ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2006, p. 3754–3762 Vol. 50, No. 11
0066-4804/06/$08.00+0 doi:10.1128/AAC.00420-05

Population Pharmacokinetics of Arbekacin in Patients Infected with Methicillin-Resistant *Staphylococcus aureus*

Yusuke Tanigawara,[1]* Reiko Sato,[1] Kunihiko Morita,[1] Mitsuo Kaku,[2] Naoki Aikawa,[3] and Kihachiro Shimizu[4]

Department of Pharmacy, Keio University Hospital, Tokyo, Japan[1]; Division of Molecular Diagnostics, Department of Clinical Medicine, Tohoku University, Graduate School of Medicine, Sendai, Japan[2]; Department of Emergency and Critical Care Medicine, Keio University Hospital, Tokyo, Japan[3]; and The Kitasato Institute, Tokyo, Japan[4]

Received 2 April 2005/Returned for modification 23 June 2005/Accepted 23 December 2005

Arbekacin, a derivative of dibekacin, is an aminoglycoside developed and widely used in Japan for the treatment of patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA). The population pharmacokinetics of arbekacin was investigated in the Japanese, using 353 patients infected with MRSA and 50 healthy or renally impaired volunteers. The age of the study population ranged from 8 to 95 years, and weight ranged from 10.8 to 107 kg. In total, 1,581 serum arbekacin concentrations were measured (primarily from routine patient care) and used to perform the present pharmacokinetic analysis. Drug concentration-time data were well described by a two-compartment open model. Factors influencing arbekacin pharmacokinetics were investigated using a nonlinear mixed-effect model analysis. The best-developed model showed that drug clearance (CL) was related to creatinine clearance (CL_{CR}), age, and body weight (WT), as expressed by CL (liter/h) = $0.0319CL_{CR}$ + (26.5/age) (CL_{CR} < 80 ml/min) and CL (liter/h) = $0.0130\ CL_{CR}$ + 0.0342WT + (26.5/age) ($CL_{CR} \geq 80$ ml/min). The volume of distribution for the central and peripheral compartments was different in healthy subjects and infected patients, and this difference was more pronounced among disease types. The elderly subjects (aged 80 years or over) exhibited, on average, a 19% greater volume for the central compartment. The volumes for the peripheral compartment were 50.6 liters in patients with pneumonia and 24.3 liters in patients with sepsis. The population pharmacokinetic parameters of arbekacin obtained here are useful for optimal use of this aminoglycoside in the treatment of MRSA-infected patients.

Arbekacin [1-*N*-(*S*)-4-amino-2-hydroxybutyl dibekacin] is an effective aminoglycoside antibiotic against methicillin-resistant *Staphylococcus aureus* (MRSA) and is stable in the presence of aminoglycoside-inactivating enzymes produced by MRSA (1, 10, 22). Arbekacin is a derivative of dideoxykanamycin B (dibekacin), developed in Japan, with specific activities against both gram-positive and gram-negative bacteria (16). The anti-MRSA potency of arbekacin was superior to that of vancomycin (1), and arbekacin showed a longer postantibiotic effect than vancomycin did (44).

In this decade, arbekacin, vancomycin, and teicoplanin have been used for the treatment of MRSA infections in Japan. Similar to other aminoglycosides, arbekacin is excreted exclusively in urine in its unchanged form via glomerular filtration, and some portion is reabsorbed by tubular reabsorption. In subjects with normal renal function receiving a single intramuscular dose of 3 mg/kg of body weight (typical half-life of arbekacin is 1.5 to 2.7 h), the apparent volume of distribution (V) is 0.28 to 0.37 liter/kg, and the total body clearance (CL) is 97 to 146 ml/min per 1.73 m^2 (6). In patients with severe renal insufficiency (creatinine clearance [CL_{CR}], <10 ml/min), the half-life is 18.5 to 46.4 h, the apparent V is 0.26 to 0.56 liter/kg, and total body CL is 8 to 12 ml/min per 1.73 m^2 (6). Thus, linear relationships are observed between arbekacin pharmacokinetics and the glomerular filtration rate.

* Corresponding author. Mailing address: Department of Hospital Pharmacy, School of Medicine, Keio University, Tokyo 160-8582, Japan. Phone: 81-(0)3-5363-3847. Fax: 81-(0)3-5269-4576. E-mail: tanigawa@sc.itc.keio.ac.jp.

Although the approved dose and dosage of arbekacin for adult patients (150 to 200 mg per day) is usually administered as a divided dose by intravenous or intramuscular injection, therapeutic drug monitoring (TDM) is often used to achieve drug concentrations within the therapeutic range for individual patients. Since patients treated with arbekacin usually suffer from severe infections, it is important to reach the target therapeutic concentration quickly. The effective peak concentration of arbekacin is presumed to be 7 to 12 μg/ml, and the safe trough concentration is less than 2 μg/ml. However, these recommended serum concentrations of arbekacin were based on other aminoglycosides, such as gentamicin, amikacin, and tobramycin. The optimal serum concentration of arbekacin for patients infected with MRSA has not been investigated previously.

In order to interpret individual TDM measurements and then apply them to dose individualization, the pharmacokinetic information in the target patient population is essential. However, only limited findings have been reported on arbekacin disposition in a small number of subjects. In the present study, we have conducted an open-label, multicenter study to characterize arbekacin pharmacokinetics and pharmacodynamics in a large population, including some patients infected with MRSA. Arbekacin concentration data obtained during routine clinical care (sparsely monitored) were collected and analyzed by a population pharmacokinetic analysis using a nonlinear mixed-effect model. The purpose of this article is to describe the population pharmacokinetics of arbekacin in Japanese patients infected with MRSA, and the concentration-response relationships are reported in a companion article (35).

(This work was presented in part at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, 14 to 17 September 2003.)

MATERIALS AND METHODS

Material. Arbekacin, O-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl-(1→4)]-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine sulfate, produced by Meiji Seika Kaisha, Ltd. (Tokyo, Japan) was used.

Population. Serum concentration data of arbekacin from 353 hospitalized Japanese patients with suspected MRSA infections were collected prospectively from 51 institutions participating in the current study, The Anti-MRSA Drug TDM Study Group (see Acknowledgments), from 1999 through 2002. These drug concentration data were collected as part of routine TDM data. The following information was also collected: gender, age, body weight (WT), and laboratory data, including serum creatinine, creatinine clearance, blood urea nitrogen at appropriate times during arbekacin treatment, and MICs of isolated pathogens. The CL_{CR} estimate calculated according to the Cockcroft-Gault equation (3) was used for any patients without actual CL_{CR} measurements. The study also accepted the associated retrospective clinical data. In cases where blood sampling was taken as part of the routine TDM and clinical laboratory testing, written informed consent and ethical approval were not necessary. Also, retrospective data on 28 healthy volunteers and 22 renally impaired volunteers (healthy subjects) were also included in the study (2, 17, 41, 42, 45). Renal impairment severity ranged from mild to severe [$CL_{CR} \geq 70$ ml/min ($n = 1$), 50 ml/min $\leq CL_{CR} < 70$ ml/min ($n = 7$), 20 ml/min $\leq CL_{CR} < 50$ ml/min ($n = 11$), $CL_{CR} < 20$ ml/min ($n = 3$)], and these individuals were not infected with MRSA. The reasons for including healthy volunteers and renally impaired volunteers in the analysis were as follows. (i) Because there is not much drug concentration data for the patients, i.e., two to four concentrations for each individual, extensive drug concentration data from volunteers are also used to build a structural pharmacokinetic model. (ii) By pooling data, we can directly compare pharmacokinetic characteristics between healthy subjects and infected patients. (iii) We included data from renally impaired volunteers in the analysis to investigate the effect of renal impairment, because there was not a representative number of patients with renal impairment among the infected patients.

Dosing schedules. In healthy or renally impaired volunteers, a single dose of 75, 100, or 200 mg was administered over 25 min by intravenous infusion to 14, 20, and 5 subjects, respectively. Three volunteers were administered 75 mg of arbekacin every 12 h for five consecutive days, three volunteers were administered 100 mg of arbekacin every 12 h for five consecutive days, and five volunteers were administered 200 mg of arbekacin every 24 h for five consecutive days. The attending physicians of 353 hospitalized patients with suspected MRSA infection ordered various dosing schedules, and these dosing schedules are summarized in Table 1. Although the arbekacin label recommends a 150- to 200-mg/day dose (twice-daily regimen), a once-daily regimen was actually used (23, 24) similar to the regimens of other aminoglycosides. A total of 236 patients received concomitant antibiotic therapy, such as β-lactams, another aminoglycoside, macrolides, quinolones, fosfomycin, and so on. It is known that there is no pharmacokinetic interaction between arbekacin and these drugs (package insert of habekacin, Meiji Seika Kaisha, Ltd., Tokyo, Japan). For 10 patients, it was unknown whether other antibiotics had been concomitantly prescribed.

TABLE 1. Distribution of dosages and dosing intervals of 353 hospitalized patients with suspected MRSA infection

Dose or dosing interval	Frequency (%)
Doses (mg)	
37.5–75	10.7
80–100	41.2
120–150	20.6
175–200	24.3
225–400	3.2
Dosing intervals (h)	
4–8	3.0
9–15	52.5
16–27	42.1
28–39	0.7
47–50	1.5

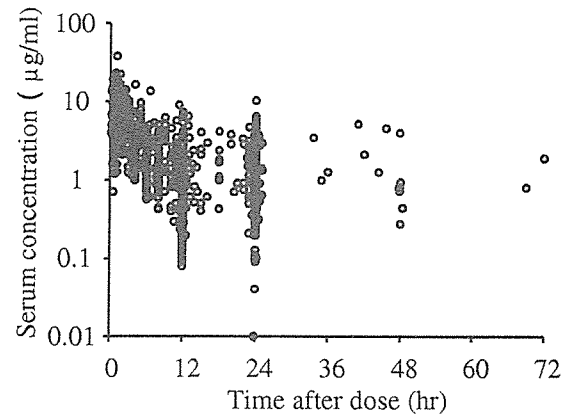

FIG. 1. Profile of serum arbekacin concentration versus time. A total of 1,581 serum concentrations versus time for arbekacin following a single intravenous infusion of 15 min to 2 h in 403 subjects are plotted.

Pharmacokinetic method. Serum arbekacin concentrations were measured as part of routine clinical monitoring at each hospital where the serum samples were taken. The doses and sample times were accurately recorded. Sera were stored at −20°C until analyzed. Arbekacin levels were measured by fluorescence polarization immunoassay (FPIA) using the TDX system (Dainabot Co., Ltd., Tokyo, Japan). The lower limit of detection was 0.4 μg/ml. The coefficients of variation for the assay were 3.0%, 3.8%, and 2.9% for arbekacin mean concentrations of 1.98, 6.10, and 11.88 μg/ml, respectively.

In a single-dose study (2, 17, 41, 42, 45), up to nine samples were drawn from healthy or renally impaired volunteers at the following time points: 0.5, 1, 1.25, 1.5, 2, 4, 6, 8, and 12 h after administration. For the multiple-dose study (42, 45), for five consecutive days, up to 32 samples were drawn from healthy volunteers at the following time points: 0.5, 1, 1.25, 1.5, 2, 4, 6, 8, and 12 h after the first dose and the last dose and immediately before and 1 h after each dose. The concentrations of arbekacin in serum were determined by one of the following three methods. A bioassay method was performed using *Bacillus subtilis* ATCC 6633 as a test organism, mycin assay agar (peptone [5 g], beef extract [3 g], and agar [15 g] in 1,000 ml of distilled water, quantum sufficiat) as the assay medium, and 0.1 M phosphate buffer (pH 8.0) as the diluent (37). The lowest detectable concentration of arbekacin by the cup-plate method was 0.016 μg/ml. Another method was high-performance liquid chromatography (HPLC) with a Tri Rotor SR 2 system analyzer (JASCO Corporation, Tokyo, Japan) and TSK gel ODS 120A-5 or 10-μm column (4Ø × 50 mm; Tosoh Corporation, Tokyo, Japan) by the postlabeling method (15). The accuracy of this HPLC assay was 2.7 to 3.8% in human serum. The lower limit of detection in serum was 0.5 μg/ml. The last method was FPIA using the TDX system. Good linear correlations were found among the bioassay, HPLC, and FPIA methods; thus, these three assays were comparable (2, 17).

Pharmacokinetic model. A population pharmacokinetic analysis was performed using the NONMEM program (version V) with a PREDPP library and the NM-TRAN preprocessor. The pharmacokinetics of arbekacin was assumed to follow a two-compartment model where elimination takes place from the central compartment. We first fitted the one- and two-compartment models with no covariates, and the results suggested that the two-compartment model better described the current data set. The change in the objective function value (ΔOBJ) between the one- and two-compartment models was 392.5 in the basic model with no covariates, and furthermore, the biphasic elimination was showed by the plot of serum concentration profile (Fig. 1). The basic parameters were total body clearance (CL), volume of distribution in the central compartment (V_1), volume of distribution in the peripheral compartment (V_2), and intercompartmental clearance (Q), and these were estimated using a model from the PREDPP library (ADVAN 3 and TRANS 4).

The interindividual variability in CL, V_1, and V_2 was assumed to obey a log-normal distribution, expressed by the following equations, because pharmacokinetic parameters are always positive and because the distribution of individual parameters is usually skewed to the right.

$$\ln CL_i = \ln CL + \eta^{CL}_i$$

$$\ln V_{1i} = \ln V_1 + \eta^{V_1}_i$$

$$\ln V_{2i} = \ln V_2 + \eta^{V_2}_i$$

where η_i denotes the difference between the individual parameter (CL_i, V_{1i}, and V_{2i}) for subject i and the typical value (CL, V_1, and V_2) predicted by the population mean. The η is distributed with a mean of zero and a variance equal to ω^2. The addition of ω on Q resulted in no improvement of model fitting. Therefore, ω for Q was not included in the population model.

The models also included estimates of the residual random error for arbekacin (ε). The residual random errors are composites of assay errors, intraindividual changes in the pharmacokinetic parameters, and model misspecification errors. The distribution of ε was assumed to be normal and was characterized by a mean of zero and a variance, σ^2, which can be estimated by NONMEM. The residual variability was modeled by an additive error according to the equation $Cp = F + \varepsilon$, where Cp is the observed serum arbekacin concentration and F is the concentration predicted from the compartmental model.

