the non-aseptic parts, *e.g.*, sputum.

Identification of bacteria and assessment of bacteria sensitivity to drugs

Assessment during the settled period was based on the microdilution method approved by The Clinical and Laboratory Standards Institute (CLSI)[6]. MIC was measured to determine sensitivity to drugs using the microwell panel PC6.1J; MicroScan Walk-Away-96® (Dade Behring Inc., Deerfield, IL). MIC of the clinically isolated strain at the beginning of dosage of the anti-MRSA agents was considered to be the primary MIC.

Blood sampling and measurement of ABK serum concentration

The attending physician took patients' blood samples of ABK serum concentration after day 3 or 4: the measured value within one hour after the dose of the drug was considered C_{peak}, and the measured value immediately prior to the dose was considered C_{trough}, safety was measured by evaluation on a randomly selected day. This laboratory sample testing was carried out with the informed consent of patients or their families. Serum concentration was measured with TDx-Arbekacin Kit® (Abbott Japan) and by fluorescence polarization immunoassay (the FPIA method).

Calculation method of PK-PD parameters of ABK

With PK parameters, we evaluated the early efficacy of the ABK and regarded the blood level after day 3 or 4 with the ABK treatment as C_{peak}. We carefully evaluated the C_{trough}, emphasizing clinical safety of the sampling data. As for PD parameters, we used the primary MIC as well as CRP of the day, or within 24 hours after the dose of the drug, for evaluating efficacy. The nonlinear logistic regression analysis was made after examining the primary analysis of the covariant in each item of these parameters. On the basis of the above analysis, the predicted value y′ was calculated with C_{peak}/MIC as x, and CRP improvement percentage as y, the objective variate (Equation 2).

Nonlinear logistic regression analysis was carried out using the nonlinear least squares method. (algorithm: Dan-Ping Gauss-Newton method).

$$y' = \gamma/(1+\alpha\times\exp(-\beta x)) \qquad \text{(Equation 2)}$$

Safety was evaluated through the analysis of BUN, Scr and Ccr. The total concentration was analyzed because the protein-binding rate is known to be low: 3–12%[7].

Statistical analysis

The computer program JMP®7 (SAS Institute Inc.) was used for the statistical analysis of data. As for evaluation of variation rate in CRP and WBC relative to the administration period, during which patients' body temperature was taken on the first day, fourth day and the last day of the dosage, homogeneity of the entire group was tested by ANOVA. The Tukey-Kramer HSD test was carried out when this analysis revealed significant differences. The both-side-risk-rate less than 5% ($p<0.05$) was regarded to be statistically significant. The study was designed as an observation study using existing data derived from clinical practice. It was carried out in accordance with the Ethical Guidelines on epidemiological studies (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare of Japan) and the law on protection of individual information, as well as the Ethical Guidelines for Clinical studies of our hospital.