Factors affecting the pharmacokinetics of arbekacin. Starting from a simple two-compartment model, covariates that might influence the pharmacokinetics of arbekacin were stepwise added one by one to the basic model. About CL, first the individual posthoc estimates of arbekacin CL were obtained from the basic model before a covariate was added into the model, and then the linear relationship between arbekacin CL and CL_{CR} was obtained. Moreover, we also obtained the upper limit of the linear relationship. Since CL_{CR} is a useful parameter describing renal function, we thought CL_{CR} as a covariate influencing arbekacin clearance was reasonable. Therefore, a fixed-effect variable, i.e., CL_{CR}, was added into the basic model. As an upper limit of the linear relationship between arbekacin CL and CL_{CR}, we explored 60, 80, 100, or 120 ml/min as possible breakpoints. Moreover, the CL was modeled as being proportional to both CL_{CR} and body weight in patients with normal renal function. For each model, the improvement in the fit obtained on addition of a fixed-effect variable into the overall model was assessed by the difference in the objective function, which is equal to −2(log likelihood difference). This difference is asymptotically distributed as χ^2 with degrees of freedom equal to the number of added/reduced parameters. A change in the objective function value of 3.84 with freedom of unity represents a statistically significant ($P < 0.05$) model improvement. Thus, the regression coefficients (θ) of the patients CL_{CR} values of ≥80 ml/min and <80 ml/min were assumed to be different.

$$CL = \theta_1 CL_{CR} \ (CL_{CR} < 80 \text{ ml/min})$$

$$CL = \theta_1 CL_{CR} + \theta_5 WT \ (CL_{CR} \geq 80 \text{ ml/min})$$

where CL is a typical value of clearance. Whether the other covariates, such as age and sex, influenced arbekacin clearance were examined by adding them one by one into the model. In the same way, we estimated a covariate influence to V_1 and V_2. All covariates investigated were as follows: (i) WT, age, elderliness, sex, and disease types on V_1 and (ii) WT, elderliness, and disease types on V_2. When the effect of elderliness was considered for V_1, even after WT and disease types were taken into account, $V_{1\ \text{elderly}} = \theta_{10} V_{1\ \text{nonelderly}}$.

The influence of elderliness was tested by two models with different breakpoints. In model 1, age of <65 years versus age of ≥65 years was tested ($\Delta OBJ = 6.5$; $P = 0.011$). In model 2, age of <80 years versus age of ≥80 years was tested ($\Delta OBJ = 10.3$; $P = 0.001$).

Since model 2 fit the data better, we chose 80 years as the breakpoint for elderliness. In addition, dividing the population into three subgroups on the basis of two breakpoints (65 and 80 years) showed no further improvement on model fitting. No covariate affected the intercompartmental clearance.

Validation of the developed population pharmacokinetic model. The bootstrap resampling procedure is often used for evaluating the stability and robustness of a population model by repeatedly fitting it to the bootstrap samples when there is no test data set (5). A bootstrap involves repeated random sampling, with replacement, of the original data set to produce another data set of the same size as the original but with a different combination of subjects. The bootstrap resampling was repeated 200 times to evaluate whether an appreciable discrepancy existed between the parameter values estimated from the original data and the estimated bootstrap mean values. The entire procedure was performed in an automated fashion using DOS batch files, Microsoft Excel routines, and Awk scripts, in conjunction with NONMEM (30). The bias, expressed as the mean prediction error of observed and model-predicted concentrations, and the precision, root mean square prediction error, from the final population model, were compared with the mean bias and mean precision obtained from the 200 bootstrap analyses.

TABLE 2. Description of patient data used in the pharmacokinetic analysis of arbekacin[a]

Characteristic	Value
No. of subjects	403
Males/females	275/128
Age (yr) (mean ± SD) [range]	61.5 ± 19.1 [8–95]
WT (kg) (mean ± SD) [range]	54.4 ± 12.7 [10.8–107]
Creatinine clearance (ml/min) (mean ± SD) [range]	88.4 ± 60.5 (52)[b] [2–458]
Serum creatinine level (mg/100 ml) (mean ± SD) [range]	1.05 ± 1.29 (385)[c] [0.2–11.5]
Healthy male volunteers	28
Renally impaired volunteers	22
Patients with pneumonia	235[d]
Septicemic patients	60[d]
Patients with other infectious diseases	68
No. of serum samples	1,581
No. of samples/subject (in repetitive dosing) (mean ± SD) [range]	3.9 ± 4.4 [1–32]

[a] All patients and volunteers were Japanese.
[b] Number of actual CL_{CR} measurements.
[c] Number of patients whose laboratory test data were available.
[d] Ten patients suffered from both pneumonia and septicemia.

RESULTS

Patients. Table 2 summarizes the characteristics of the subjects participating in the current study. Their ages ranged from 8 to 95 years, their weights ranged from 10.8 to 107 kg, and 128 of the patients were female. Two children who were 8 years old were included, and the other children were more than 16 years olds. A total of 215 subjects were older than 65 years, and 66 subjects were older than 80 years. Most of the starting dose regimens were 100 mg twice a day (32.6% of all patients). At the end of treatment, however, the majority of dose regimens were 200 mg once a day (31.2% of all patients) compared with 20.7% taking 100 mg twice a day.

A total of 1,581 serum samples were obtained from 403 subjects, for an average of 3.92 samples per subject, a median of 2 samples per subject, and a range of 1 to 32 points per subject. For 89.2% of the subjects, more than two serum samples were taken to determine arbekacin concentration. Many samples were drawn at the end of infusion and/or immediately before the next administration. Figure 1 contains a plot of all serum concentrations versus postdose sampling time.

Population pharmacokinetic parameters of arbekacin. Table 3 shows the results of hypothesis testing for each factor that was included in the full model. In patients with a CL_{CR} of ≥80 ml/min, both θ_5 and θ_6 were significantly different from zero, indicating that CL was related to both body weight and creatinine clearance. In contrast, in patients with CL_{CR} of <80 ml/min, only CL_{CR} was a significant factor, while body weight showed an insignificant effect, suggesting that the CL in this population has a simple relationship with CL_{CR}. These findings suggest that the arbekacin dose is usually determined on the basis of a patient's renal function but that body weight must be taken into account for patients with normal renal function. The estimated arbekacin clearance determined by the

TABLE 3. Hypothesis testing for factors affecting pharmacokinetics of arbekacin

Question	Model compared	OBJ	ΔOBJ (−2l.l.d.)[a]	*P* value
	Full model[b]	2,949.705		
Is CL proportional to CL_{CR}?				
CL_{CR} < 80 ml/min	Full model vs $\theta_1 = 0$	3,094.280	144.575	<0.001
CL_{CR} ≥ 80 ml/min	Full model vs $\theta_5 = 0$	2,963.974	14.269	<0.001
Is CL proportional to patient WT? (CL_{CR} ≥ 80 ml/min)	Full model vs $\theta_6 = 0$	2,968.591	18.886	<0.001
Is CL inversely proportional to age?	Full model vs $\theta_7 = 0$	2,971.777	22.072	<0.001
Do patients with pneumonia or sepsis have different V_1 values?	Full model vs $\theta_8 = 1$	3,006.228	56.523	<0.001
Do patients with other infections have different V_1 values?	Full model vs $\theta_9 = 1$	2,969.434	19.729	<0.001
	Full model vs $\theta_9 = \theta_8$	2,954.717	5.012	0.025
Do elderly people have different V_1 values?	Full model vs $\theta_{10} = 1$	2,955.665	5.960	0.014
Do patients with infectious diseases other than pneumonia have different V_2 values?	Full model vs $\theta_{11} = 1$	2,972.816	23.111	<0.001
Do patients with pneumonia have different V_2 values?	Full model vs $\theta_{12} = 1$	2,953.524	3.819	0.05
	Full model vs $\theta_{12} = \theta_{11}$	2,966.097	16.392	<0.001

[a] −2l.l.d., −2(log likelihood difference).

[b] $CL = \theta_1 CL_{CR} + (\theta_7/\text{age})$ (CL_{CR} < 80 ml/min), $CL = \theta_5 CL_{CR} + \theta_6 WT + (\theta_7/\text{age})$ (CL_{CR} ≥ 80 ml/min) $V_{1\ \text{healthy}} = \theta_2 WT$, $V_1 = \theta_8 V_{1\ \text{healthy}}$ (pneumonia or sepsis), $V_1 = \theta_9 V_{1\ \text{healthy}}$ (infections other than pneumonia and sepsis), $V_{1\ \text{elderly}} = \theta_{10} V_{1\ \text{nonelderly}}$, $V_{2\ \text{healthy}} = \theta_3$, $V_2 = \theta_{11} V_{2\ \text{healthy}}$ (except pneumonia), $V_2 = \theta_{12} V_{2\ \text{healthy}}$ (pneumonia), $Q = \theta_4$.

Bayesian method using the basic model versus CL_{CR} is shown in Fig. 2.

The population mean of V_1 was 0.170 (liter/kg). Patients with pneumonia or sepsis increased the V_1 value significantly by 60% (θ_8), and patients with infections with the exceptions of pneumonia and sepsis increased the V_1 value significantly by 40% (θ_9) compared to subjects who were not infected. Figure 3 shows the individual V_1 values for healthy subjects and patients with infectious diseases classified by the type of illness. These V_1 values were calculated by the Bayesian method using the final model. Moreover, the elderly subjects over 80 years showed a 19% increase in V_1.

The V_2 was 15.7 liters in healthy subjects, and the V_2 in patients with infectious diseases was larger than that of healthy subjects. The V_2 value in patients with pneumonia is especially large, i.e., 3.2 times larger than the V_2 value in healthy subjects and twice as large as the V_2 value in patients with infections with the exception of pneumonia.

The final estimates for the population pharmacokinetic parameters of arbekacin are summarized in Table 4. Fig. 4 shows scatter plots of predictions versus observed concentrations and weighted residual versus predictions. The interindividual variability in CL, V_1, and V_2 were estimated as 38.8, 37.1, and 164.6%, respectively, and intraindividual residual variability for arbekacin concentrations was 1.07 μg/ml.

Model validation. The final model was fitted repeatedly to 200 bootstrap-resampled data sets. The average parameter values obtained from the bootstrap analyses and the final estimates from the original data set are compared in Table 5.

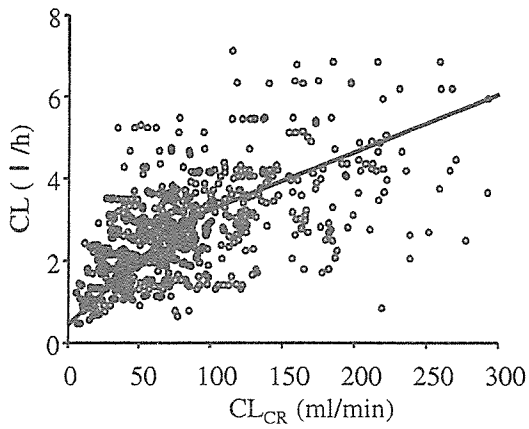

FIG. 2. Estimated individual clearance of arbekacin versus creatinine clearance actually measured or estimated by the Cockroft-Gault method. The two lines represent the population mean described in the final model with a break at 80 ml/min of creatinine clearance.

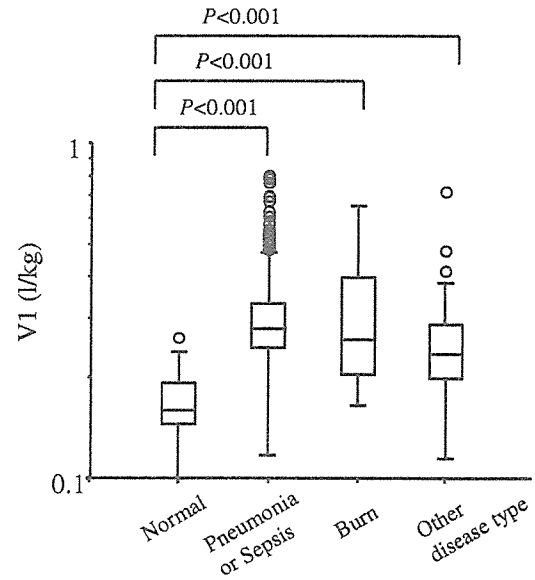

FIG. 3. Box and whisker plots showing V_1 values for healthy subjects (n = 50) and patients with infectious diseases classified by the type of illness, pneumonia or sepsis (n = 285), burn (n = 15), or other disease type (n = 53). V_1 values (liter/kilogram) calculated by the Bayesian method and 25, 50, and 75 percentiles, whiskers at ± 1.5 times the interquartile range, and outliers are denoted. The differences between healthy subjects and patients with various diseases were tested by the Dunnett test. The data were log transformed to approximate a normal distribution.

TABLE 4. Final estimates of population pharmacokinetic parameters for arbekacin

Final estimate of population arbekacin pharmacokinetic parameter
Population mean parameters
CL (liter/h) = $0.0319CL_{CR}$ + (26.5/age) (CL_{CR} < 80 ml/min)
CL (liter/h) = $0.0130CL_{CR}$ + 0.0342WT + (26.5/age) (CL_{CR} ≥ 80 ml/min)
V_1 (liter/kg) = 0.170WT for healthy subjects (no infections)
V_1 (liter/kg) = 0.272WT for patients with pneumonia or sepsis
V_1 (liter/kg) = 0.238WT for patients with infections other than pneumonia and sepsis
$V_{1\ elderly}$ (liter) = $1.19V_{1\ nonelderly}$ (elderly, ≥80 yr old)
V_2 (liter) = 15.7 for healthy subjects
V_2 (liter) = 50.6 for patients with pneumonia
V_2 (liter) = 24.3 for patients with infections other than pneumonia
Q (liter/h) = 3.84
Interindividual variability
ω (CL) = 38.8%
ω (V_1) = 37.1%
ω (V_2) = 164.6%
Intraindividual residual variability (σ = 1.07 μg/ml)

Apart from the largest difference of 16% (θ_{11}), the other parameter differences were less than 6%. The result of bootstrap analysis validation indicated that the reliability and robustness of the parameter estimates and thus the population pharmacokinetic model was acceptable. The bias, expressed as the mean prediction error, of the final model was 0.066 μg/ml, while the mean bias (95% confidence interval) obtained from the 200 bootstrap analyses was 0.068 μg/ml (0.058 to 0.077 μg/ml). The precision, expressed as root mean square prediction error from the final population model was 2.06 μg/ml, and the mean precision (95% confidence interval) obtained from the 200 bootstrap analyses was 2.07 μg/ml (2.05 to 2.08 μg/ml).

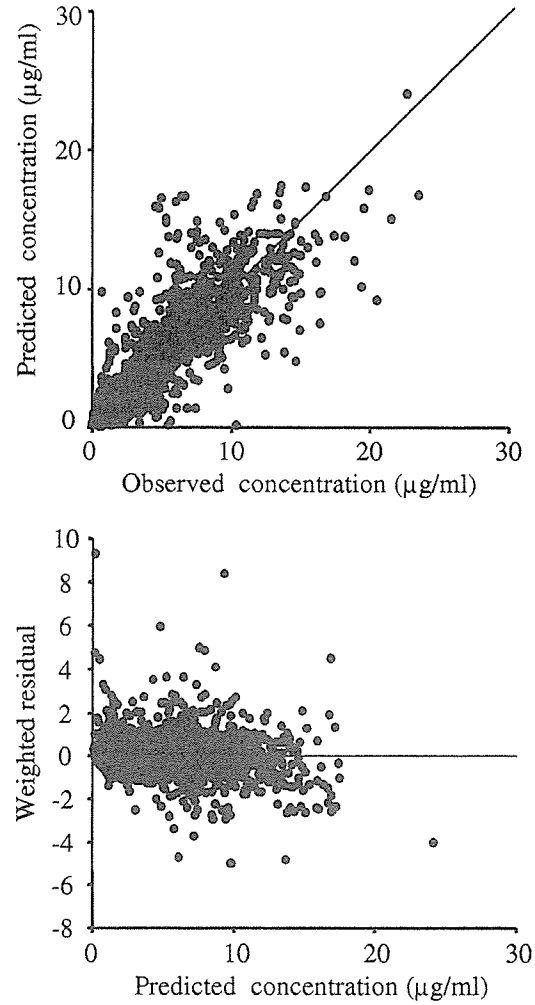

FIG. 4. Scatter plots of predictions versus observed concentrations and weighted residual versus predictions.