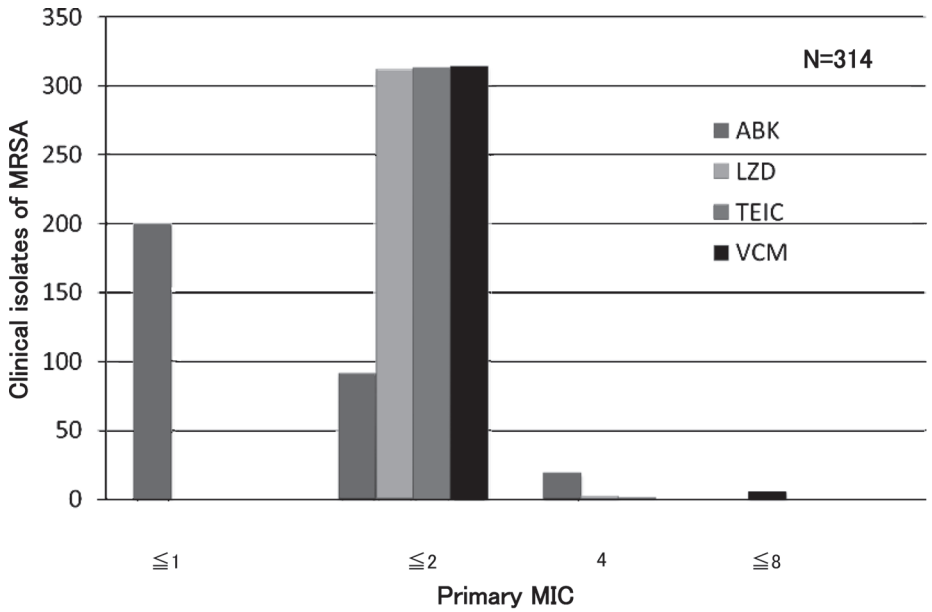
Results

There were 660 cases dosed with anti-MRSA agents in our hospital from April 2006 to August, 2007. Of these, 110 cases were with ABK, 82 cases with LZD, 170 cases with TEIC, and 298 cases with VCM. A total of 314 strains of MRSA were isolated. The data of primary MIC are shown on Fig. 1.

Efficacy of relative variation rate in CRP and WBC

The analytic objects were 14 cases with dosage of ABK, 26 of LZD, 29 of TEIC and 80 of VCM. The excluded patients with less than 30% CRP included 16 cases with dosage of ABK, 6 of LZD, 26 of TEIC and 42 of VCM. There were significant differences among these groups within the administration period ($p<0.05$). Comparison revealed a significantly shorter administration period in the ABK and the VCM treatment groups, than in the TEIC treatment group. The statistical analysis according to patients' body temperature taken on the first day, fourth day and the last day after the dosage, revealed a significant difference with ABK and VCM on the first and the last days ($p<0.05$, Table 1). Patients were divided into three groups according to the administration period: days 1–3, days 4–7 and days 8–14. The relative variation rate in CRP of the anti-MRSA agents showed no significant difference in any pairwise comparison of the group of days 1–3 ($p=0.0536$, ANOVA, Fig. 2-1).

Fig. 1. Distribution of primary MIC against clinically isolated MRSA strains.



ABK: arbekacin, LZD: linezolid, TEIC: teicoplanin, VCM: vancomycin
MIC : minimal inhibitory concentration

Table 1. Patient characteristics.

	Gender (M/F)	Age (years)	Daily dose (mg)	Administration (days)	Serum concentration		Body temperature(Mean±S.D.)		
					C_{peak} [a]	C_{trough} [b]	Day 0	Day 4	After administration
ABK	14(9/5)	72.5 (33–84)	125 (75–400)	7(4–17) *	10.5 (4.1–26.2)	1.7 (0.4–3)	37.7±0.47 **	37.5±0.60	37.3±0.51 **
LZD	26(20/6)	66.5 (19–82)	900 (600–1200)	11(4–28)	–	–	38.0±0.71	37.6±0.64	37.2±0.70
TEIC	29(19/10)	63.0 (17–91)	400 (200–800)	13.5(3–68) *	–	13.8 (6.4–31.2)	38.0±0.98	37.5±0.53	37.3±0.54
VCM	80(45/35)	63.0 (16–87)	1000 (300–2000)	11(3–59)	11.0 (1.2–31.6)		38.4±0.98	37.7±0.69	37.4±0.84
					Median(range)				

* Statistically significant by Student's *t*-test ($p<0.05$)
** Tukey-Kramer HSD test ($p<0.05$)
ABK: arbekacin, LZD: linezolid, TEIC: teicoplanin, VCM: vancomycin
[a] C_{peak}: the serum arbekacin concentration 1 hour after administration
[b] C_{trough}: the serum arbekacin (teicoplanin) concentration immediately before administration

In the group of days 4–7, there were significant differences among the drugs concerning the relative variation rate in CRP ($p<0.001$, ANOVA). There was a significant reduction of CRP in the VCM, LZD and ABK treatment groups, compared to the TEIC treatment group ($p<0.01$, Fig. 2-1).

In the group of days 8–14, there were also significant differences among the drugs concerning the relative variation rate in CRP ($p<0.01$, ANOVA). Here there was a significant reduction of CRP in the LZD ($p<0.05$, Fig. 2-1), VCM and ABK treatment groups, compared to the TEIC treatment group ($p<0.01$, Fig. 2-1).

The relative variation rate in WBC was analyzed in the same way as CRP, dividing the patients according to the drug administration period: days 1–3, days 4–7 and days 8–14. The relative variation rate of decrease of WBC varied significantly (ANOVA) in the days 4–7 group. Comparison revealed a significant decrease of WBC in the LZD treatment group relative to the TEIC group ($p<0.05$, Fig. 2-2).

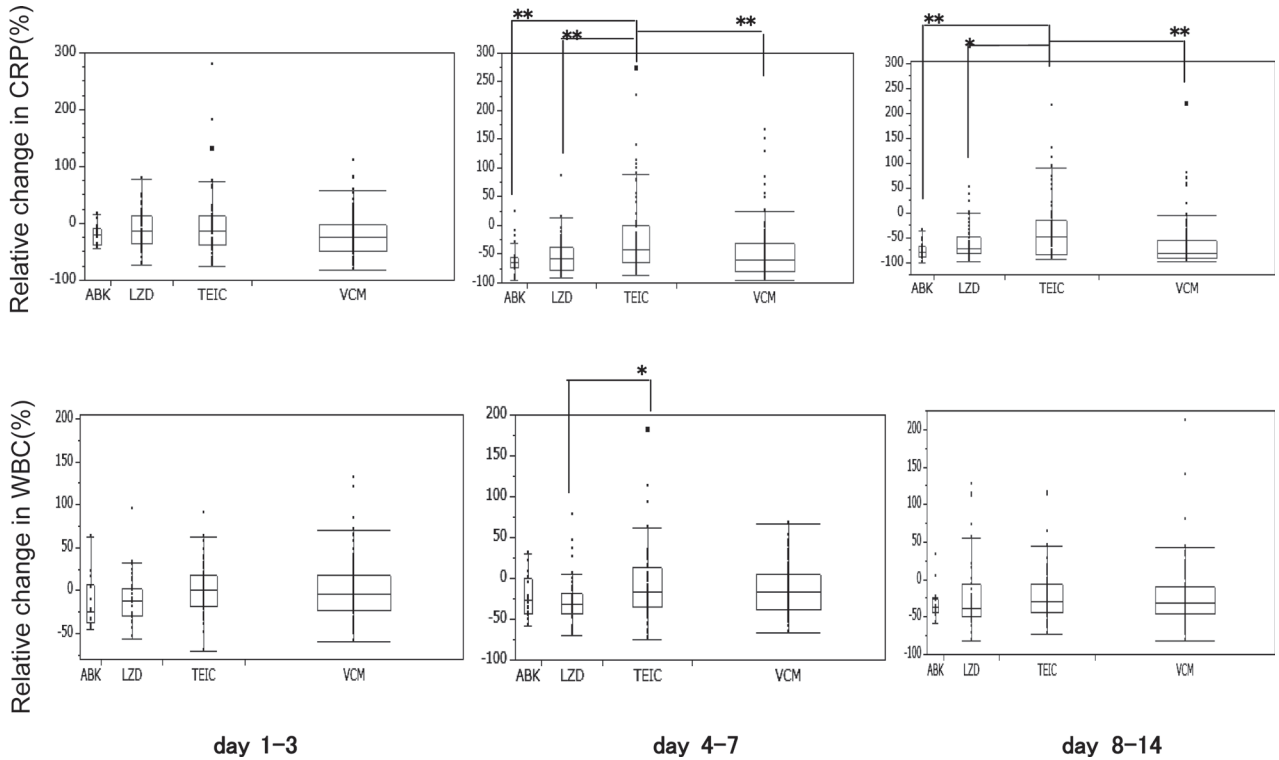
Pharmacokinetic and pharmacodynamic analyses of ABK

Mainly ABK was analyzed because the administration period of this agent was the shortest among that of other anti-MRSA agents. In the group of days 4–7 and days 8–14, ABK was significantly showed improvement among the drugs concerning the relative variation rate in CRP. Data at 6 points in the cases were included in the efficacy evaluation. The median C_{peak} for the 6 points was 7.8μg/mL (range: 4.1–26.2) (Table 2). When the percent CRP improvement was plotted against the C_{peak} of ABK, the variance was large and no correlation was noted (Fig. 3-1). The

Fig. 2. Relative change in CRP and WBC in relation to the administration period (day 1–3, 4–7, 8–14).