TABLE 5. Bootstrap validation of the estimated population pharmacokinetic parameters in the final model

Parameter[a]	Final model estimate (95% CI)[b]	Bootstrap mean[c] (95% CI)	Difference (%)[d]
θ_1	0.0319 (0.021–0.043)	0.0322 (0.021–0.045)	0.85
θ_2	0.17 (0.153–0.187)	0.167 (0.146–0.187)	−2.0
θ_3	15.7 (12.1–19.3)	14.9 (8.99–20.3)	−5.1
θ_4	3.84 (3.07–4.61)	4.01 (3.08–6.35)	4.3
θ_5	0.013 (0.0013–0.0247)	0.0123 (0.0014–0.0242)	−5.1
θ_6	0.0342 (0.0042–0.0642)	0.0362 (0.0062–0.0639)	5.8
θ_7	26.5 (3.57–49.0)	27 (6.16–53.3)	1.9
θ_8	1.6 (1.42–1.78)	1.62 (1.44–1.89)	1.2
θ_9	1.4 (1.20–1.60)	1.43 (1.22–1.70)	1.9
θ_{10}	1.19 (1.01–1.38)	1.17 (0.75–1.36)	−1.7
θ_{11}	1.55 (1.08–2.02)	1.81 (1.04–4.32)	16.0
θ_{12}	3.22 (2.36–4.08)	3.1 (1.21–4.71)	−3.9
ω_1^2	0.151 (0.082–0.220)	0.152 (0.084–0.236)	0.91
ω_2^2	0.138 (0.102–0.174)	0.142 (0.103–0.220)	3.1
ω_3^2	2.71 (0.20–5.22)	2.72 (0.022–6.61)	0.39
σ^2	1.15 (0.74–1.56)	1.12 (0.70–1.54)	−2.5

[a] θs are the population mean parameters. Refer to the footnote of Table 3 for the denotation of each θ parameter.
[b] 95% CI, 95% confidence interval.
[c] Mean of 200 bootstrap repetitions.
[d] The difference between the final model estimate and bootstrap mean is calculated as follows: [(bootstrap mean − final model estimate)/final model estimate] × 100.

DISCUSSION

Arbekacin is an aminoglycoside antibiotic widely used in Japan for the treatment of patients infected with MRSA. The TDM of arbekacin is conducted as part of routine patient care for optimization of individual arbekacin therapy, similar to other aminoglycosides. It was reported that the rate and extent of bacterial killing by aminoglycosides are concentration dependent (12, 26, 27), and the occurrence of oto- and nephrotoxicity is partly related to aminoglycoside exposure (9, 34). Therefore, the pharmacokinetic information of arbekacin in the target patient population is necessary not only for dose individualization but also for analysis of exposure-response relationships.

In recent years, the population pharmacokinetic models of aminoglycosides were reported for gentamicin (33), amikacin (32), and tobramycin (4). In the present study, we developed the population pharmacokinetic model and obtained its parameters for arbekacin in patients infected with MRSA. Simultaneously, factors affecting the pharmacokinetics of arbekacin were found by using nonlinear mixed-effect modeling. Although the pharmacokinetics of arbekacin was studied previ-

ously, only a small amount of data was published (13, 39) and these reports used a one-compartment model. The one-compartment model trends towards overestimation of concentration at early time points and underestimation at later times (33). Alternatively, the serum concentration profiles of arbekacin were fitted to a two-compartment model in this study, because enough data were obtained to perform a population pharmacokinetic analysis. Five to 32 serum concentrations were obtained from each healthy volunteer, and more than two samples per individual were obtained from 89% of the patients.

CL_{CR} is one of the most important factors affecting arbekacin disposition, because arbekacin is mainly excreted by glomerular filtration. The percentage of urinary excretion for a 24-h period was 70 to 85% following intravenous infusion in healthy volunteers (45). The dependence of arbekacin CL on CL_{CR} was more obvious in patients with insufficient renal function, while patients with a normal range of CL_{CR} values showed less dependence, since they had sufficient renal function. In this study, we used the Cockcroft-Gault equation for the estimation of CL_{CR}, because this equation is the most widely used formula in clinical practice. It has also been suggested that aminoglycoside clearance itself may be a better predictor for renal function than CL_{CR} is (14); however, we often need to decide the first dose using population pharmacokinetic parameters before therapeutic drug monitoring. Therefore, we need a predictor for renal function other than aminoglycoside clearance. We estimated the CL_{CR} value of 80 ml/minute for the breakpoint and classified two groups (Table 4 and Fig. 2). The breakpoint depends on the data; for example, 85 ml/minute was used for a population analysis of vancomycin (46), and a small pharmacokinetic study of arbekacin suggested 60 ml/minute (36). For many drugs, body size parameters, such as body weight, have been suggested as factors responsible for individual variability in pharmacokinetic parameter estimates. In this analysis, body weight was used as a covariate to help explain the variability in nonrenal clearance for patients with normal renal function. Moreover, CL of arbekacin was inversely proportional to age, even after correction by CL_{CR} (Table 4). This was probably due to several factors that are common in the elderly, such as diminished cardiac function, concomitant illness, and concurrent drug therapy. Zaske et al. reported that the gentamicin clearance decreased in elderly patients with normal renal function; clearance of patients older than 80 years was 60% that of young patients (47).

The volume of distribution of arbekacin significantly increased in patients with pneumonia, sepsis, and other infectious diseases secondary to burns compared to noninfected subjects (Table 4). The present result was in agreement with several previous studies in that the V values of aminoglycosides were larger in infected patients. For example, the mean V of gentamicin or tobramycin in patients with sepsis was significantly larger than that in healthy volunteers (by 60%) (29), and Marik showed that the APACHE II score, severity of illness scoring system, and the V of amikacin had a correlation coefficient of 0.7 (21). Longley et al. (20) suggested that patients with AIDS may have an increased aminoglycoside V. Due to lower body weight and decreased serum albumin concentrations, the AIDS patients could have increased extracellular body water because the percentage of water may be increased in nutritionally deficient people. It was shown that the V of gentamicin was increased in the critically ill, and Triginer et al. showed that the change in V for single-dose gentamicin was dependent on time, and then they suggested that larger maintenance doses were required to achieve peak therapeutic levels during the initial days of therapy (43). Moreover, Tang et al. (40) reported that the hyperdynamic septic patients had a higher V of gentamicin than hypodynamic septic and control patients and that V for the critically ill infected surgical patients was linked to the cardiac index and severity of disease. This is consistent with the hypothesis that the increased airway pressure and then intrathoracic pressure will compromise the peripheral venous return, which in turn induces fluid retention and increased V (40). Recently, Lingvall et al. (19) reported a 14% increase in V in septic neonates using population pharmacokinetic analysis, which indicated that gentamicin V increased during sepsis not only in adults but also in neonates. It is widely accepted that increased V in patients with sepsis during the acute phase of this disease has been attributed to increased capillary permeability, resulting in extravascular fluid sequestration following vigorous fluid resuscitation (43).

Arbekacin is a highly charged drug that is minimally protein bound (25) and insoluble in lipids (31), seems to have a volume distribution similar to that of the extracellular space, similar to those of other aminoglycosides (21). Therefore, it is thought that a larger V is caused by the increased extracellular space because an infectious disease often results in diffuse microcapillary injury with endothelial damage and interstitial tissue edema. In this study, the average V value for the peripheral compartment in patients with pneumonia was particularly large compared to the V_2 value in patients with sepsis and threefold larger than that of healthy volunteers (Table 4). In addition, the variability of individual V values in patients with pneumonia was much larger than that of healthy subjects (Fig. 3).

Several drugs exhibit altered pharmacokinetics in burn patients. Studies on the pharmacokinetics of intravenous ciprofloxacin (8, 18) showed that ciprofloxacin clearance decreased in burn patients, and a moderate inverse correlation was noted between percent body surface area burned and total body clearance of ciprofloxacin. In the present study, it was also observed that the V values of arbekacin in burn patients increased compared with those of healthy subjects. We examined whether there was any correlation between individual V values and the burn index, which indicates the area and degree of serious injury, but no statistically significant correlation was obtained. A possible explanation for the lack of correlation was that many patients were infected with MRSA more than a week after the burn injury, and the timing of arbekacin dose was different from that typically used during the most serious burn stage.

Age was also a factor influencing the V of arbekacin in this study, and elderly people aged 80 years or over showed a V_1 increase of 19% (Table 4). This result is in agreement with previous reports, for example, elderly people aged 65 years or over showed an arbekacin V_1 increase of 19% (36), and the V of gentamicin increased by 22% in elderly people over 60 years compared with young subjects under 40 years (47). Since aminoglycosides are minimally protein bound and insoluble in

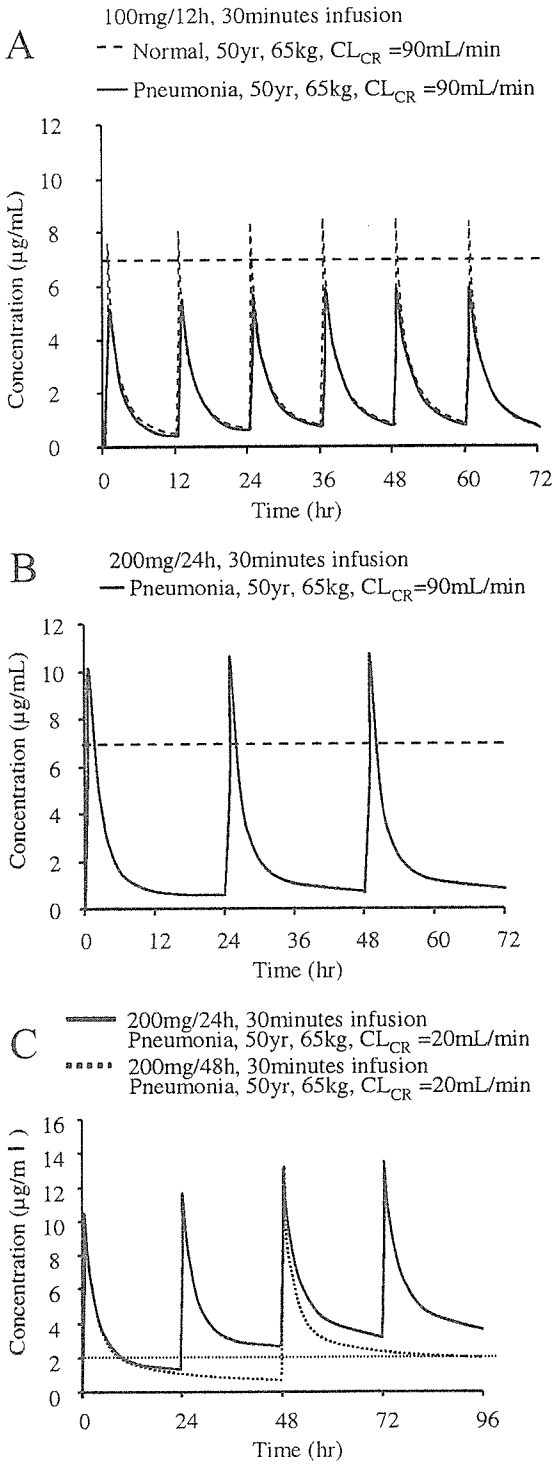

FIG. 5. Simulated serum arbekacin concentration profiles in different situations. (A) Comparison of data from a healthy subject and a patient with pneumonia with the same background and dosage regimen (100 mg/12 h). (B) Simulation curve of data for a pneumonia patient with a once-daily regimen (200 mg/24 h). (C) Simulation curve of data for a patient with pneumonia with renal impairment. The target peak concentration is not lower than 7 μg/ml (broken lines), and the trough concentration is lower than 2 μg/ml (dotted line).

lipids, the increase in V in the elderly is contrary to the increase in total body weight fat fraction in the elderly. The mechanism for altering V in aged subjects has not been clarified.

On the basis of the estimated population pharmacokinetic parameters, we simulated the serum arbekacin concentration-versus-time curves for healthy subjects and patients with pneumonia (Fig. 5). The current labeled dosage for arbekacin (100 mg twice daily) never achieves the peak level of 6 μg/ml in patients with pneumonia (Fig. 5A), while the same dose and dosage can reach 7 μg/ml in healthy subjects (Fig. 5A). In contrast, when the same daily dose (200 mg) was administered once daily to pneumonia patients, the peak level of arbekacin reached 10 μg/ml, suggesting a higher expected efficacy (Fig. 5B). Serum arbekacin concentration profiles were also simulated for other infections with similar results, i.e., the standard dosage regimen did not reach the effective peak concentration for infected patients. To prevent nephrotoxicity caused by aminoglycosides, the trough concentration should be sufficiently low. A widely accepted target trough level is <2 μg/ml, but for once-a-day administration, a trough level of <1 μg/ml should be maintained as a safety margin (28). Nephrotoxicity by aminoglycosides is generally reversible upon discontinuing treatment or upon careful monitoring and control of serum drug concentration. The present population pharmacokinetic parameters for arbekacin are extremely useful when considering the most suitable dose and dosing regimen for individual patients. For example, in a pneumonia patient with CL_{CR} of 20 ml/min, the pharmacokinetic simulation suggested a 200-mg dose administered by 48-hour dosing interval (Fig. 5C).

At present in Japan, the antibiotics used for the treatment of MRSA are arbekacin, vancomycin, and teicoplanin. Vancomycin and teicoplanin are glycopeptide antibiotics, which possess antimicrobial efficacy to gram-positive bacteria but not gram-negative pathogens. The advantage of arbekacin includes activity against both gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*. Moreover, there has been a severe problem since the emergence of MRSA strains resistant to vancomycin and teicoplanin (11, 38). In contrast, resistance to arbekacin is rarely seen, because arbekacin is not inactivated by aminoglycoside-modifying enzymes. A new metabolite of arbekacin has been identified from arbekacin-resistant strains of MRSA (7) and does not appear to cause any clinical complications.

In conclusion, a population pharmacokinetic model and parameters for arbekacin were obtained from 1,581 serum concentrations of 403 subjects. The population mean clearance in patients with a CL_{CR} of <80 ml/min was related to CL_{CR} and age, while clearance in patients with a CL_{CR} of ≥80 ml/min was associated with CL_{CR}, age, and WT. The volume of distribution was different in noninfected and infected subjects, and also among different disease types. When patients were over 80 years, age also affected the central volume of distribution. The present results are useful for the initial dosage recommendation as well as for individualization of arbekacin dosing via TDM. The population pharmacokinetic parameters are also useful in analyzing relationships between drug exposure and response as described in a companion article (35).