Fig.2–1

Fig.2–2



The dosing period was divided into three periods: days 1–3, days 4–7 and days 8–14.
For each period, the mean relative change in CRP in response to each anti-MRSA agent was calculated.
If ANOVA revealed significant inter-group differences, pairwise comparison and statistical tests were performed.
Tukey–Kramer HSD test, $*p<0.05$, $**p<0.01$

Table 2. Characteristic of arbekacin using for PK-PD analysis.

Characteristics			
C_{peak} (6 points)	(μg/mL)	7.8	(4.1 — 26.2)
C_{trough}(25 points)	(μg/mL)	0.7	(0.4 — 4.7)
MIC of ABK	(μg/mL)	1	(1 — 8)
AST	(IU/L)	27	(6 — 92)
ALT	(IU/L)	29	(3 — 253)
BUN	(mg/dL)	14	(7 — 92)
Serum creatinine	(mg/dL)	0.6	(0.21 — 7.17)
Creatinine clearance	(mL/min)	82.2	(7.74 — 224.20)
			Median(range)

C_{peak}: the serum arbekacin concentration 1 hour after administration,
C_{trough}: the serum arbekacin concentration immediately before administration,
MIC of ABK: minimal inhibitory concentration of arbekacin,
AST: aspartate aminotransferase,
ALT: alanine aminotransferase,
BUN: blood urea nitrogen.

MIC of ABK in the 6 points was 1 or 2μg/mL. In the analysis of CRP reduction relating to C_{peak}, a significant regression curve was obtained for C_{peak}/MIC and CRP reduction. The percentage of the CRP reduction rate was sufficiently high at the level close to 10μg/mL (Fig. 3-2). The equation for prediction (y′) was obtained by the nonlinear least squares method (Equation 3).

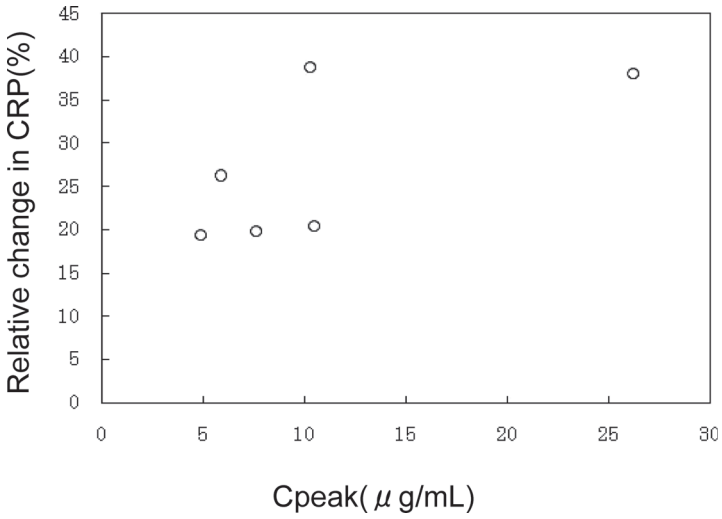
$$y' = 39.29/(1 + 5.46 \times \exp(-0.34 \times x))$$
$$x: C_{peak}/MIC \qquad \text{(Equation 3)}$$

Data on C_{trough} at 25 points in 24 patients were included in the safety evaluation. Data on patients with disease associated with compromised renal function, or disease involving the risk for such a function, are shown in Table 2, including overlapped cases. C_{trough} was often high in patients with compromised renal function (Fig. 4-1, 4-2). Very strict management was enforced for these cases.

Discussion

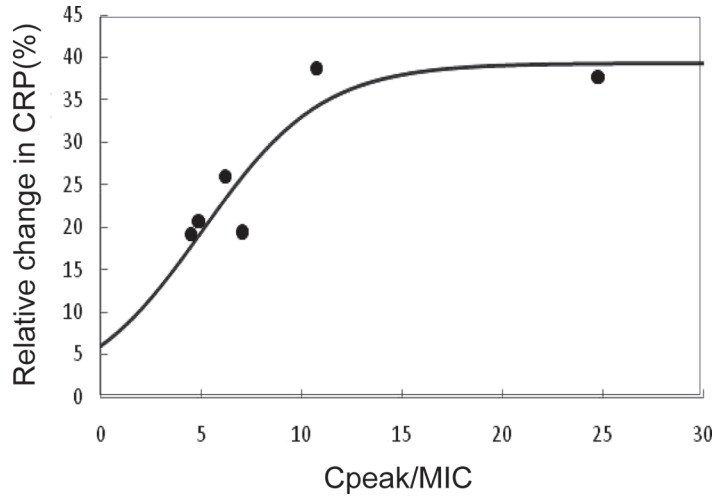
MRSA is currently one of the most drug-resistant bacteria extant, causing in-hospital infections and being comparable to *Pseudomonas aeruginosa*. If susceptible hosts are infected with MRSA, the infection will be intractable, often leading to such severe conditions as pneumonia and sepsis. Fig. 1 summarizes the MIC of various drugs against MRSA at the start of treatment with the drugs. ABK is expected to play a significant role, in view of the several reports published, concerning vancomycin-intermediate resistant *Staphylococcus aureus* (VISA)[8] or