ACKNOWLEDGMENTS

The following institutions in Japan participated in the Anti-MRSA Drug TDM Study Group: Sapporo City General Hospital, Sapporo Medical University Hospital, Yamagata University Hospital, Niigata City General Hospital, Kanazawa Medical University Hospital, Gunma University Hospital, Saiseikai Maebashi Hospital, Kawasaki Medical School Kawasaki Hospital, Kawasaki Medical School Hospital, Saitama Medical Center Saitama Medical School, Saitama Medical School Hospital, Dokkyo University Koshigaya Hospital, Asahi General Hospital, Toho University School of Medicine Sakura Hospital, Toho University School of Medicine Omori Hospital, Nippon Medical School Hospital, Nippon Medical School Tama-Nagayama Hospital, Keio University Hospital, Tokyo Medical University Hospital, Tokyo Women's Medical University Hospital, Nihon University Itabashi Hospital, Kyorin University Hospital, Showa University Hospital, Showa University Fujigaoka Hospital, Kitasato University Hospital, St. Marianna University School of Medicine Hospital, Okayama University Hospital, Hiroshima University Medical Hospital, Kagawa Medical University Hospital, Kurume University Hospital, Fukuoka University Hospital, Kyushu University Hospital, Kumamoto University Hospital, Kagoshima City Hospital, Hamamatsu Rosai Hospital, Hamamatsu University Hospital, Nagoya-shi Koseiin Geriatric Hospital, Nagoya City University Hospital, Maizuru Kyosai Hospital, Kyoto Second Red Cross Hospital, Kansai Rosai Hospital, Kansai Medical University Hospital, Bell Land General Hospital, Osawa Hospital, Gunma Prefectural Cancer Center, Fujioka General Hospital, Tsurugaya Hospital, Hidaka Hospital, Zensyukai Hospital, Motojima General Hospital, and Tone Central Hospital.

REFERENCES

1. **Aoki, Y.** 1994. Bactericidal activity of arbekacin against methicillin-resistant Staphylococcus aureus. Comparison with that of vancomycin. Jpn. J. Antibiot. **47**:640–646.
2. **Arakawa, S., H. Maeda, A. Fujii, S. Kamidono, K. Hamada, S. Miyazaki, and S. Hara.** 1989. Clinical study of aminoglycoside on renal dysfunction. Pharmacokinetics of arbekacin and its elimination effects by hemodialysis and adsorption with charcoal. Acta Urol. Jpn. **35**:697–704.
3. **Cockcroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16**:31–41.
4. **de Hoog, M., R. C. Schoemaker, J. W. Mouton, and J. N. van den Anker.** 1997. Tobramycin population pharmacokinetics in neonates. Clin. Pharmacol. Ther. **62**:392–399.
5. **Ette, E. I.** 1997. Stability and performance of a population pharmacokinetic model. J. Clin. Pharmacol. **37**:486–495.
6. **Fillastre, J. P., A. Leroy, G. Humbert, B. Moulin, P. Bernadet, and S. Josse.** 1987. Pharmacokinetics of habekacin in patients with renal insufficiency. Antimicrob. Agents Chemother. **31**:575–577.
7. **Fujimura, S., Y. Tokue, H. Takahashi, T. Nukiwa, K. Hisamichi, T. Mikami, and A. Watanabe.** 1998. A newly recognized acetylated metabolite of arbekacin in arbekacin-resistant strains of methicillin-resistant Staphylococcus aureus. J. Antimicrob. Chemother. **41**:495–497.
8. **Garrelts, J. C., G. Jost, S. F. Kowalsky, G. J. Krol, and J. T. Lettieri.** 1996. Ciprofloxacin pharmacokinetics in burn patients. Antimicrob. Agents Chemother. **40**:1153–1156.
9. **Goodman, E. L., J. Van Gelder, R. Holmes, A. R. Hull, and J. P. Sanford.** 1975. Prospective comparative study of variable dosage and variable frequency regimens for administration of gentamicin. Antimicrob. Agents Chemother. **8**:434–438.
10. **Hamilton-Miller, J. M. T., and S. Shah.** 1995. Activity of the semi-synthetic kanamycin B derivative, arbekacin against methicillin-resistant Staphylococcus aureus. J. Antimicrob. Chemother. **35**:865–868.
11. **Hiramatsu, K., N. Aritaka, H. Hanaki, S. Kawasaki, Y. Hosoda, S. Hori, Y. Fukuchi, and I. Kobayashi.** 1997. Dissemination in Japanese hospitals of strains of Staphylococcus aureus heterogeneously resistant to vancomycin. Lancet **350**:1670–1673.
12. **Kashuba, A. D. M., A. N. Nafziger, G. L. Drusano, and J. S. Bertino, Jr.** 1999. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob. Agents Chemother. **43**:623–629.
13. **Kimura, T., K. Sunakawa, N. Matsuura, H. Kubo, S. Shimada, and K. Yago.** 2004. Population pharmacokinetics of arbekacin, vancomycin, and panipenem in neonates. Antimicrob. Agents Chemother. **48**:1159–1167.
14. **Kirkpatrick, C. M. J., S. B. Duffull, E. J. Begg, and C. Frampton.** 2003. The use of a change in gentamicin clearance as an early predictor of gentamicin-induced nephrotoxicity. Ther. Drug Monit. **25**:623–630.
15. **Komiya, I., N. Mitomi, and M. Nishio.** 1986. Assay method of HBK in biological fluids. II. High-performance liquid chromatographic assay method. Chemotherapy **34**:82–86.
16. **Kondo, S., K. Iinuma, H. Yamamoto, K. Maeda, and H. Umezawa.** 1973. Syntheses of 1-N-{(S)-4-amino-2-hydroxybutyryl}-kanamycin B and -3′, 4′-dideoxykanamycin B active against kanamycin-resistant bacteria. J. Antibiot. **26**:412–415.
17. **Kumon, H., A. Mizuno, Y. Nasu, M. Tsugawa, M. Kishi, and H. Ohmori.** 1989. Pharmacokinetics of arbekacin in healthy volunteers and patients with renal insufficiency. Jpn. J. Antibiot. **42**:200–207.
18. **Lesne-Hulin, A., P. Bourget, F. Ravat, C. Goudin, and J. Latarjet.** 1999. Clinical pharmacokinetics of ciprofloxacin in patients with major burns. Eur. J. Clin. Pharmacol. **55**:515–519.
19. **Lingvall, M., D. Reith, and R. Broadbent.** 2005. The effect of sepsis upon gentamicin pharmacokinetics in neonates. Br. J. Clin. Pharmacol. **59**:54–61.
20. **Longley, J. M., D. G. Pittman, and F. D. Newby.** 1991. Altered aminoglycoside volume of distribution in patients with acquired immunodeficiency syndrome. Clin. Pharm. **10**:784–786.
21. **Marik, P. E.** 1993. Aminoglycoside volume of distribution and illness severity in critically ill septic patients. Anaesth. Intensive Care **21**:172–173.
22. **Matsuhashi, Y., and H. Yamamoto.** 1988. The enzymatic mechanisms of resistance to aminoglycoside antibiotics in methicillin-cephem-resistant Staphylococcus aureus. Jpn. J. Antibiot. **41**:523–529.
23. **Matsuno, T., N. Suzuki, S. Kawai, S. Han, Y. Mizutani, H. Fujii, and M. Takahashi.** 1999. A method of effective administration for arbekacin (ABK)-2. Jpn. J. Ther. Drug Monit. **15**:309–313.
24. **Matsuo, H., J. Hayashi, K. Ono, K. Andoh, Y. Andoh, Y. Sano, K. Saruki, J. Tanaka, M. Yamashita, K. Nakamura, and K. Kubo.** 1997. Administration of aminoglycosides to hemodialysis patients immediately before dialysis: a new dosing modality. Antimicrob. Agents Chemother. **41**:2597–2601.
25. **Mitomi, N., T. Matsumoto, M. Fujigaki, I. Komiya, and F. Kai.** 1987. Absorption, distribution, and excretion of arbekacin after intravenous and intramuscular administration in rats. Jpn. J. Antibiot. **40**:357–364.
26. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J. Infect. Dis. **155**:93–99.
27. **Moore, R. D., C. R. Smith, and P. S. Lietman.** 1984. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am. J. Med. **77**:657–662.
28. **Nicolau, D. P., C. D. Freeman, P. P. Belliveau, C. H. Nightingale, J. W. Ross, and R. Quintiliani.** 1995. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob. Agents Chemother. **39**:650–655.
29. **Oparaoji, E. C., E. E. Cornwell III, E. Hekmat, R. Lun Cheong, J. S. Adir, and S. Siram.** 1993. Aminoglycoside volume of distribution in postoperative patients with septic shock. Clin. Pharm. **12**:131–134.
30. **Parke, J., N. H. G. Holford, and B. G. Charles.** 1999. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. Comput. Methods Programs Biomed. **59**:19–29.
31. **Ristuccia, A. M., and B. A. Cunha.** 1985. An overview of amikacin. Ther. Drug Monit. **7**:12–25.
32. **Romano, S., M. M. Fdez de Gatta, M. V. Calvo, D. Caballero, A. Dominguez-Gil, and J. M. Lanao.** 1999. Population pharmacokinetics of amikacin in patients with haematological malignancies. J. Antimicrob. Chemother. **44**: 235–242.
33. **Rosario, M. C., A. H. Thomson, D. I. Jodrell, C. A. Sharp, and H. L. Elliott.** 1998. Population pharmacokinetics of gentamicin in patients with cancer. Br. J. Clin. Pharmacol. **46**:229–236.
34. **Rybak, M. J., B. J. Abate, S. Lena Kang, M. J. Ruffing, S. A. Lerner, and G. L. Drusano.** 1999. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob. Agents Chemother. **43**:1549–1555.
35. **Sato, R., Y. Tanigawara, M. Kaku, N. Aikawa, and K. Shimizu.** 2006. Pharmacokinetic-pharmacodynamic relationship of arbekacin for treatment of patients infected with methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **50**:3763–3769.
36. **Shibasaki, S., N. Mitomi, T. Matsumoto, N. Morishita, T. Matsuno, H. Fujii, Y. Tanigawara, and K. Okumura.** 2000. Population pharmacokinetic analysis of arbekacin in Japanese. Jpn. J. Ther. Drug Monit. **17**:47–53.
37. **Shinkai, S., N. Ishiwatari, and M. Fujita.** 1986. Assay method of HBK in biological fluids. I. Microbiological assay method. Chemotherapy **34**:72–81.
38. **Sieradzki, K., P. Villari, and A. Tomasz.** 1998. Decreased susceptibilities to teicoplanin and vancomycin among coagulase-negative methicillin-resistant clinical isolates of staphylococci. Antimicrob. Agents Chemother. **42**:100–107.
39. **Suzuki, K., K. Tanikawa, and T. Matsuzaki.** 2003. Pharmacokinetics and dosing of arbekacin in preterm and term newborn infants. Pediatr. Int. **45**:175–179.
40. **Tang, G. J., J. J. Tang, B. S. Lin, C. W. Kong, and T. Y. Lee.** 1999. Factors affecting gentamicin pharmacokinetics in septic patients. Acta Anaesthesiol. Scand. **43**:726–730.
41. **Tominaga, T., H. Kishi, T. Niijima, T. Kawamura, M. Oshi, H. Nitoh, and I. Saitoh.** 1988. A study on the pharmacokinetics of HBK in patients with renal impairment. Nishinihon J. Urol. **50**:129–134.
42. **Totsuka, K., K. Shimizu, N. Mitomi, T. Niizato, and M. Araake.** 1994. Evaluation of once-daily administration of arbekacin. Experimental study

and determination of pharmacokinetic properties in man. Jpn. J. Antibiot. **47**:676–692.
43. **Triginer, C., I. Izquierdo, R. Fernandez, J. Rello, J. Torrent, S. Benito, and A. Net.** 1990. Gentamicin volume of distribution in critically ill septic patients. Intensive Care Med. **16**:303–306.
44. **Watanabe, T., K. Ohashi, K. Matsui, and T. Kubota.** 1997. Comparative studies of the bactericidal, morphological and antibiotic effects of arbekacin and vancomycin against methicillin-resistant Staphylococcus aureus. J. Antimicrob. Chemother. **39**:471–476.
45. **Yamamoto, Y., M. Koyama, and K. Nakagawa.** 1986. Phase-one clinical study on HBK. Chemotherapy **34**:104–116.
46. **Yasuhara, M., T. Iga, H. Zenda, K. Okumura, T. Oguma, Y. Yano, and R. Hori.** 1998. Population pharmacokinetics of vancomycin in Japanese adult patients. Ther. Drug Monit. **20**:139–148.
47. **Zaske, D. E., R. J. Cipolle, J. C. Rotschafer, L. D. Solem, N. R. Mosier, and R. G. Strate.** 1982. Gentamicin pharmacokinetics in 1,640 patients: method for control of serum concentrations. Antimicrob. Agents Chemother. **21**: 407–411.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2006, p. 3763–3769 Vol. 50, No. 11
0066-4804/06/$08.00+0 doi:10.1128/AAC.00480-05

Pharmacokinetic-Pharmacodynamic Relationship of Arbekacin for Treatment of Patients Infected with Methicillin-Resistant *Staphylococcus aureus*

Reiko Sato,[1] Yusuke Tanigawara,[1]* Mitsuo Kaku,[2] Naoki Aikawa,[3] and Kihachiro Shimizu[4]

Department of Pharmacy, Keio University Hospital, Tokyo, Japan[1]; Division of Molecular Diagnostics, Department of Clinical Medicine, Tohoku University, Graduate School of Medicine, Sendai, Japan[2]; Department of Emergency and Critical Care Medicine, Keio University Hospital, Tokyo, Japan[3]; and The Kitasato Institute, Tokyo, Japan[4]

Received 12 April 2005/Returned for modification 24 July 2005/Accepted 11 July 2006

Arbekacin is widely used in Japan for the treatment of patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA). In this study, we have determined the optimal concentration targets of arbekacin for both efficacy and safety. A pharmacokinetic-pharmacodynamic analysis was performed to relate exposure to the drug and clinical cure/improvement or nephrotoxicity. Since we have reported the population pharmacokinetic parameters for arbekacin in the preceding paper (Y. Tanigawara, R. Sato, K. Morita, M. Kaku, N. Aikawa, and K. Shimizu, Antimicrob. Agents Chemother. 50:3754–3762, 2006), individual exposure parameters, such as area under the concentration-time curve (AUC), peak concentration (C_{max}), AUC/MIC, C_{max}/MIC, and trough concentration (C_{min}) were estimated by the Bayesian method. Logistic regression was used to describe the relationship between exposure to the drug and the probability of clinical cure/improvement or nephrotoxicity. For the clinical efficacy analysis, 174 patients confirmed to have an MRSA infection were evaluated. The C_{max}, C_{min}, and AUC of arbekacin were associated with the probability of clinical cure/improvement during monotherapy. It was shown that the probability of cure/improvement rose when the C_{max} of arbekacin was increased, with an odds ratio of 6.7 for a change in C_{max} from 7.9 to 12.5 μg/ml ($P = 0.037$). For the nephrotoxic risk analysis, 333 patients were included, regardless of whether a pathogen was identified. Logistic regression analysis revealed C_{min} and AUC as risk factors of nephrotoxicity ($P < 0.005$). The estimated probabilities of arbekacin-induced nephrotoxicity were 2.5, 5.2, and 13.1% when the C_{min} values were 1, 2, and 5 μg/ml, respectively. The present findings are useful for optimizing the individual dose of arbekacin for the treatment of MRSA-infected patients.

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria have acquired stable resistance against most clinically available antibiotics. At present, MRSA infection is treated mainly with vancomycin. However, clinical isolates of *S. aureus* with reduced susceptibility to vancomycin, known as glycopeptide-intermediate *S. aureus* or vancomycin-intermediate *S. aureus* have recently been reported in Japan, the United States, and Europe (5, 16, 20). On the other hand, in Japan, arbekacin has been successfully used to treat MRSA infections for more than 10 years.

Arbekacin, a derivative of dibekacin, is active against MRSA and both gram-positive and gram-negative bacteria (8). Moreover, arbekacin is not affected by the inactivating enzymes produced by MRSA (9). A killing curve study demonstrated that the bactericidal activity of arbekacin depended critically on its concentration (1). As with other aminoglycosides, arbekacin is eliminated exclusively into the urine as the unchanged form via glomerular filtration and tubular reabsorption. There is a linear relationship between arbekacin pharmacokinetics and the glomerular filtration rate (4).

Although therapeutic drug monitoring (TDM) of arbekacin has become a common practice to maintain drug concentrations within a therapeutic range, the target concentrations of arbekacin used to monitor efficacy and toxicity are determined simply on the basis of knowledge of other aminoglycosides, such as gentamicin, amikacin, and tobramycin (12, 15, 22). To date, the exposure-response relationship for arbekacin in patients infected with MRSA has not been established.

For aminoglycosides, there is evidence that the efficacy in patients with gram-negative bacterial infections is influenced by the early onset of a high peak concentration/MIC ratio (3, 6, 7, 11). In these studies, to estimate the correlation of pharmacokinetic-pharmacodynamic indices with therapeutic outcomes in patients receiving aminoglycosides, the peak concentration was obtained from measurements 1 h after infusion (11) or extrapolated from the actual concentration obtained approximately 30 min after the end of a 30-minute infusion (3, 6, 7).

In the companion article (21), we reported the population pharmacokinetic parameters of arbekacin for patients infected with MRSA. Once population pharmacokinetic parameters have been obtained, the Bayesian forecasting method is applicable for predicting the serum drug concentration-time curve in each patient on the basis of a limited number of drug concentration measurements. These predicted serum drug concentration profiles are useful to estimate individual exposure parameters to arbekacin and to analyze the relationship between exposure and response.

In the present study, we analyzed the pharmacokinetic-phar-

* Corresponding author. Mailing address: Department of Hospital Pharmacy, School of Medicine, Keio University, Tokyo 160-8582, Japan. Phone: 81-(0)3-5363-3847. Fax: 81-(0)3-5269-4576. E-mail: tanigawa@sc.itc.keio.ac.jp.

TABLE 1. Distribution of doses and dosing intervals of hospitalized patients with suspected MRSA infection

Dose or dosing interval	Frequency (%)
Doses (mg)	
37.5–70	1.7
75	10.3
100	43.7
130–150	20.7
200	22.4
400	1.2
Dosing intervals (h)	
8–10	1.7
11–12	50.0
20–24	46.6
48–72	1.7

macodynamic relationship of arbekacin to determine the drug exposure parameters that correlate with the efficacy and safety of this drug and to obtain the optimal target values of these parameters.

(This work was presented in part at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, 14 to 17 September 2003.)

MATERIALS AND METHODS

Patients. Clinical data were obtained from a noninterventional observational study performed at 51 institutions, members of The Anti-MRSA Drug TDM Study Group (see Acknowledgments) from 1999 through 2002 (21). The serum drug concentration data of hospitalized patients treated with arbekacin for a suspected MRSA infection were collected as routine therapeutic drug monitoring data. The following information was also collected: sex, age, body weight, and laboratory data at appropriate times during arbekacin treatment. Regarding laboratory data, a calculated creatinine clearance (CL_{CR}, evaluated by the Cockcroft-Gault equation) was used for each patient. The most common regimen was 150 to 200 mg/day once or twice a day. However, the dosage of arbekacin of each patient was individualized on the basis of the TDM data, and various dosing schedules were used according to physicians' decisions (summarized in Table 1). Not only each dose but also the dosing interval varied, and the dosing regimen was changed within an individual patient during treatment as needed. The clinical response and toxicity were assessed by the physicians in charge and then confirmed by the study committee on the basis of the overall outcome data. Clinical cure was assessed as the resolution of signs and symptoms on the basis of the concentration of C-reactive protein, patient temperature, leukocyte count, eradication of pathogen from serum, and X-ray findings. Toxicity was assessed on the basis of clinical laboratory tests and the causal relationship between drug treatment and occurrence/recovery of adverse events. Since blood samples were taken as part of the routine patient care for TDM and laboratory testing, written informed consent and approval from each institutional review board were not necessary, but the highest standard of privacy policy was applied.

MIC determination. The MICs of arbekacin against isolated pathogens were determined at each laboratory by the standard method, which was the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) (formerly National Committee for Clinical Laboratory Standards [NCCLS]) (14).

Drug concentration monitoring. The infusion of arbekacin lasted from 15 min to 2 h. Exact times of dosing and blood sampling were always recorded. An arbekacin assay was performed as part of the routine laboratory test at each hospital using the same reagents and common protocols. Arbekacin concentrations were determined by a fluorescence polarization immunoassay using TDX arbekacin assay kit (Dainabot Co., Ltd., Tokyo, Japan). The assay coefficients of variation were 3.0, 3.8, and 2.9% for mean arbekacin concentrations at 1.98, 6.10, and 11.88 μg/ml, respectively. The lower limit of detection was 0.4 μg/ml (coefficient of variation, 9.7%).

Estimation of individual drug exposure. Complete details on the population pharmacokinetic modeling and results for arbekacin are described in the companion article (21). Briefly, arbekacin pharmacokinetics was described using a two-compartment model with elimination of the central compartment. The pharmacokinetic parameters included total body clearance (CL), volume of distribution in the central compartment, volume of distribution in the peripheral compartment, and intercompartmental clearance. The population mean CL was related to CL_{CR}, age, and body weight (WT), as expressed by the following equations.

$$CL(\text{liter/h}) = 0.0319CL_{CR} + (26.5/\text{age}) \text{ (for subjects with a } CL_{CR} \text{ of } <80 \text{ ml/min)}$$

$$CL(\text{liter/h}) = 0.0130CL_{CR} + 0.0342WT + (26.5/\text{age}) \text{ (for subjects with a } CL_{CR} \text{ of } \geq 80 \text{ ml/min)}$$

The Bayesian forecasting method was employed to estimate individual pharmacokinetic parameters using serum drug concentration measurements and the population parameters. Figure 1 shows the scatter plot of individual predicted concentrations versus observed concentrations. The estimated parameters allowed us to predict an individual serum concentration-time curve and to estimate the area under the serum concentration-time curve from time zero to 24 h (AUC_{0-24}), peak concentration (C_{max}), and trough concentration (C_{min}). The C_{max} and C_{min} values were estimated for individual patients at the end of the infusion and immediately before starting the next infusion, respectively.

Evaluation of clinical response. Clinical response was determined at the end of therapy by the physicians in charge and then confirmed by the experts on the study committee. Patients' response to therapy was classified as follows. (i) A cure was defined as resolution of clinically significant signs, such as patient temperature, leukocyte count, C-reactive protein, eradication of the pathogen from serum, and improvement or resolution of X-ray findings. (ii) Improvement was defined as partial resolution of clinically significant signs or improvement or resolution of X-ray findings. (iii) Slight improvement was defined as slight resolution of clinically significant signs or improvement or resolution of X-ray findings. (iv) Failure was defined as no response to therapy. (v) Indeterminate was defined as unable to evaluate because the patient was not available for the follow-up evaluation. Cure and improvement were both considered an effective response. Failure was considered an ineffective response.

All patients were evaluated for treatment-related adverse events regardless of whether the clinical response could be evaluated. Nephrotoxicity was determined on the basis of laboratory data, such as serum creatinine and blood urea nitrogen levels.

Pharmacodynamic analysis. Data were analyzed with SAS (version 8). The analysis of patient data included sex, combination therapy, disease type (pneumonia, sepsis, others), and use of antifungals as categorical variables, as well as age, body weight, CL_{CR}, MIC, and pharmacokinetic-pharmacodynamic indices, including C_{max}, C_{min}, AUC_{0-24}, AUC_{cum} (cumulative AUC, which was calculated as the sum of AUC_{0-24} values throughout the treatment period), first-C_{max} (C_{max} of the first dose), C_{max}/MIC, AUC_{0-24}/MIC, and first-C_{max}/MIC as continuous variables. Because the clinical response was determined at the end of the therapy, the C_{min} value used for the exposure-toxicity analysis was the arbekacin concentration immediately before the last administration. As for C_{max}, the highest C_{max} value during the treatment period was used to examine the potential

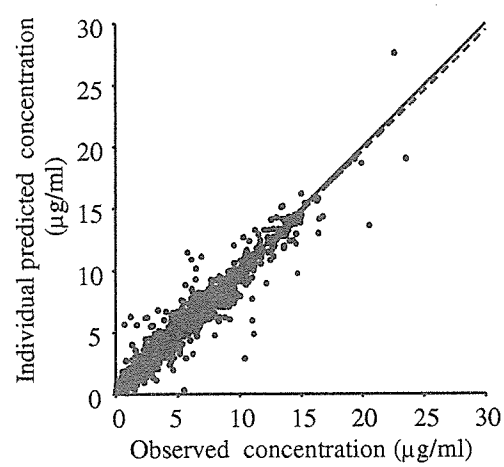

FIG. 1. Scatter plot of individual predictions versus observed concentrations. Lines of identity (solid line) and regression (broken line) are shown.

association with the probability of cure/improvement, because the individual C_{max} values were varied during the treatment due to changes in dose and dosing interval according to TDM. In most cases, the highest C_{max} was provided by the optimal dosing regimen adjusted by TDM. Furthermore, the first-C_{max}, which was the peak concentration of the first dose, was also tested, because a previous paper (6) reported that the higher C_{max}/MIC of an aminoglycoside within the first 48 h was associated with temperature resolution and leukocyte count resolution. The C_{max}/MIC and AUC_{0-24}/MIC were also considered as categorical variables, which were divided into breakpoints of C_{max}/MIC or AUC_{0-24}/MIC. Breakpoints were determined using classification and regression tree (CART) analysis with SPSS (version 13).

The pharmacokinetic-pharmacodynamic indices were calculated on the basis of the total concentrations of arbekacin, because the protein binding rate of arbekacin is as low as 3 to 12% (10). Moreover, the variables of MIC and pharmacokinetic-pharmacodynamic indices were assumed to show a log normal distribution. Therefore, the values for these variables were transformed (natural logarithmic transformation).

To clarify the relationship between pharmacokinetic-pharmacodynamic indices and use of arbekacin, the probability of cure/improvement was analyzed by the stratification of antibiotic monotherapy with arbekacin or combination therapy. For the analysis of probability of cure/improvement, the logistic regression model was used with a covariate of each variable, where cure/improvement and failure were coded as 1 and 0, respectively. These covariates as well as the interaction between two covariates were analyzed using the multivariate logistic regression model. The method used to select the variables in the model was stepwise selection, the significance level of the score chi-square test of entering an effect into the model (SLENTLY) was 0.20, and the significance level of the Wald chi-square test for an effect stay in the model (SLSTAY) was 0.20.

For the analysis of nephrotoxicity, the univariate and multivariate logistic regression model were used with covariates. The indices MIC, C_{max}/MIC, AUC_{0-24}/MIC, and first-C_{max}/MIC were excluded from the covariates, because MIC means the sensitivity of pathogen against antibiotics and is not concerned with toxicity. On the other hand, total dose and antibiotic combination therapy were added. The occurrence and absence of nephrotoxicity were coded as 1 and 0, respectively. In the multivariate logistic regression model, the analysis was carried out with covariates that were found to be significant in the univariate logistic regression model.

RESULTS

Study population and drug exposure parameters. Of the 353 patients included in the drug monitoring (21), 174 were regarded as having an MRSA infection, and the antibiotic MIC for the pathogen was determined in 101 cases. This group of 174 patients was used for the primary efficacy analysis in an attempt to link predictor variables to the probability of an effective response. Patient characteristics and their drug exposure parameters are summarized in Table 2. Of the 174 patients, 128 were assessed as cured or improved and 28 were assessed as no response to therapy or failure. There were 109 patients who received a combination therapy, and in most cases, the concomitant antibiotics were beta-lactams. Antifungals were not regarded as combination therapy, because antifungals do not affect bacteria; however, antifungals were used when other medical treatment was not effective or when the patient was immunocompromised even if the pathogen was not identified. The factor whether the patient was treated with an antifungal was tested as a covariate for clinical cure/improvement. The average durations of arbekacin treatment were 12.5 (4 to 41) and 11.1 (4 to 22) days in patients with clinical cure/improvement and clinical failure, respectively. The duration of treatment did not differ significantly between these two groups ($P > 0.3$, Wilcoxon's rank sum test).

On the other hand, for the nephrotoxic risk analysis, 333 patients were included regardless of whether a pathogen was identified. Of the 353 patients who were included in the pharmacokinetic analysis (21), 20 were excluded because the physicians in charge could not assess an adverse event or could not determine the time when toxicity appeared. Nephrotoxicity was observed in 15 patients, and the C_{min} value used for the exposure-risk analysis was the arbekacin concentration immediately before the day toxicity appeared.

TABLE 2. Characteristics of patients infected with MRSA and their drug exposure parameters

Characteristic or parameter[a]	Value
No. of patients	174
Males/females	113/61
Age (yr) (mean ± SD) [range]	63.6 ± 18.7 [8–93]
Wt (kg) (mean ± SD) [range]	53.4 ± 13.6 [10.8–107]
CL_{CR} (ml/min) (mean ± SD) [range]	96.2 ± 67.7 [7.8–458]
Serum creatinine concn (mg/100 ml) (mean ± SD) [range]	0.91 ± 1.00 (173)[b] [0.2–6.9]
MIC (μg/ml) (mean ± SD) [range]	1.15 ± 1.33 (101)[b] [0.125–8]
First-C_{max} (μg/ml) (mean ± SD) [range]	7.8 ± 3.9 [1.8–35.3]
C_{max} (μg/ml) (mean ± SD) [range]	10.9 ± 4.2 [3.4–35.8]
C_{min} (μg/ml) (mean ± SD) [range]	1.74 ± 1.57 [0.03–9.7]
AUC_{0-24} (μg · h/ml) (mean ± SD) [range]	79.3 ± 47.5 [25.7–325]
AUC_{cum} (μg · h/ml) (mean ± SD) [range]	971 ± 708 [172–5,197]
First-C_{max}/MIC (mean ± SD) [range]	13.1 ± 10.7 (101)[b] [0.6–54.9]
C_{max}/MIC (mean ± SD) [range]	18.4 ± 14.7 (101)[b] [0.7–76.1]
AUC_{0-24}/MIC (mean ± SD) [range]	133 ± 137 (101)[b] [5.8–1,008]
Patients with the following disease types:	
Pneumonia	121[c]
Sepsis	23[c]
Other infections	32
Patients treated with combination therapy	
None	64
Beta-lactam	97
Aminoglycoside	2
Macrolide	1
Quinolone	3
Fosfomycin	12
Other antibiotics	7
Patients treated with antifungal	
No	148
Yes	25

[a] Abbreviations: first-C_{max}, peak concentration of the first dose; C_{max}, the highest peak concentration during the treatment period; C_{min}, trough concentration immediately before the last administration during treatment; AUC_{0-24}, the area under the serum drug concentration-time curve from time zero to 24 h, which was calculated by dividing the sum of AUC value for the treatment period into treatment days; AUC_{cum}, the sum of AUC values after each dose event.