Fig. 3-1. Pharmacokinetic and pharmacodynamic analyses of ABK plotting CRP against C_{peak}.



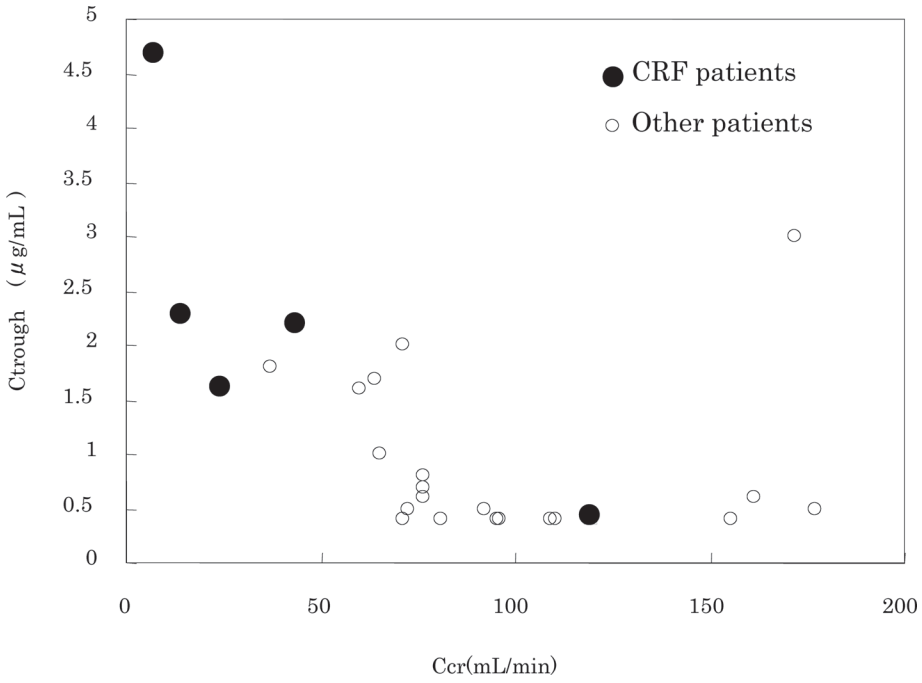
As for PK and PD parameters, C_{peak} and CRP on day 3–4 served as an indicator of early efficacy.
C_{peak}: the serum arbekacin concentration 1 hour after administration,
CRP: C-reactive protein

Fig. 3-2. Pharmacokinetic and pharmacodynamic analyses of ABK (nonlinear logistic regression curve, plotting CRP against C_{peak}/MIC).