[b] Number of patients whose laboratory test data were available.

[c] Two patients suffered from both pneumonia and septicemia.

Probability of cure/improvement. The results of univariate and multivariate logistic regression analyses of factors affecting the probability of cure/improvement by arbekacin monotherapy are summarized in Tables 3 and 4, respectively.

In the univariate logistic regression analysis, the P values for C_{max}, C_{min}, and AUC_{0-24} were 0.14, 0.02, and 0.15, respectively. The P value for sepsis was less than 0.1 ($P = 0.072$). In the multivariate logistic regression analysis, C_{max}, C_{min}, AUC_{0-24}, and age were selected as explanatory variables by stepwise selection. The coefficients of C_{max} and C_{min} were positive, while those of AUC_{0-24} and age were negative, implying that the probability of cure/improvement rose when the C_{max} of arbekacin increased. The odds ratio (95% confidence interval) for a C_{max} change from the 25 to the 75 percentile, which was 7.9 to 12.5 μg/ml, was calculated as 6.7 (1.1 to 39). The prospective values of probability of clinical cure/improvement as a function of C_{max}, obtained by the multivariate logistic regression analysis in Table 4, are shown in Fig. 2.

TABLE 3. Univariate logistic regression analysis of factors affecting the probability of clinical cure/improvement by arbekacin monotherapy (n = 60)

Variable[a]	Coefficient	SE	P value	Odds ratio	
				Estimate	95% CI[b]
WT	−0.019	0.025	0.44	0.98	0.94–1.0
Age	0.006	0.026	0.83	1.01	0.96–1.1
Sex	−0.041	0.785	0.96	0.96	0.21–4.5
CL_{CR}	−0.005	0.007	0.49	1.00	0.98–1.0
Pneumonia	1.147	0.786	0.14	3.15	0.67–15
Sepsis	−1.526	0.850	0.072	0.22	0.04–1.1
Antifungal	−0.762	0.912	0.40	0.47	0.08–2.8
C_{max}[c]	1.605	1.100	0.14	4.98	0.58–43
C_{min}[c]	1.529	0.649	0.02	4.62	1.3–16
AUC_{0-24}[c]	1.488	1.029	0.15	4.43	0.59–33
AUC_{cum}[c]	1.106	0.697	0.11	3.02	0.77–12
First-C_{max}[c]	1.274	0.810	0.12	3.58	0.73–17
MIC[c,d]	0.834	0.730	0.25	2.30	0.55–9.6
C_{max}/MIC[c,d]	−0.288	0.625	0.65	0.75	0.22–2.6
AUC_{0-24}/MIC[c,d]	−0.104	0.514	0.84	0.90	0.33–2.5
First-C_{max}/MIC[c,d]	−0.420	0.688	0.54	0.66	0.17–2.5

[a] Abbreviations: WT, body weight; Sex, male versus female (odds ratio of female to male); Pneumonia, patients with pneumonia; Sepsis, patients with sepsis; Antifungal, use of systemic antifungal agent.
[b] 95% CI, 95% confidence interval.
[c] These values were transformed (natural logarithmic transformation).
[d] Analysis was conducted on data for 33 patients whose MIC was measured.

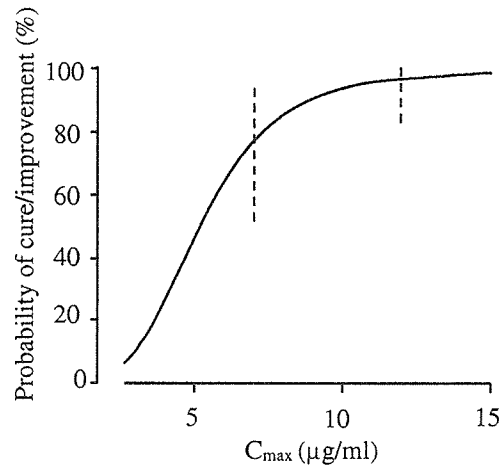

FIG. 2. Prospective values of probability of clinical cure/improvement by arbekacin monotherapy as a function of C_{max} obtained by a multivariate logistic regression model. The value of AUC_{0-24} is set at 60 μg · h/ml, which corresponds to a standard dose (200 mg/day), and C_{min} is set at 1.0 μg/ml for a patient 60 years old with normal renal function. The broken vertical lines represent the 95% confidence intervals.

The results of univariate logistic regression analysis of factors affecting the probability of cure/improvement by combination therapy are shown in Table 5. For C_{max}/MIC and AUC_{0-24}/MIC ([μg · h/ml]/[μg/ml]), the breakpoints were determined to be 25 and 186, respectively. The P values of the variables of a C_{max}/MIC ratio of >25 and a AUC_{0-24}/MIC ratio of >186 were 0.02. A C_{max}/MIC ratio of >25 was associated with 100% probability of cure/improvement, whereas patients with a C_{max}/MIC ratio of ≤25 showed 66% probability of cure/improvement. A AUC_{0-24}/MIC ratio of >186 was associated with 100% probability of cure/improvement, whereas patients with a AUC_{0-24}/MIC ratio of ≤186 showed 66% probability of cure/improvement. Figure 3 shows the relationships between pharmacodynamic indices (C_{max}/MIC and AUC_{0-24}/MIC) and the probability of cure/improvement by combination therapy. Moreover, the P values of the pneumonia and sepsis variables were 0.087 and 0.017, respectively. Other P values were over 0.2. The coefficient of the pneumonia variable was positive, while that of sepsis was negative. In other words, the probability of cure/improvement for pneumonia and not sepsis was higher, because in this study population, 79% of the patients who did not have sepsis had pneumonia. In the multivariate logistic regression analysis, no variable was selected as explanatory variables by stepwise selection.

Risk of nephrotoxicity. The results of univariate logistic regression analysis for factors that affected the probability of nephrotoxicity are summarized in Table 6. Among the pharmacokinetic parameters, C_{min} (P = 0.0026) and AUC_{0-24} (P =

TABLE 4. Results of multivariate logistic regression analysis of factors affecting the probability of clinical cure/improvement by arbekacin monotherapy (n = 60)

Covariate	Coefficient	SE	P value	Odds ratio	
				Estimate	95% CI[a]
Intercept	26.77	13.08	0.041		
C_{max}[b]	4.08	1.95	0.037	59.19	1.29–>999
C_{min}[b]	5.42	2.04	0.008	224.93	4.09–>999
AUC_{0-24}[b]	−7.30	3.62	0.044	<0.001	<0.001–0.82
Age	−0.06	0.04	0.161	0.94	0.87–1.02

[a] 95% CI, 95% confidence interval.
[b] These values were transformed (natural logarithmic transformation).

TABLE 5. Univariate logistic regression analysis of factors affecting the probability of clinical cure/improvement by combination therapy (n = 95)

Variable[a]	Coefficient	SE	P value	Odds ratio	
				Estimate	95% CI[b]
WT	−0.016	0.021	0.45	0.99	0.95–1.03
Age	0.002	0.013	0.89	1.00	0.98–1.03
Sex	0.317	0.575	0.58	1.37	0.44–4.24
CL_{CR}	0.002	0.004	0.56	1.00	1.00–1.01
Pneumonia	0.926	0.540	0.087	2.52	0.88–7.28
Sepsis	−1.515	0.633	0.017	0.22	0.06–0.76
Antifungal	−0.565	0.657	0.39	0.57	0.16–2.06
C_{max}[c]	−0.388	0.700	0.58	0.68	0.17–2.67
C_{min}[c]	−0.175	0.298	0.56	0.84	0.47–1.51
AUC_{0-24}[c]	0.007	0.499	0.99	1.01	0.38–2.68
AUC_{cum}[c]	0.194	0.403	0.63	1.21	0.55–2.68
First-C_{max}[c]	−0.483	0.554	0.38	0.62	0.21–1.83
MIC[c,d]	−0.304	0.337	0.37	0.74	0.38–1.43
C_{max}/MIC[c,d]	0.269	0.331	0.42	1.31	0.68–2.51
AUC_{0-24}/MIC[c,d]	0.344	0.309	0.27	1.41	0.77–2.59
First-C_{max}/MIC[c,d]	0.159	0.299	0.59	1.17	0.65–2.11
C_{max}/MIC > 25[d,e]	2.18		0.02	8.86	1.32–∞
AUC_{0-24}/MIC > 186[d,e]	2.18		0.02	8.86	1.32–∞

[a] Abbreviations are described in footnotes *a* of Tables 2 and 3.
[b] 95% CI, 95% confidence interval.
[c] These values were transformed (natural logarithmic transformation).
[d] Analysis was conducted for 57 patients whose MIC was measured.
[e] Variable was categorized by the breakpoint, and exact logistic analysis was used.

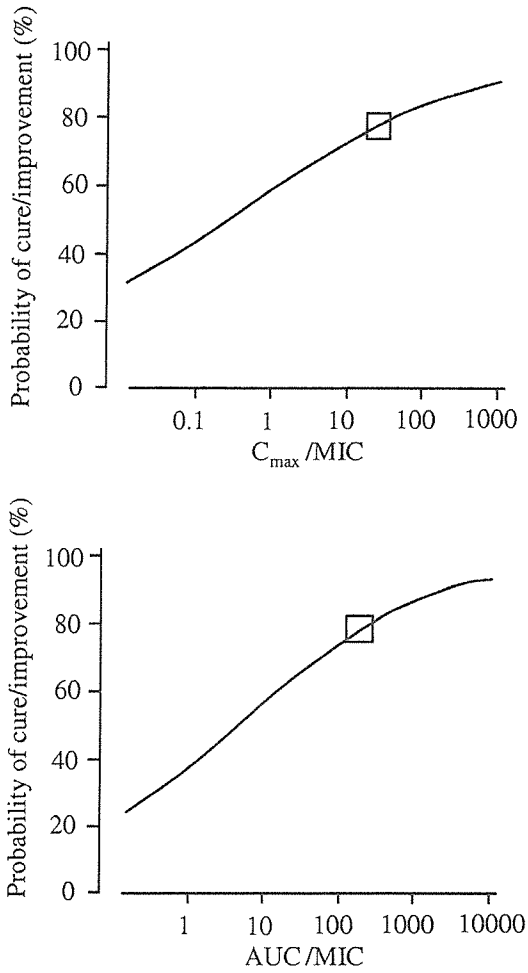

FIG. 3. Probability of clinical cure/improvement by combination therapy, as estimated by univariate logistic regression analysis. The squares represent breakpoints for C_{max}/MIC and AUC_{0-24}/MIC of arbekacin as determined by CART analysis.

0.0008) were significantly associated with the probability of occurrence of nephrotoxicity. As for patient factors, age (P = 0.038) and CL_{CR} (P = 0.045) significantly related to the probability of nephrotoxicity. Therefore, C_{min}, AUC_{0-24}, age, and CL_{CR} were analyzed by using the multivariate logistic regression model. In the multivariate logistic regression analysis, the P value of each covariate was over 0.15.

The estimated probability of arbekacin-induced nephrotoxicity as a function of C_{min} or AUC, obtained by univariate logistic regression analysis, is shown in Fig. 4. The estimated probabilities of arbekacin-induced nephrotoxicity were 2.5, 5.2, and 13.1% when C_{min} was 1, 2, and 5 μg/ml, respectively. The estimated probabilities were 1.3, 4.0, and 9.4% when AUC was 40, 80, and 140 μg · h/ml, respectively.

DISCUSSION

Arbekacin has been successfully used in Japan to treat patients infected with MRSA for more than 10 years already. However, the optimal pharmacokinetic and pharmacodynamic targets for efficacy and safety of arbekacin remain uncertain.

A number of pharmacokinetic-pharmacodynamic indices have been studied for correlation with clinical outcomes of aminoglycosides. These pharmacokinetic-pharmacodynamic indices include the first peak serum drug concentration, second peak drug concentration, AUC_{0-24} on day 1, AUC_{0-24} at steady state, and when the MIC is known, the ratio of these quantities to MIC (6, 11). Moore et al. (11) showed that a strong association existed between elevated maximal and mean peak concentration/MIC ratios and the clinical response to gentamicin, tobramycin, or amikacin. The site of infection was also related to clinical outcome, and infection by *Pseudomonas aeruginosa* was an additional risk factor for clinical failure (11). Kashuba et al. reported that the first measured C_{max}/MIC predicted the number of days to temperature resolution and the second measured C_{max}/MIC predicted the number of days to leukocyte count resolution. CART analysis produced breakpoints for C_{max}/MIC (6). On the other hand, Tod et al. found no correlation between clinical outcome and peak concentration, AUC, or their ratio with MIC for isepamicin (23). In the clinical setting, evaluation of the exposure-response relationship is often difficult because of the presence of many confounding factors. For example, success might be observed in spite of a low peak concentration/MIC or AUC/MIC ratio when the strain is sensitive to concurrently administered antibiotics, and failure might be observed in spite of a high peak concentration/MIC or AUC/MIC ratio when the duration of treatment is insufficient or the dosing interval is too long. Recently, Mouton et al. (13) demonstrated the relationship between efficacy of tobramycin for treatment of infectious exacerbations in 16 patients with cystic fibrosis and tobramycin AUC/MIC when all patients received the same dosing regimen.

We examined the exposure-response relationship by dividing the study population into a monotherapy group and a

TABLE 6. Univariate logistic regression analysis of factors affecting the probability of nephrotoxicity caused by arbekacin treatment (n = 333)

Variable[a]	Coefficient	SE	P value	Odds ratio	
				Estimate	95% CI[b]
WT	0.007	0.020	0.73	1.01	0.97–1.05
Age	0.044	0.021	0.038	1.05	1.00–1.09
Sex	−0.360	0.596	0.55	0.70	0.22–2.24
CL_{CR}	−0.013	0.007	0.045	0.99	0.97–1.00
Pneumonia	0.360	0.596	0.55	1.43	0.45–4.61
Sepsis	−0.307	0.774	0.69	0.74	0.16–3.35
Antifungal	0.578	0.668	0.39	1.78	0.48–6.60
Combination therapy	0.407	0.596	0.49	1.50	0.47–4.83
Total dose	−0.001	0.000	0.07	1.00	1.00–1.00
C_{max}[c]	1.082	0.750	0.15	2.95	0.68–12.83
C_{min}[c]	1.098	0.365	0.0026	3.00	1.47–6.13
AUC_{0-24}[c]	1.653	0.494	0.0008	5.22	1.98–13.75
AUC_{cum}[c]	0.265	0.367	0.47	1.30	0.64–2.68
First-C_{max}[c]	−0.327	0.578	0.57	0.72	0.23–2.24

[a] Abbreviations: Combination therapy, patients with antibiotic combination therapy; Total dose, the sum of the doses of arbekacin during the treatment period; C_{min}, trough concentration immediately before the last administration during treatment, but when nephrotoxicity was observed, the C_{min} indicated the trough concentration immediately before the day toxicity appeared. Other abbreviations are described in footnotes *a* of Tables 2 and 3.