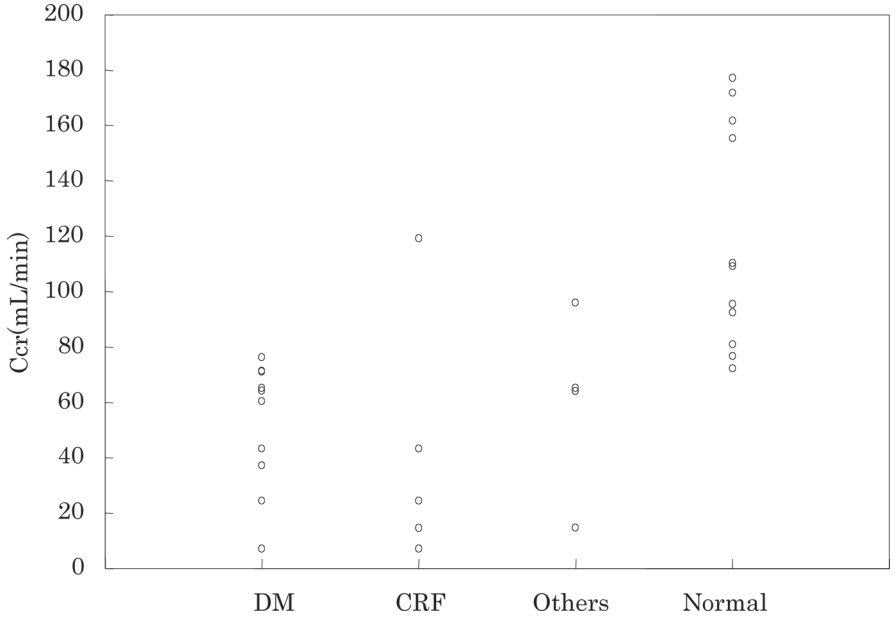
As for PK and PD parameters, C_{peak} and CRP on day 3–4 served as an indicator of early efficacy, and primary MIC served as indicators of efficacy.
The MIC of ABK is all sensitive.
C_{peak}: the serum arbekacin concentration 1 hour after administration,
MIC: minimal inhibitory concentration,
CRP: C-reactive protein

Fig. 4-1. ABK plotting C_{trough} against Ccr (other and CRF patients).



C_{trough}: the drug concentration immediately before the next dose was deemed as the trough concentration, Ccr: creatinine clearance, CRF: chronic renal failure, Others: others low renal function disease.

Fig. 4-2. Ccr plotting against renal function in each disease group.



Ccr: creatinine clearance, DM: diabetes mellitus, CRF: chronic renal failure, Others: others low renal function disease, Normal: normal renal function.

β-lactam antibiotic-induced vancomycin-resistant *Staphylococcus aureus* (BIVR)[9,10]. Four drugs (ABK, LZD, TEIC and VCM that DAP is excluded) are approved as anti-MRSA agents in Japan and MIC_{90} in each agent differs little[1–3]. However, the administration period for the same disease tends to vary among these drugs[11] and the percent reduction of inflammatory reactions tends to differ depending on the administration period. We have previously evaluated early inflammatory parameters and reported that CRP showed a significant decrease with the group of ABK in comparison with the group of VCM and TEIC in the period of days 1–3[4]. According to another report, the clinical efficacy of ABK was superior to that of VCM and TEIC[12]. With such a background, we extended the survey period of our study and analyzed early inflammatory reactions in response to treatment with anti-MRSA agents at the different dosing periods, using the relative variation rate of CRP and WBC as indicators. Furthermore, using PK and PD parameters of ABK, analysis of new concepts with a nonlinear logistic model was carried out, which evaluated the efficacy in a more clinically feasible way by predicting the efficacy on early inflammatory reactions and by adopting the PK-PD parameters published previously[13–16].

The relative variation rate of CRP did not differ significantly among the four anti-MRSA agents in the group of days 1–3. However, the CRP decrease during days 1–3 tended to be greater with ABK than with the other three drugs (Fig. 2-1). Kurazono, *et al.*, compared the acute bactericidal activity in terms of MIC of ABK, LZD, TEIC and VCM, and indicated that ABK exercised the most potent activity[1]. There was no significant difference in the outcome in ABK or any other drugs in the group of days 1–3. One possible reason for this result is that there were fewer cases with ABK in the present study, compared to the cases with other drugs previously studied. As for the effects of TEIC on CRP, this antibiotic was significantly inferior to the other three drugs in the period of days 4–7 and 8–14 (Fig. 2-1). As for the effects on early inflammatory parameters, this antibiotic was lower than the other three in the period of days 1–3, although the difference was not statistically significant. Usefulness of ABK has been endorsed since its once-daily administration was approved in Japan in March 2008[17]. During this present survey, this drug was administered once daily to 76 of the 110 cases and twice daily to the remaining 34 cases. ABK is known to exert a concentration-dependent bactericidal activity, and is expected to yield excellent results when administrated once daily[13,14,17,18]. The present survey did not involve evaluation of the clinical efficacy of single-dose ABK. If single-dose analysis is performed, it is expected that efficacy in alleviating early inflammatory reactions will be marked. In view of the well-known characteristics of TEIC (large distribution volume and low clearance)[19], this drug is expected to exert higher clinical efficacy when the initial loading dose level is increased. In previous studies of high-dose TEIC therapy reported by several investigators[20–22], excellent clinical efficacy was noted and no serious adverse reaction was observed, verifying this expectation. An initial trough concentration of TEIC is low in this survey. Therefore, this survey is thought that TEIC loading dose is a few. Treatment with LZD resulted in a significant decrease of CRP in the

group of days 1–3 and 4–7, compared to treatment with TEIC ($p<0.05$, $p<0.01$) (Fig. 2-1). LZD is known to show its effective transfer to tissues, and can suppress the formation of cytokines as well[23]. These features of LZD probably explain the data obtained in the present study regarding inflammatory parameters. Regarding the change of WBC, the efficacy of LZD was significantly different from that of TEIC only in the group of days 4–7 (Fig. 2-2). Although care is required regarding bone marrow suppression, which is a serious adverse effect of LZD, the present study revealed no significant difference in such suppression among the drugs, suggesting the reliability of the LZD data obtained in the present study. As for the relative variation rate in CRP, VCM reduced CRP more significantly than TEIC in the group of days 4–7 and 8–14 ($p<0.01$). In the group of days 1–3, the effect of TEIC on inflammatory parameters was the second highest next to ABK. The data shown in Fig. 2 also indicate a stable level of CRP reduction during the treatment with VCM, and is therefore expected to consistently exert stable efficacy. There was no case with low CRP value this time, but it is necessary to be aware that we must be very careful when CRP does show low value under conditions of severe infection.

PK-PD analylsis of ABK was carried out using the data on serum ABK concentration measured during the first 3 or 4 days of treatment. The CRP response rate was plotted against C_{peak} as a preliminary analysis, but the variance was too large (Fig. 3-1). When we corrected the MIC for C_{peak}, the variation became smaller, and then a useful nonlinear logistic regression curve for C_{peak}/MIC and CRP response rate was yielded (Fig. 3-2). It is indicated that the predicted CRP response rate of early inflammatory parameters will decrease about 40% if C_{peak}/MIC is high during the first 4 days of ABK treatment. However, we must add that this decrease rate of approximately 40% was the maximum rate among those cases with good analytical results. It will be necessary to increase the number of cases in order to improve reliability[24]. There were no cases with sepsis this time, nor any serious cases with low CRP value.

Regarding the relation of body temperature to the predicted WBC improvement curve following treatment with AGs against infections caused by Gram-negative bacterium (GNB), Kashuba *et al.*, reported that the improvement rate tends to rise as the C_{peak}/MIC during the initial treatment period becomes higher[25]. In the future, it will be important to conduct this sort of study in a larger subject population, involving calculation of AUC on the basis of PK, and evaluation of AUC/MIC[26,27].

In the case of ABK, it has been reported that C_{trough} is associated with its adverse effects and that the incidence of nephropathy rises as C_{trough} becomes higher[14]. In the present study, C_{trough} was higher in patients with impaired renal function (Fig. 4-1). Ccr tended to be lower in the group of DM, CRF and other groups compared to the disease-free normal group (Fig. 4-2). Some patients who were under hemodialysis were included in the group of CRF, and the C_{trough} immediately prior to hemodialysis was adopted in this group, which resulted an apparent high C_{trough} (Fig. 4-1). These patients continued to receive TDM management and showed no serious adverse reactions.

The present study was carried out in a clinical setting and the treatment plan was tailored to TDM in the individual cases. Particularly strict management was enforced as to renal dysfunction. As a result, no serious adverse reaction was noted in any cases. We retrospectively evaluated the clinical efficacy of the above four agents in a clear-cut manner with CRP and WBC during the administration period. It needs to analyze with DAP in the future. Henceforth, it will be necessary to make an incorporative investigation with the bacteriological evaluation, the analysis against each disease, the analysis of pediatric patients, the analysis of breast X-ray images in this study. The definite statement we can issue at the present time is that the use of TDM allows prediction of early response of inflammatory parameters in patients, except those who may have risk factors (*e.g.*, impaired renal function and auditory disorder)[28,29], or those who may have a high primary MIC. We can also state that ABK, which is expected to be effective also against GNB[30], is a promising first-line anti-MRSA agent.

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