[b] 95% CI, 95% confidence interval.

[c] These values were transformed (natural logarithmic transformation).

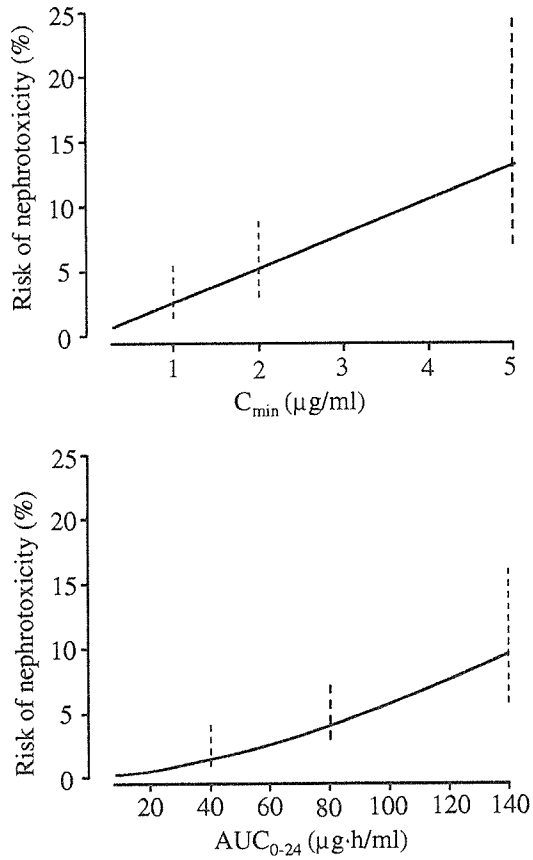

FIG. 4. Probability of arbekacin-induced nephrotoxicity, as estimated by univariate logistic regression analysis. The broken vertical lines represent the 95% confidence intervals.

combination therapy group. This was because clinical cure was related to the eradication of pathogens present, some of which might be sensitive to other concurrently administered antibiotics. Five pharmacokinetic indices, C_{max}, C_{min}, AUC_{0-24}, AUC_{cum}, and first-C_{max}, were considered to relate to the probability of cure/improvement by arbekacin monotherapy with P values of <0.2, whereas C_{max}/MIC and AUC/MIC did not relate to efficacy. The isolated microorganisms showed adequate sensitivity to arbekacin (MICs of <1 mg/liter for most isolates).

In our analysis, the first-C_{max} was not selected as an explanatory valuable. The present study was a noninterventional observational study that allowed various doses and dosing intervals as shown in Table 1. Moreover, the dose was changed on the basis of TDM when the initial dose was insufficient to reach a therapeutic concentration. The clinical efficacy was judged at the end of therapy. Therefore, the treatment success depended on neither the first dose nor the first-C_{max}, but the adjusted dose after TDM or a maximal C_{max} during the treatment period.

By the multivariate logistic regression analysis, C_{max}, C_{min}, AUC_{0-24}, and age were selected as factors affecting efficacy, and the probability of cure/improvement rose when the C_{max} of arbekacin was increased after a standard dose (200 mg/day) (Fig. 2). Since the data were collected from a noninterventional observational study, several confounding factors made interpretation of the results complex. For example, many patients started with a twice-daily regimen and then switched to a once-daily regimen with a higher C_{max} (expecting higher efficacy) but with unchanged AUC_{0-24} when the total daily dose was kept constant. In such cases, C_{max} can be associated with efficacy, whereas AUC_{0-24} cannot be related to efficacy. Variations in doses, dosing intervals, and infusion durations in individual patients are major differences from the experimental fixed-regimen studies.

By using combination therapy, Kashuba et al. assessed concurrent beta-lactam therapies but were unable to find any statistical relationship between concomitant antibiotic therapy and temperature or leukocyte count (6). On the other hand, there is interest in synergistic activity, because arbekacin is typically combined with a broad-spectrum beta-lactam or other antibiotics. Rybak et al. reported that CB-181963, a novel cephalosporin with MRSA activity, plus an aminoglycoside, such as arbekacin, was the most potent combination against *S. aureus*, such as MRSA and vancomycin-resistant *S. aureus* in vitro (M. J. Rybak, C. M. Cheung, and W. J. Brown, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1150, p. 14, 2003). In the present study, the breakpoints of C_{max}/MIC and AUC_{0-24}/MIC in combination therapy were determined to be 25 and 186, respectively. Patients with a C_{max}/MIC ratio of >25 or with a AUC_{0-24}/MIC ratio of >186 showed 100% probability of cure/improvement. The estimated breakpoint value for AUC_{0-24}/MIC ratio (186) is consistent with clinical data reported by Kashuba et al. (6) where AUC/MIC ratios of 150 and 175 were associated with 90% probability of temperature resolution and leukocyte count resolution by 7-day aminoglycoside therapy, respectively. However, in the multivariate logistic regression analysis, no variable was selected as explanatory variables by stepwise selection. It was probably due to the insufficient power of detection; because the MIC was measured for only 57 patients, the C_{max}/MIC and AUC_{0-24}/MIC indices were available for only 57 patients.

It is well-known that the use of aminoglycosides is associated with the occurrence of nephrotoxicity. Similarly, the major drawback of arbekacin treatment is the risk of nephrotoxicity. In an animal study (2), gentamicin showed the highest degree of tubular reabsorption, netilmicin showed the lowest, and dibekacin and amikacin showed intermediate degrees of reabsorption. Nephrotoxicity of arbekacin is considered less severe than that induced by gentamicin but more severe than that induced by amikacin. In this study, we observed that higher C_{min} and AUC_{0-24} values were associated with a greater risk of developing renal impairment. Extensive data from animal models and clinical studies suggest that administration of aminoglycosides once daily results in lower occurrence rates of aminoglycoside-associated nephrotoxicity. Rybak et al. demonstrated that both the probability of occurrence and the time to occurrence of aminoglycoside nephrotoxicity were influenced by the administration schedule (19). The probability of nephrotoxicity as a function of AUC differed when the aminoglycoside was administered once daily or twice daily. Moreover, Rougier et al. developed a model for aminoglycoside nephrotoxicity that took into account both pharmacokinetic and pharmacodynamic variability (18). The simulations for aminoglycoside nephrotoxicity showed that with more-frequent administration, nephrotoxicity appeared

more rapidly and that the decrease in renal function was greater and lasted longer.

The present study was a noninterventional observational study, and the dose regimen was modified for individual patients to attain the target concentration on the basis of TDM. Still, the importance of monitoring C_{min} to reduce the risk of nephrotoxicity regardless of patient factors was identified. Although concomitant use of vancomycin increases the risk of aminoglycoside nephrotoxicity (19), arbekacin is not administrated with vancomycin. Thus, combination therapy did not affect the risk of arbekacin nephrotoxicity in this study.

The possible influences by treatment period or cumulative dose on the risk of nephrotoxicity have also been investigated. In our study, however, the treatment period was not identified by logistic regression analysis as a risk factor for occurrence of nephrotoxicity. Because TDM usually works well, most patients are administered arbekacin for a longer period of time without developing nephrotoxicity. To avoid nephrotoxicity, extension of dosing interval is recommended when C_{min} is high. No correlation was observed between C_{min} and time to the occurrence of nephrotoxicity.

In conclusion, in this study, C_{max} was associated with the clinical response, i.e., a higher C_{max} can increase the probability of achieving clinical cure/improvement. Moreover, monitoring C_{min} was important to avoid nephrotoxicity, and a target C_{min} of <2 μg/ml was considered preferable. This information will be highly useful for optimal treatment using arbekacin in patients infected with MRSA.

ACKNOWLEDGMENTS

We thank M. Matsumoto, Y. Iwama, and H. Akiyama, statisticians from Meiji Seika Kaisha, Ltd., for their commitment and help in implementing this study. We also greatly appreciated discussing this study project with K. Hosaka, K. Kurihara, S. Shibasaki, K. Aizawa, M. Imae, and T. Tatebayashi, who belong to the clinical research group of Meiji Seika Kaisha, Ltd.

The following institutions in Japan participated in The Anti-MRSA Drug TDM Study Group: Sapporo City General Hospital, Sapporo Medical University Hospital, Yamagata University Hospital, Niigata City General Hospital, Kanazawa Medical University Hospital, Gunma University Hospital, Saiseikai Maebashi Hospital, Kawasaki Medical School Kawasaki Hospital, Kawasaki Medical School Hospital, Saitama Medical Center Saitama Medical School, Saitama Medical School Hospital, Dokkyo University Koshigaya Hospital, Asahi General Hospital, Toho University School of Medicine Sakura Hospital, Toho University School of Medicine Omori Hospital, Nippon Medical School Hospital, Nippon Medical School Tama-Nagayama Hospital, Keio University Hospital, Tokyo Medical University Hospital, Tokyo Women's Medical University Hospital, Nihon University Itabashi Hospital, Kyorin University Hospital, Showa University Hospital, Showa University Fujigaoka Hospital, Kitasato University Hospital, St. Marianna University School of Medicine Hospital, Okayama University Hospital, Hiroshima University Medical Hospital, Kagawa Medical University Hospital, Kurume University Hospital, Fukuoka University Hospital, Kyushu University Hospital, Kumamoto University Hospital, Kagoshima City Hospital, Hamamatsu Rosai Hospital, Hamamatsu University Hospital, Nagoya-shi Koseiin Geriatric Hospital, Nagoya City University Hospital, Maizuru Kyosai Hospital, Kyoto Second Red Cross Hospital, Kansai Rosai Hospital, Kansai Medical University Hospital, Bell Land General Hospital, Osawa Hospital, Gunma Prefectural Cancer Center, Fujioka General Hospital, Tsurugaya Hospital, Hidaka Hospital, Zensyukai Hospital, Motojima General Hospital, and Tone Central Hospital.

REFERENCES

1. **Aoki, Y.** 1994. Bactericidal activity of arbekacin against methicillin-resistant Staphylococcus aureus. Comparison with that of vancomycin. Jpn. J. Antibiot. **47**:640–646.
2. **Brion, N., J. Barge, I. Godefroy, F. Dromer, C. Dubois, A. Contrepois, and C. Carbon.** 1984. Gentamicin, netilmicin, dibekacin, and amikacin nephrotoxicity and its relationship to tubular reabsorption in rabbits. Antimicrob. Agents Chemother. **25**:168–172.
3. **Deziel-Evans, L. M., J. E. Murphy, and M. L. Job.** 1986. Correlation of pharmacokinetic indices with therapeutic outcome in patients receiving aminoglycosides. Clin. Pharm. **5**:319–324.
4. **Fillastre, J. P., A. Leroy, G. Humbert, B. Moulin, P. Bernadet, and S. Josse.** 1987. Pharmacokinetics of habekacin in patients with renal insufficiency. Antimicrob. Agents Chemother. **31**:575–577.
5. **Hiramatsu, K., H. Hanaki, T. Ino, K. Yabuta, T. Oguri, and F. C. Tenover.** 1997. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J. Antimicrob. Chemother. **40**:135–136.
6. **Kashuba, A. D. M., A. N. Nafziger, G. L. Drusano, and J. S. Bertino, Jr.** 1999. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob. Agents Chemother. **43**:623–629.
7. **Kashuba, A. D. M., J. S. Bertino, Jr., and A. N. Nafziger.** 1998. Dosing of aminoglycosides to rapidly attain pharmacodynamic goals and hasten therapeutic response by using individualized pharmacokinetic monitoring of patients with pneumonia caused by gram-negative organisms. Antimicrob. Agents Chemother. **42**:1842–1844.
8. **Kondo, S., K. Iinuma, H. Yamamoto, K. Maeda, and H. Umezawa.** 1973. Syntheses of 1-n-(S)-4-amino-2-hydroxybutyryl-kanamycin B and -3′,4′-dideoxykanamycin B active against kanamycin-resistant bacteria. J. Antibiot. **26**:412–415.
9. **Matsuhashi, Y., and H. Yamamoto.** 1988. The enzymatic mechanisms of resistance to aminoglycoside antibiotics in methicillin-cephem-resistant Staphylococcus aureus. Jpn. J. Antibiot. **41**:523–529.
10. **Mitomi, N., T. Matsumoto, M. Fujigaki, I. Komiya, and F. Kai.** 1987. Absorption, distribution, and excretion of arbekacin after intravenous and intramuscular administration in rats. Jpn. J. Antibiot. **40**:357–364.
11. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J. Infect. Dis. **155**:93–99.
12. **Moore, R. D., C. R. Smith, and P. S. Lietman.** 1984. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am. J. Med. **77**:657–662.
13. **Mouton, J. W., N. Jacobs, H. Tiddens, and A. M. Horrevorts.** 2005. Pharmacodynamics of tobramycin in patients with cystic fibrosis. Diagn. Microbiol. Infect. Dis. **52**:123–127.
14. **National Committee for Clinical Laboratory Standards.** 1996. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 4th ed. Approved standard M7–A4. NCCLS, Wayne, Pa.
15. **Nicolau, D. P., C. D. Freeman, P. P. Belliveau, C. H. Nightingale, J. W. Ross, and R. Quintiliani.** 1995. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob. Agents Chemother. **39**:650–655.
16. **Ploy, M. C., C. Grelaud, C. Martin, L. de Lumley, and F. Denis.** 1998. First clinical isolate of vancomycin-intermediate *Staphylococcus aureus* in a French hospital. Lancet **351**:1212.
17. Reference deleted.
18. **Rougier, F., D. Claude, M. Maurin, A. Sedoglavic, M. Ducher, S. Corvaisier, R. Jelliffe, and P. Maire.** 2003. Aminoglycoside nephrotoxicity: modeling, simulation, and control. Antimicrob. Agents Chemother. **47**:1010–1016.
19. **Rybak, M. J., B. J. Abate, S. L. Kang, M. J. Ruffing, S. A. Lerner, and G. L. Drusano.** 1999. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob. Agents Chemother. **43**:1549–1555.
20. **Sieradzki, K., R. B. Roberts, S. W. Haber, and A. Tomasz.** 1999. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. N. Engl. J. Med. **340**:517–523.
21. **Tanigawara, Y., R. Sato, K. Morita, M. Kaku, N. Aikawa, and K. Shimizu.** 2006. Population pharmacokinetics of arbekacin in patients infected with methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **50**:3754–3762.
22. **Thomson, A. H., N. Duncan, B. Silverstein, S. Alcock, and D. Jodrell.** 1996. Antimicrobial practice. Development of guidelines for gentamicin dosing. J. Antimicrob. Chemother. **38**:885–893.
23. **Tod, M., C. Minozzi, G. Beaucaire, D. Ponsonnet, J. Cougnard, and O. Petitjean.** 1999. Isepamicin in intensive care unit patients with nosocomial pneumonia: population pharmacokinetic-pharmacodynamic study. J Antimicrob. Chemother. **44**:99–108.

覚えておきたい国際感染症の知識

日本脳炎

森田　公一
Morita Kouichi
長崎大学熱帯医学研究所病原体解析部門分子構造解析分野教授

●要旨：日本脳炎はコガタアカイエカなどの蚊が媒介する急性ウイルス性脳炎である。わが国では現在，超低流行の状況であるが1950～60年代にかけて年間，数千名の患者が発生し社会的な問題であった。今も夏になると日本脳炎ウイルスの活動は確認されるので高齢者や小児では感染予防のためにワクチン接種を継続することが望ましい。また，熱帯アジアでは現在でも年間20,000名を超える患者発生がみられ，海外渡航者には注意を喚起する必要がある。
●Key Words：日本脳炎，アルボウイルス，コガタアカイエカ

はじめに

わが国で1950～1960年代に猛威をふるった日本脳炎は，現在では年間に発生する患者数が10人を下回り社会的にも話題になることはなくなった。しかし，ウイルスは毎年夏になると自然界の蚊から分離されており今も警戒は必要である。また，目を熱帯アジアに向けると年間20,000名を超える患者が発生しており，熱帯の国々では依然として重要な保健衛生上の問題である。アジアの国々への渡航者が増加している現在，国内における臨床の場でも輸入感染症として注意が必要であり，また今から渡航する人々には，とくに小児や高齢者へワクチン接種の必要性や個人レベルでの蚊の対策などの情報提供が必要である。

Ⅰ　疫学・背景

日本脳炎ウイルスの活動範囲は図1に示したように日本，韓国，中国などの東アジアからベトナム，タイ，フィリピン，インドネシアなどの東南アジアさらにはインド，パキスタンの一部までの西アジア，さらにはパプアニューギニア，オーストラリア北部にまで及んでおり患者発生が報告されている。これらの地域で日本脳炎ウイルスが活発に活動できるのは，多量の降雨により広い淡水域で繁殖するコガタアカイエカなどの媒介蚊が多数生息する環境を提供しているからである。とくにアジアモンスーン地域では伝統的な稲作との関連が深く，ネパールなど近年，灌漑施設が整備され大規模な稲作が導入さ

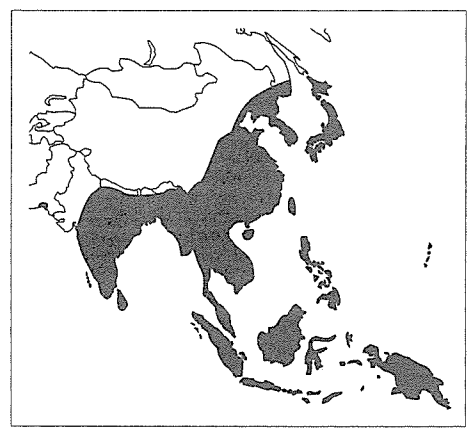

図1●日本脳炎ウイルスの地理的分布

れた地域では患者が爆発的に増加している。

一方，わが国では1966年の2,301名に及ぶ流行の後，日本脳炎患者の発生は激減し，現在では年間10名以下の低流行状況が継続している(図2)。この理由としては①1960年代から日本脳炎ワクチンの集団接種が開始されたこと，②頻繁に水田から水を抜く農耕方法(稲の根がはることで米の収穫が増加する)が普及したことや多量の農薬の使用により媒介蚊の数が減少したこと，③蚊へのウイルス供給源であるブタを飼育している養豚場が水田から離れた辺縁地域へ移動したこと，④生活様式の変化，とくにエアコンの普及などでヒトが蚊に刺される機会が減少したことなどが原因として考えられる[1)2)]。同様な日本脳炎患者数の著明な減少は隣国である韓国，台湾でも経験されているが，これらの国々でも学童への大規模なワクチン接種を開始したのちに患者が激減した。一方，インドなどワクチンが行き渡らない他のアジアの国々では依然として数万にも及ぶ多くの患者の発生が報告されている[3)]。

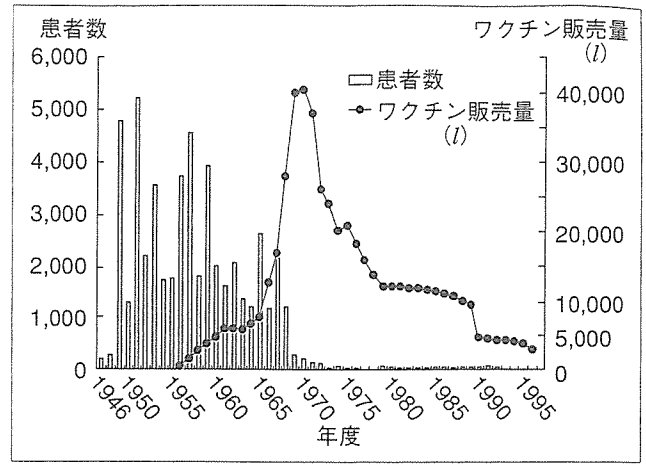

図2　日本における日本脳炎患者数とワクチン販売量の推移

Ⅱ　病原体

日本脳炎ウイルスはフラビウイルス科に分類される1本の(+)鎖RNAを遺伝子としてもつエンベロープ(脂質の2重膜)に包まれたウイルスであり，70%アルコールや界面活性剤などの通常の消毒薬で容易に不活化する。日本脳炎ウイルスに近縁で同様に中枢神経感染を起こすフラビウイルスとしてウエストナイルウイルス(西ナイルウイルス)がある。

Ⅲ　潜伏期，感染可能期

潜伏期間はウイルスに感染した蚊に刺されて，1～2週間である。日本脳炎患者から直接感染することはない。これは患者血清中のウイルス量がきわめて低いレベルであるためである。

Ⅳ　感染経路

日本脳炎ウイルスは主としてコガタアカイエカにより媒介される。日本脳炎ウイルスに感染したコガタアカイエカの唾液腺では日本脳炎ウイルスはよく増殖し，蚊がヒトを吸血する際にウイルスが体内に注入されることで感染する。ブタは日本脳炎ウイルスに高感受性であり，ウイルスをもった蚊に吸血される際に感染し，高いレベルのウイルス血症を起こし蚊へのウイルス供給源となるため，ウイルス増殖動物としてもっとも重要である。とくに日本においては6～9月にかけて日本脳炎ウイルスは図3に示すような感染環により蚊とブタとの間で感染を繰り返すことでウイルス汚染蚊の数が増幅される。したがって，日本における日本脳炎の発生は7～9月にかけて患者発生のピークがみられる。

Ⅴ　症　状

日本脳炎の三主徴候(高熱・頭痛・意識障害)や髄膜刺激症状などがみられる。日本脳炎ウイルスに感染したヒトの多くは不顕性感染か軽度の発熱で推移するが，感染者300～3,000人に1人の割合で脳炎が発症すると見積もられている。脳炎を発症した場合はきわめて重篤であり，脳炎患者の約1/3は死亡し，死を免れた者でも半数には精神障害，運動障害などの重い神経系の障害が残る。脳炎患者の初発症状は発熱・頭痛で発症する場合が多い。小児の患者では腹痛・下痢などの消化器症状を初発症状とする場合がある。発症後2～4日の間，頭痛，高熱，

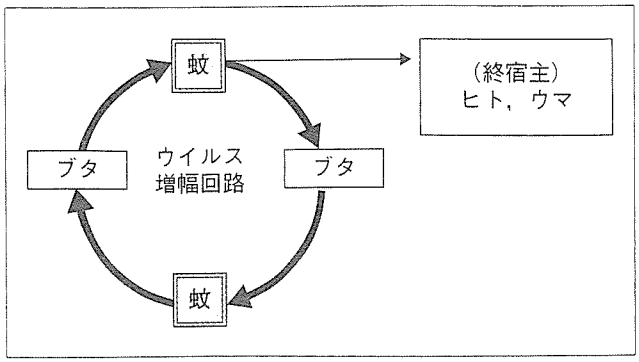

図3　日本脳炎ウイルス感染環

悪寒，食欲不振，嘔気，嘔吐，傾眠の状態が継続し，進行すると項部硬直，Kernig 症候，筋強剛などの髄膜刺激症状が顕著となり，意識障害，異常反射，四肢麻痺(とくに上肢)，痙攣，昏睡が出現してついには死に至る。経過中に呼吸不全，バビンスキー反射陽性，てんかん発作などの諸徴候がみられる場合は予後が悪く，たとえ死を免れても重い精神障害，運動麻痺などの後遺症が残る[4]。回復後は強固な終生免疫が獲得され2度感染することはない。

Ⅵ　合併症

神経麻痺による呼吸障害により細菌性肺炎などを発症する場合がある。

Ⅶ　検　　査

一般検査として末梢血検査では白血球増多，髄液検査では圧上昇，リンパ球増多，タンパク増加，糖は正常ないし軽度上昇など一般的な無菌性髄膜炎の所見がみられる。画像診断検査としてCTおよびMRI検査において異常が認められる場合がある。多くは両側性に視床，基底核に異常所見を認める[5]。剖検例でも病理学的に同部位に異常が確認される。血清学的検査では日本脳炎ウイルス特異的抗体の検出が必須である。①ペア血清を用いてHI，CF，またはIgG-ELISA抗体価の4倍以上の上昇，あるいは②血清または髄液中の日本ウイルス特異的IgM抗体陽性(HI検査では2-ME感受性抗体が陽性またはIgM-ELISA抗体陽性)のいずれか一つの所見が必要である。とくに髄液中の日本脳炎特異的IgMの検出は中枢神経内でのウイルス増殖を意味するので診断的価値が高いとされる。ウイルス学的検査として，死亡例では脳組織からのウイルスの分離またはPCRによるウイルス遺伝子の検出を行う。

鑑別疾患としては細菌性，結核性，真菌性の髄膜炎，ヘルペス脳炎，他のフラビウイルスによる脳炎(ダニ媒介性脳炎やウエストナイル脳炎)，脳血管障害などがあり，注意を要する。

ナースへのアドバイス：日本脳炎

みやざき県南中核病院呼吸器科　板橋　繁

<観察のポイント・看護の要点>

本疾患は今までのマラリア，デング熱，ウエストナイル脳炎と異なり，本邦も含めたアジアで流行している感染症である。ただし，本文にもあるようにわが国での流行は低頻度であり，アジアモンスーン地帯からの帰国者・旅行者での発症に注意しなければならない。

日本脳炎ウイルスの感染は多くの場合，軽症あるいは不顕性感染ですむが，脳炎を発症するときわめて危険な状況となる。特異的治療法(有効な抗ウイルス薬)がなく，対症療法で切り抜けるしかないため，脳炎の徴候を早期に発見するように努める。具体的には発熱・頭痛・嘔気嘔吐などであるが，小児では消化器症状(腹痛・下痢)が初発症状であることもあり，注意を要する。

<患者・家族への対応・指導>

本疾患においてヒトは終末宿主であり，ヒトからヒトに感染することはない。したがって患者を隔離する必要もなく，特別な注意は不要である。

<院内感染対策>

日本脳炎ウイルスはエンベロープを有するので熱処理や消毒薬に対する抵抗性は弱い。とくに脳炎を発症している時期では患者血液中のウイルス量はきわめて少ない。具体的な対策はデング熱ウイルスと同じでよい。「デング熱・デング出血熱」の項を参照のこと。

り検査を適切に実施して正しい実験室診断を行うことが重要である。とくにウエストナイル脳炎は今のところ日本には存在しないが，米国では流行しており確実に鑑別することが必要である。日本脳炎は新感染症予防法において全数把握の新四類感染症に分類されており，診断した場合は直ちにもよりの保健所に届けなければならない。

Ⅷ 治　療

日本脳炎ウイルスに対する抗ウイルス薬はないので特異的な治療はなく，対症療法のみである。すなわち，発熱，脳浮腫，脳圧亢進，痙攣，呼吸障害に対する処置，および合併症(細菌性肺炎など)の予防のための処置が重要である。状況に応じて気道および輸液ルートを確保し，解熱剤，抗痙攣薬(セルシン®，アレビアチン®)，高浸透圧薬(グリセオール®，マニトール®)，ステロイドホルモンを適時投与する。合併症予防のため，抗生物質の投与を行う。前述したように患者が脳炎を発症した時点ではウイルス血症はすでに終わっており二次感染の心配はなく患者を隔離する必要はない。また，日本脳炎ウイルスは遷延感染することはないので後遺症なく回復した場合は特別なケアは必要ないが，運動機能や知能の障害を残して治癒した場合には機能回復のためのリハビリテーションを行う。

Ⅸ 感染対策

日本脳炎のもっとも確実な予防方法としてワクチンの接種が推奨される。現在日本で認可されているワクチンは不活化ワクチンで，初回接種においては１～４週間の間隔で２回の接種を行い，１年後に１回の追加接種を行う。その後は数年おきに１回の追加免疫を行うことで感染予防に有効な抗体価が維持される。日本脳炎ワクチン接種による重篤な副作用(神経系の障害)の出現頻度は，被接種者100万人に１人あるいはそれ以下と見積もられており，きわめて安全なワクチンの一つである。しかし，接種部位の腫脹・発赤などの軽・中程度の副作用の出現頻度には人種間で差がみられヨーロッパ系の白人では頻度が高いと報告されており適切なインフォームド・コンセントが必要である。

ワクチン接種が可能でない場合は，個人レベルでの媒介蚊対策も有用である。すなわち，日本脳炎流行地域に出かける場合には長袖，長ズボンなどを着用し，肌の露出部には蚊忌避剤を塗布する。また就寝時には蚊取り線香や殺虫剤，蚊帳などを適切に使用して蚊に刺されないようすることが重要である。

おわりに

わが国において，日本脳炎は超低流行状況が持続している。しかし，ワクチン接種が不要と考えるのは時期尚早である。患者数は少ないものの，毎年夏には関東から九州，沖縄まで日本脳炎ウイルスの活動が確認されており，相変わらずコガタアカイエカからは日本脳炎ウイルスが分離される。また近年の研究では日本脳炎ウイルスは東南アジアから日本へ頻繁に運ばれている事実も明らかになっている[6]。いったん発症した場合の高い致命率や，救命された場合でも重篤な後遺症を残すことを考えれば，日本脳炎に対する警戒を緩めることなく，感染リスクの高い小児や学童，高齢者への日本脳炎ワクチンの接種は少なくともウイルスの活動が確認される地域では継続することが今しばらくは必要である。

●引用・参考文献●

1) 五十嵐章：日本脳炎とデング熱/デング出血熱．医学のあゆみ，177：924-929，1996.
2) Igarashi, A.：Control of Japanese encephalitis in Japan；Immunization of Humans and Animals, and Vector Control. Current Topics in Microbiology and immunology, 267：139-152, 2002.
3) World Health Organization (Geneva)：The World Health Report 1996. pp. 49-50.
4) 小林譲：日本脳炎の臨床．臨床とウイルス，13：166-172，1985.
5) Shoji, H., Hiraki, Y., et al.：Japanese encephalitis in the Kurume region of Japan；CT and MRI findings. J. Neurology, 236：255-259, 1989.
6) Nga, P. T., Parquet, M. C., Cuong, V. D., et al.：Shift in JEV genotype circulating in northern Vietnam；Implication for frequent introductions of JEV from Southeast Asia to East Asia. Journal of General Virology, 85：1625-1631, 2004.